An Efficient Method for the Large-Scale Preparation of 3-*O*-Acetyl-11-oxo-β-boswellic Acid and Other Boswellic Acids[‡]

Johann Jauch*[a] and Jochen Bergmann[a]

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3-*O*-Acetyl-11-oxo-β-boswellic acid (AKBA), found in incense, is a potent inhibitor of 5-lipoxygenase, p38 and p42 MAP kinase and topoisomerases. Starting from crude extracts from incense, procedures are presented for the efficient large-scale synthesis of AKBA and other boswellic acids

Introduction

A steadily increasing number of people suffer from chronic inflammatory diseases[1] like rheumatoid arthritis, chronic bronchitis, asthma, chronic inflammatory bowel diseases (ulcerative colitis and Crohn's disease) as well as chronic inflammatory skin diseases (atopic dermatitis and psoriasis).

Whereas the causes of these diseases are often unknown,[1] the role of the immune system[1,2] and underlying biochemical pathways[1,3] of inflammatory processes are much better understood. One of these pathways is the arachidonic acid cascade: arachidonic acid is transformed into prostaglandins and leukotrienes with the aid of cyclooxygenases and lipoxygenases, respectively.[2,3] Whereas several prostaglandins are responsible for the induction of inflammatory processes,[1] leukotriene B5 (LTB5) in particular is responsible for the maintenance[1,4] of the inflammation and therefore for the chronic progress of the disease. In fact, in the above-mentioned diseases, patients show increased LTB5 levels.[4]

The key enzyme in the conversion of arachidonic acid into LTB5 is 5-lipoxygenase (5-LOX). Treatment of inflammatory diseases is, in principle, possible by applying 5-LOX inhibitors, and the pharmaceutical industry has made great efforts to develop such therapeutics, although with only moderate success.[5]

Indian and African folk medicine uses ethanolic extracts of the resin of *Boswellia serrata* ROXB (incense) to treat inflammatory diseases. Some years ago, Ammon and coworkers[6] became aware of the therapeutic potential of incense and started a research program to elucidate the substances responsible for the inhibition of inflammations. During their work, the β-boswellic acids[7] **1a**−**1d** (Figure 1) were re-discovered and identified as very potent 5-LOX inhibitors.

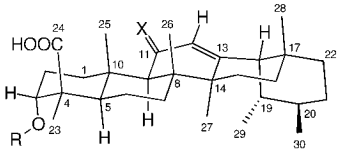

Figure 1. Structures of four β-boswellic acids found in incense

Over the last few years, other pharmacological properties[8] of pure β-boswellic acids have been studied and it was found that they also act as efficient inhibitors of the topoisomerases I and IIa[8a,9] and as potent inhibitors of the MAP-kinases p38 and p42.[10] Boswellic acids are therefore very fascinating molecules and there is an increasing demand for these substances for pharmaceutical and medicinal studies.

Unfortunately, the concentration of the most active boswellic acid, 3-*O*-acetyl-11-oxo-β-boswellic acid AKBA (**1d**), in extracts from *Boswellia* resins is in the range of 0.1−3% and it is therefore very difficult and time consuming to isolate large amounts of this compound. The procedure used in previous studies for the isolation of β-boswellic acids was developed by Winterstein et al.,[7a] with preparative HPLC as the final purification step.[9]

Here, we wish to report a simple and efficient strategy[11] for the large-scale synthesis of AKBA (**1d**) and the other boswellic acids.

[‡] Chemistry of Boswellic Acids, 1.

[a] Institut für Organische Chemie und Biochemie, Technische Universität München,
Lichtenbergstrasse 4, 85747 Garching, Germany
Fax: (internat.) +49-89/289-13329
E-mail: johann.jauch@ch.tum.de

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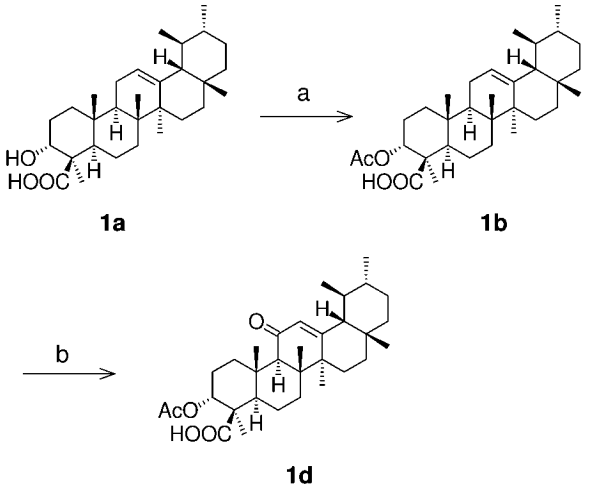
Results and Discussion

Whereas the concentration of AKBA (**1d**) in incense is very low, the concentrations of the other β-boswellic acids in extracts from incense are much higher, ranging from 10−21% for β-boswellic acid BA (**1a**), 0.05−6% for 3-*O*-acetyl-β-boswellic acid (ABA; **1b)** and 2.5−7.5% for 11-oxo-β-boswellic acid (KBA; **1c**). If it were possible to convert the complex mixture of acids obtained from incense into AKBA (**1d)**, this would present a simple method for the large-scale preparation of **1d** and other boswellic acids.

First, we transformed BA[12] (**1a**) into AKBA (**1d**) through a sequence of acetylation and allylic oxidation. Acetylation of **1a** was straightforward with Ac_2O/pyridine/DMAP (Steglich base) in CH_2Cl_2, leading to **1b**, which was used in the next step without further purification. To introduce the required carbonyl group in the 11-position, we decided to use the known photo-oxidation with NBS/water/dioxane.[13] After 4 h **1b** had been completely converted into **1d** (Scheme 1).

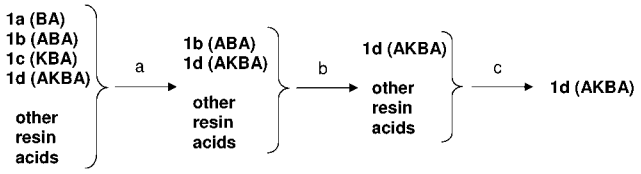


Scheme 1. Synthesis of AKBA (**1d**) from pure BA (**1a**); a: Ac_2O/py/DMAP, CH_2Cl_2, room temp., 2 h; b: NBS/$CaCO_3$/H_2O/hν, dioxane, room temp., 4 h

Next, the simple two-step synthesis mentioned above was applied to the crude mixture of resin acids obtained from a diethyl ether extract of finely ground *Boswellia* resin by standard methods.

Reaction of the resin acids with Ac_2O/pyridine/DMAP converts all hydroxy acids like BA (**1a**) and KBA (**1c**) into the acetylated derivatives ABA (**1b**) and AKBA (**1d**). Obviously, we have reduced the diversity of the mixture but increased the amount of **1b** and **1d**.

In the second step, the mixture of the acetylated acids is photo-oxidized with NBS/water/dioxane to transform allylic CH_2 groups into carbonyl groups. Thus, we again reduced the diversity of the mixture and converted **1b** into **1d** (Scheme 2), thereby increasing the amount of AKBA (**1d**) from 0.1−3% up to 25−35%, depending on the *Boswellia* species and the quality of the corresponding resin.



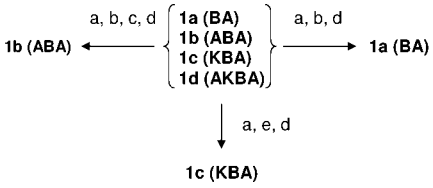
Scheme 2. "Focussing" approach to large-scale synthesis of AKBA (**1d**); a: Ac_2O/pyridine/DMAP, CH_2Cl_2, room temp., 4 h; b: NBS/$CaCO_3$/hν, dioxane/H_2O, room temp., 6 h; c: i. flash chromatography with silica gel, pentane/diethyl ether (4:1) + 0.5% HOAc; ii. flash chromatography with RP-18 silica gel, CH_3OH/H_2O (9:1); iii. crystallization from CH_3OH (optional)

The described method has the additional advantage that purification of a compound which makes up 25−35% of a mixture is much easier than purification of a compound which makes up only 0.1−3% of a mixture. From the crude reaction mixture **1d** is isolated by two consecutive chromatographic steps. First, we used silica gel as the stationary phase (pentane/diethyl ether, 4:1 + 1% HOAc), followed by flash chromatography on RP-18 silica gel (methanol/water, 9:1).

With this approach it is possible to synthesize 10−20 g of pure AKBA (judged by NMR spectroscopy and HPLC) in one run with standard laboratory equipment, which is 10−20 times more than obtainable through conventional isolation methods in the same time.

For large scale synthesis of BA (**1a**), ABA (**1b**) and KBA (**1c**) it is, in principle, possible to start from AKBA (**1d**). Deacetylation leads to KBA (**1c)** in quantitative yield. Reduction of the carbonyl group in the enone substructure of KBA with Li/*t*BuOH in HMPA[14] yields BA (**1a**) which, upon reacetylation, can be transformed into ABA.

More efficiently, the boswellic acid derivatives **1a**, **1b** and **1c** are obtained by directly applying the above-mentioned robust and reliable reactions to the crude mixture of resin acids, as summarized in Scheme 3.



Scheme 3. a: 0.5 N KOH in *i*PrOH, reflux, 5 h; b:[15] Li/*t*BuOH, HMPT, room temp., 3 h; c: Ac_2O/py/DMAP, CH_2Cl_2, room temp., 4 h; d) i. flash chromatography with silica gel, pentane/diethyl ether (4:1) + 0.5% HOAc; ii. flash chromatography with RP-18 silica gel, CH_3OH/H_2O (9:1); iii. crystallization from CH_3OH (optional); e: NBS/$CaCO_3$/H_2O, dioxane, hν, room temp., 6 h

Conclusion

We have provided a very simple and efficient method for the large-scale synthesis of boswellic acids, which is the

basis for extensive biological testing and for further chemical modifications of these pharmacologically highly interesting substances. Additionally, from a combinatorial point of view, we have transformed a natural product library of resin acids, containing about 36% β-boswellic acids and other resin acids (64%), into a new library, which now consists of about 36% of *one* defined β-boswellic acid and chemically modified resin acids (64%). Possibly, these modified compounds show interesting biological properties as well. Analysis and biological testing of these modified resin acids is currently underway. Our results along these lines will be reported in due course.

Experimental Section

General Remarks: Resin from *Boswellia sacra* FLUECK. ["Gum Olibanum (Frankincense) Oman white No. 1"] was purchased from G. Eggebrecht, Süderau, Germany. It is important to note that with resin from other *Boswellia* species we got inferior results (lower yields of boswellic acids, which were more difficult to purify). Dichloromethane was dried by distillation from calcium hydride. The peroxides in dioxane were removed by filtration through basic aluminium oxide. Reactions with dioxane as solvent were run under N_2 to prevent peroxide formation. Flash chromatography was performed with silica gel from Merck, Darmstadt, Germany, with particle size 40−63 μm (normal phase) and with RP-18 silica gel prepared according to the literature.[16] For the complete assignment of the NMR signals[17] we recorded ^{1}H, H,H-COSY, HMQC, HMBC, HMQC-COSY and NOESY spectra (Bruker AV 500) and ^{13}C, DEPT90 and DEPT135 spectra (Bruker AV 360). These were processed with the programs NPNMR and MestReC.[18] NMR Spectra were calibrated against the residual solvent peaks δ_C ($CDCl_3$) = 77.0 ppm and δ_H ($CHCl_3$) = 7.26 ppm. Mass spectra were recorded on a Finnigan MAT 8200 in EI mode. Melting points were determined in open tubes without correction. Optical rotations were measured on a Perkin−Elmer Polarimeter 241 MC.

3-*O*-Acetyl-11-oxo-β-boswellic acid (1d). Acetylation: The crude mixture of resin acids (25 g) obtained from resins of *Boswellia sacra* was dissolved in 30 mL of CH_2Cl_2. With stirring, 16 mL of pyridine (15.8 g, 0.2 mol), 12.5 mL of acetic anhydride (12.5 g, 0.18 mol) and 3 g of DMAP (25 mmol) were added successively. The temperature was raised to about 40 °C (gentle reflux of the solvent) and was stirred for 4 h. The reaction mixture was then quenched with ice-cold HCl (1 N, ca. 300 mL) and, after separation of the phases, the aqueous phase was extracted with diethyl ether (3 × ca. 100 mL). The combined organic phases were dried with $MgSO_4$. Filtration and evaporation of the solvent in vacuo yielded 28 g of an orange foam, which was pulverized and used in the next step.

Photo-Oxidation: The above acetylated resin acids were dissolved in 2 L of peroxide-free dioxane. 200 mL of water, 21 g of $CaCO_3$ and 24 g of NBS were added subsequently and the flask was flushed with N_2. The mixture was stirred vigorously for 6 h while being irradiated with visible light (4−6 energy-saving bulbs, total 44−66 W). After filtration, the solvent was evaporated in vacuo and the residue (brown foam) was purified by flash chromatography with silica gel (pentane/diethyl ether, 4:1 (v/v) + 0.5 vol % HOAc), followed by flash chromatography with RP-18 silica gel (methanol/water, 9:1 v/v). After evaporation of the methanol in vacuo, the aqueous residue was extracted with dichloromethane (3 × 100 mL). Drying of the combined organic extracts with $MgSO_4$, filtration and evaporation gave a white foam of pure AKBA (purity >98% as judged by NMR spectroscopy and HPLC). If desired, this material can be recrystallized once from methanol giving colorless crystals (purity >99%). Yield: 8.9 g.

It is important to note that the reactions were monitored simply by TLC on silica gel (pentane/diethyl ether, 2:1 + 1 vol % HOAc) and simultaneously on RP-18 TLC plates (methanol/water, 19:1). M.p. 271−274 °C (decomposition; ref.[7c] 271 °C; ref.[8d] 275−276 °C). $[\alpha]_D^{20}$ = +82 (*c* = 1.25, $CHCl_3$) (ref.[7c] 87; *c* = 4.2; $CHCl_3$; ref.[8d] +92; *c* = 1.2; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ = 5.56 (s, 1 H, H12), 5.32 (t, *J* = 2.8 Hz, 1 H, H3), 2.56 (dt, *J* = 13.2 Hz, 3.5 Hz, 1 H, H1β), 2.41 (s, 1 H, H9), 2.24 (tdd, *J* = 14.3 Hz, 4.4 Hz, 2.7 Hz, 1 H, H2β), 2.10 (td, *J* = 13.6 Hz, 4.9 Hz, 1 H, H16α), 2.09 (s, 3 H, H32, -CH_3 acetyl), 1.96−1.84 (m, 2 H, H15β, H6β), 1.74 (dq, *J* = 14.2 Hz, 3.6 Hz, 1 H, H6α), 1.68 (td, *J* = 13.1 Hz, 4.0 Hz, 1 H, H7α), 1.61 (dq, *J* = 15.4 Hz, 3.2 Hz, 1 H, H2α), 1.56 (dd, *J* = 11 Hz, 1.7 Hz, 1 H, H18), 1.52−1.43 (m, 3 H, H7β, H21α, H22α), 1.41 (dd, *J* = 12.3 Hz, 2.1 Hz, 1 H, H5), 1.42−1.40 (m, 1 H, H19), 1.35 (s, 3 H, H27), 1.32−1.26 (m, 2 H, H21β, H22β), 1.24 (s, 3 H, H23), 1.211 (m, 1 H, H1α), 1.20 (m, 1 H, H15α), 1.20 (s, 3 H, H26), 1.15 (s, 3 H, H25), 1.02 (ddt, *J* = 13.6 Hz, 5.0 Hz, 2.0 Hz, 1 H, H16β), 0.99−0.93 (m, 1 H, H20), 0.95 (br. d, *J* = 2.4 Hz, 3 H, H30), 0.83 (s, 3 H, H28), 0.81 (d, 6.0 Hz, 3 H, H29) ppm. ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ = 199.2 (C11, C=O), 182.0 (C24, COOH), 170.2 (C31, C=O acetyl), 164.9 (C13, =C<), 130.5 (C12, $_H$>C=), 73.1 (C3, >CHO-), 60.3 (C9, >CH-CO-), 59.1 (C18, >CH-), 50.5 (C5, >CH-), 46.5 (C4, >C<$_{COOH}$), 45.1 (C8, >C<), 43.8 (C14, >C<), 40.9 (C22; −CH_2-), 39.3 (C19; >CH-), 39.2 (C20, >CH-), 37.4 (C10, >C<), 34.6 (C1, -CH_2-), 34.0 (C17, >C<), 32.9 (C7, -CH_2-), 30.9 (C21, -CH_2-), 28.8 (C28, -CH_3), 27.5 (C16, -CH_2-), 27.2 (C15, -CH_2-), 23.8 (C23, -CH_3), 23.5 (C2, -CH_2-), 21.3 (C32, -CH_3 acetyl), 21.1 (C30, -CH_3), 20.5 (C27, -CH_3), 18.7 (C6, -CH_2-), 18.4 (C26, -CH_3), 17.3 (C29, -CH_3), 13.2 (C25, -CH_3) ppm. EI-MS (70 eV, 230 °C): *m*/*z* = 512 (14) [M^+], 497 (1) [$M - CH_3]^+$, 273 (100), 232 (50), 135 (40). HRMS: calculated: 512.35016; found 512.35122.

β-Boswellic Acid (1a). Decetylation: The crude mixture of resin acids (25 g) was dissolved in 250 mL of 1 N KOH in *i*PrOH. The reaction mixture was refluxed for 5 h. After cooling to room temperature, most of the *i*PrOH was removed in vacuo. The remaining residue was acidified with 300 mL of 1 N HCl and the resulting white mixture was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried with $MgSO_4$. After filtration, the solvent was evaporated in vacuo to give an orange-brown oil. To remove residual acetic acid completely, the oil was taken up in toluene and the solvents evaporated again. This procedure was repeated twice. Finally, the resulting dark brown foam was dissolved in diethyl ether and the solvents evaporated again in vacuo to give an orange foam (22 g) of deacetylated resin acids, which was easily pulverized and used in the next step.

Reduction: Lithium powder (765 mg, 0.11 mol) was added to the above deacetylated resin acids. After flushing the flask with N_2 or Ar, 200 mL of dry HMPA and 5 mL of *tert*-butanol were added from a syringe. After stirring for ca. 15 min the reaction mixture turned dark blue. Stirring was continued until the blue color disappeared (ca. 3−4 h) and then cooled in an ice bath. The reaction mixture was quenched with 300 mL of ice cold 1 N HCl and extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed thoroughly with water to remove the HMPA completely, dried with $MgSO_4$, filtered and the solvents evaporated to give a brown oil. This oil was purified by flash chromatography on silica gel with pentane/diethyl ether (4:1 v/v) + 0.5% HOAc,

followed by flash chromatography with RP-18 silica gel (methanol/water, 9:1). After evaporation of the methanol in vacuo, the aqueous residue was extracted with dichloromethane (3 × 100 mL). Drying of the combined organic extracts with $MgSO_4$, filtration and evaporation of the solvents gave 7.8 g of a white foam of pure BA (purity > 98% as estimated by NMR spectroscopy and HPLC). M.p. 232−236 °C (decomposition; ref.[7c] 228−230 °C; ref.[8d] 227−229). $[\alpha]_D^{20}$ = +86 (*c* = 0.54, $CHCl_3$) (ref.[7c] +108; *c* = 2.59, $CHCl_3$; ref.[8d] +112.7; *c* = 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ = 5.14 (t, *J* = 3.5 Hz, 1 H, H12), 4.08 (t, 2.8 Hz, 1 H, H3), 2.23 (tdd, *J* = 14.5 Hz, 4.2 Hz, 2.8 Hz, 1 H, H2β), 2.01 (td, *J* = 13.6 Hz, 4.7 Hz, 1 H, H16α), 1.96−1.89 (m, 2 H, H11α, H11β), 1.88−1.78 (m, 2 H, H6β, H15β), 1.73−1.67 (m, 1 H, H6α), 1.63−1.52 (m, 3 H, H2α, H7α, H9), 1.51−1.46 (m, 2 H, H1β, H5), 1.44−1.36 (m, 3 H, H7β, H21β, H22α), 1.36−1.34 (m, 1 H, H19), 1.35 (s, 3 H, H23), 1.32 (br. s, 2 H, H1α, H18), 1.30−1.24 (m, 2 H, H21α, H22β), 1.09 (s, 3 H, H27), 1.05 (s, 3 H, H26), 1.03−0.98 (m, 1 H, H15α), 0.93−0.91 (m, 1 H, H20), 0.921 (d, *J* = 6.0 Hz, 3 H, H30), 0.89−0.86 (m, 1 H, H16β), 0.81 (s, 3 H, H28), 0.79 (d, *J* = 6.0 Hz, 3 H, H29) ppm. ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ = 183.4 (C24, COOH), 139.5 (C13, =C<), 124.4 (C12, $_H$>C=), 70.7 (C3, >CH-OH), 59.0 (C18, >CH-), 49.0 (C5, >CH-), 47.3 (C4, >C<), 46.7 (C9, >CH-), 42.2 (C14, >C<), 41.5 (C22, -CH_2-), 39.9 (C8, >C<), 39.6 (C19, >CH-), 39.5 (C20, >CH-), 37.5 (C10, >C<), 33.8 (C1, -CH_2-), 33.7 (C17, >C<), 33.0 (C7, -CH_2-), 31.2 (C21, -CH_2-), 28.8 (C28, -CH_3), 28.0 (C16, -CH_2-), 26.4 (C15, -CH_2-), 26.1 (C2, -CH_2-), 24.2 (C23, >CH-), 23.4 (C11, -CH_2-), 23.2 (C27, -CH_3), 21.4 (C30, -CH_3), 19.6 (C6, -CH_2-), 17.4 (C29, -CH_3), 16.8 (C26, -CH_3), 13.2 (C25, -CH_3) ppm. EI-MS (70 eV, 175 °C): *m*/*z* = 456 (11) [M^+], 238 (17), 218 (100), 203 (14), 189 (11), 133 (11), 109 (10), 95 (12). HRMS: calculated: 456.36035; found 456.35981.

3-*O*-Acetyl-β-boswellic Acid (1b): This compound was obtained by a combination of the procedures above according to Scheme 3. Yield: 8.5 g from 25 g of crude resin acids. M.p. 251−253 °C (decomposition; ref.[7c] 253 °C; ref.[8d] 254−256 °C). $[\alpha]_D^{20}$ = +54 (*c* = 1.00, $CHCl_3$) (ref.[7c] +47; *c* = 2.58, $CHCl_3$; ref.[8d] +141; *c* = 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ = 5.14 (t, *J* = 3.5 Hz, 1 H, H12), 5.30 (t, 2.8 Hz, 1 H, H3), 2.14 (m, 1 H, H2β), 2.10 (s, 3 H, H32), 2.01 (td, *J* = 13.6 Hz, 4.7 Hz, 1 H, H16α), 1.95−1.89 (m, 2 H, H11α, H11β), 1.88−1.77 (m, 2 H, H6β, H15β), 1.74−1.68 (m, 1 H, H6α), 1.67−1.62 (m, 1 H, H2α), 1.60 (dd, *J* = 10.1 Hz, 7.3 Hz, 1 H, H9), 1.57−1.47 (m, 2 H, H1β, H7α), 1.47−1.41 (m, 3 H, H5, H7β, H22α), 1.41−1.35 (m, 1 H, H21β), 1.35−1.30 (m, 2 H, H18, H19), 1.30−1.25 (m, 2 H, H21α, H22β), 1.24 (s, 3 H, H23), 1.22−1.16 (m, 1 H, H1α), 1.12 (s, 3 H, H27), 1.04 (s, 3 H, H26), 1.04−0.98 (m, 1 H, H15α), 0.92 (d, *J* = 6.0 Hz, 3 H, H30), 0.90 (s, 3 H, H25), 0.92−0.85 (m, 2 H, H16β, H20), 0.80 (s, 3 H, H28), 0.79 (d, *J* = 7.0 Hz, 3 H, H29) ppm. ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ = 182.5 (C24, COOH), 170.3 (C31, C=O acetyl), 139.5 (C13, =C<), 124.5 (C12, $_H$>C=), 73.2 (C3, >CHO-), 59.2 (C18, >CH-), 50.6 C5, >CH-), 46.8 (C9, >CH-), 46.7 (C4, >C<), 42.7 (C14, >C<), 41.5 (C22, -CH2-), 40.0 (C8, >C<), 39.8 (C19, >CH-), 39.6 (C20, >CH-), 37.4 (C10, >C<), 34.5 (C1, -CH2-), 33.8 (C17, >C<), 33.1 (C7; -CH_2-), 31.3 (C21, -CH_2-), 28.8 (C28; -CH_3), 28.1 (C16, -CH_2-), 26.6 (C15, -CH_2-), 23.7 (C23, >CH_3), 23.6 (C2, -CH_2), 23.4 (C11, -CH_2-), 23.3 (C27, -CH_3), 21.4 (C30, -CH_3), 21.3 (C32, -CH_3 acetyl), 19.6 (C6, -CH_2-), 17.5 (C29, -CH_3), 16.9 (C26, -CH_3), 13.3 (C25, -CH_3) ppm. EI-MS (70 eV, 220 °C): *m*/*z* = 498 (8 M^+), 218 (100), 203 (13), 95 (13). HRMS: calculated: 498.37091; found 498.37158.

11-Oxo-β-boswellic Acid (1c): This compound was obtained by a combination of the procedures above according to Scheme 3. Yield: 8.0 g from 25 g of crude resin acids. M.p. 194−195 °C (decomposition; ref.[7c] 195 °C; ref.[8d] 197−198 °C). $[\alpha]_D^{20}$ = +121 (*c* = 1.11, $CHCl_3$) (ref.[7c] +129; *c* = 4.2, $CHCl_3$; ref.[8d] +79; *c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ = 5.54 (s, 1 H, H12), 4.07 (t, *J* = 2.8 Hz, 1 H, H3), 2.51 (dt, *J* = 13.2 Hz, 3.5 Hz, 1 H, H1β), 2.42 (s, 1 H, H9), 2.30 (t br. t, 14.5 Hz, 3.5 Hz, 1 H, H2β), 2.08 (td, *J* = 13.6 Hz, 4.7 Hz, 1 H, H16β), 1.92−184 (m, 2 H, H15β, H6β), 1.71 (m, 1 H, H6α), 1.65 (dd, *J* = 12.9 Hz, 4.1 Hz, 1 H, H7α), 1.57−1.51 (m, 2 H, H2α, H18), 1.49−1.41 (m, 4 H, H5, H7β, H21α, H22β), 1.39−1.37 (m, 1 H, H19), 1.35 (d, *J* = 3.8 Hz, 1 H, H22α), 1.33 (s, 3 H, H23), 1.32 (br. d, *J* = 3.2 Hz, 2 H, H1α, H21β), 1.30 (s, 3 H, H27), 1.22 (br. d, 3.5 Hz, 1 H, H15α), 1.17 (s, 3 H, H26), 1.12 (s, 3 H, H25), 1.00 (br. d, *J* = 13.6 Hz, 1 H, H16β), 0.93 (br. s, 4 H, H20, H30), 0.81 (s, 3 H, H28), 0.78 (d, *J* = 6.3 Hz, 3 H, H29) ppm. ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ = 199.4 (C11, >CO), 182.7 (C24, COOH), 164.9 (C13, =C<), 130.6 (C12, $_H$>C=), 70.5 (C3, >CH-OH), 60.5 (C9, >CH-), 59.1 (C18, >CH-), 48.9 (C5, >CH-), 47.3 (C4, >C<), 45.1 (C8, >C<), 43.8 (C14, >C<), 40.9 (C22, -CH_2-), 39.31 (C19, >CH-), 39.3 (C20, >CH-), 37.6 (C10, >C<), 34.0 (C17, >C<), 33.9 (C1, -CH_2-), 32.9 (C7, -CH_2-), 30.9 (C21, -CH_2-), 28.9 (C28, -CH_3), 27.6 (C16, -CH_2-), 27.2 (C15, -CH_2-), 26.3 (C2, -CH_2-), 24.3 (C23, -CH_3), 21.1 (C30, -CH_3), 20.6 (C27, -CH_3), 18.9 (C6, -CH_2), 18.4 (C26, -CH_3), 17.4 (C29, -CH_3), 13.2 (C25, -CH_3) ppm. EI-MS (70 eV, 200 °C): *m*/*z* = 470 (18) [M^+], 287 (10), 273 (100), 232 (51), 135 (25). HRMS: calculated: 470.33960; found 470.33945.

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