5-*Epi*-Incensole: Synthesis, X-Ray Crystal Structure and Absolute Configuration by Means of ECD and VCD Studies in Solution and Solid State

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ABSTRACT

Incensole (**1**) and its acetate (**2**), found in incense, demonstrate interesting biological activities. Incensole acetate (**2**) was prepared on large-scale employing the Paul and Jauch protocol from the crude extracts of the *Boswellia papyrifera* Hochst. 5-*Epi*-incensole (**3**), obtained as colorless crystals, was prepared from incensole acetate via three steps viz., deacetylation, oxidation and reduction. The structure of 5-*epi*-incensole (**3**) was elucidated by means of spectroscopic data analysis, and the absolute configuration was established by single crystal X-ray analysis in combination with electronic and vibrational circular dichroism. In particular, applicability of the solid-state ECD/TDDFT protocol to a compound endowed with only two non-conjugated alkene chromophores was verified.

1. Introduction

A number of 14-membered ring containing diterpenoids (such as the cembranoid family) have been reported from different natural sources. It is interesting to note that these 14-membered carbocyclic isoprenoids possess a unique structural diversity.[1] Moreover oxygenation and stereochemical patterns in some cembranoids are fairly complex. Incensole (**1**), for example, has a flexible 14-membered ring which incorporates an additional tetrahydrofuran ring. Incensole (**1**) and its acetate (**2**) (Scheme 1) have shown anti-inflammatory, neuroprotective, antiproliferative, cytotoxic, and antidepressive-like properties.[2] Due to their interesting biological activities and varied structural patterns, incensole (**1**) and its acetate (**2**) have received special attention with respect to their isolation and synthesis. Incensole (**1**) was first reported by Corsano and Nicoletti[3] in 1967

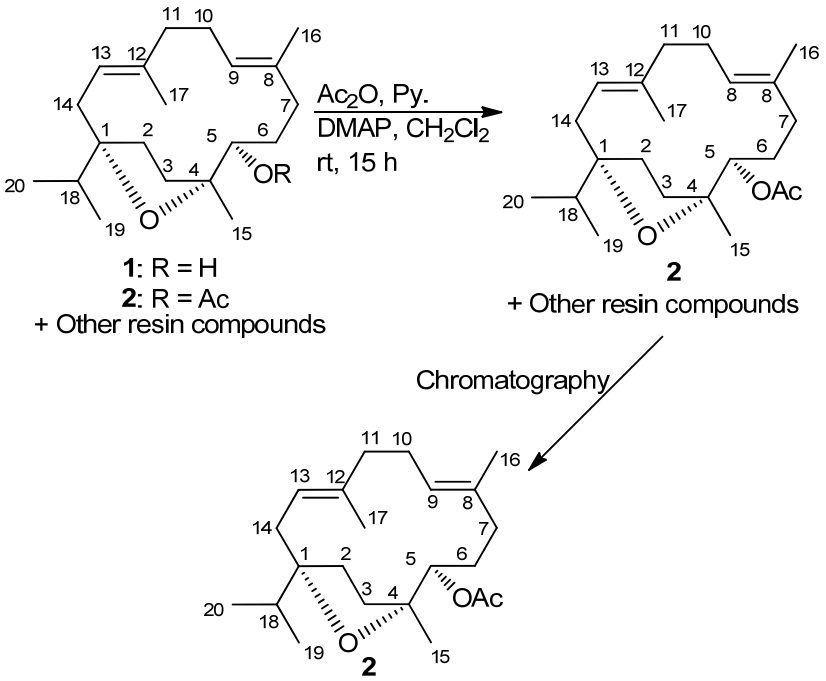
from *Boswellia carterii* Birdw followed by later reports from the same species [4-10] as well as from *B. papyrifera.*[10] Due to the biological importance of incensole (**1**), two independent total syntheses have also been reported.[11,12] In the present work, incensole acetate (**2**) was prepared on large-scale following Jauch's protocol,[11] using crude extracts of the *Boswellia papyrifera* Hochst. According to previous literature[3] incensole (**1**) is oily in nature while 5-*epi*-incensole (**3**) is solid. Unfortunately, it is not possible to get incensole (**1**) in crystal form suitable for X-ray analysis from any solvent. The current study was aimed to get the crystal structure of 5-*epi*-incensole (**3**) in order to characterize it by means of X-ray, solid-state ECD, ECD in solution and VCD. 5-*Epi*-incensole (**3**) was prepared from incensole acetate (**2**) via three steps viz., deacetylation, oxidation and reduction (Scheme 2). The structure and relative configuration of 5-*epi*-incensole (**3**) was elucidated by NMR and X-ray studies, and the absolute configuration was unequivocally confirmed by three different chiroptical methods viz., solid-state ECD, ECD in solution and VCD. In particular, the applicability of the solid-state ECD/TTDFT protocol to a compound showing a weak ECD spectrum due to the presence of two non-conjugated alkene groups as the only chromophores, was tested.

2. Results and Discussion

2.1. Synthesis and structure elucidation

Production of incensole (**1**)/incensole acetate (**2**) on large scale was necessary for preparing semi-synthetic derivatives, especially to get crystals suitable for X-ray structure determination of any derivative. Thus incensole acetate (**2**) was prepared on large-scale following Jauch's protocol,[11] starting from the crude extracts of the *Boswellia papyrifera* Hochst. This latter plant was chosen due to the relatively high content of (**1**) and (**2**)

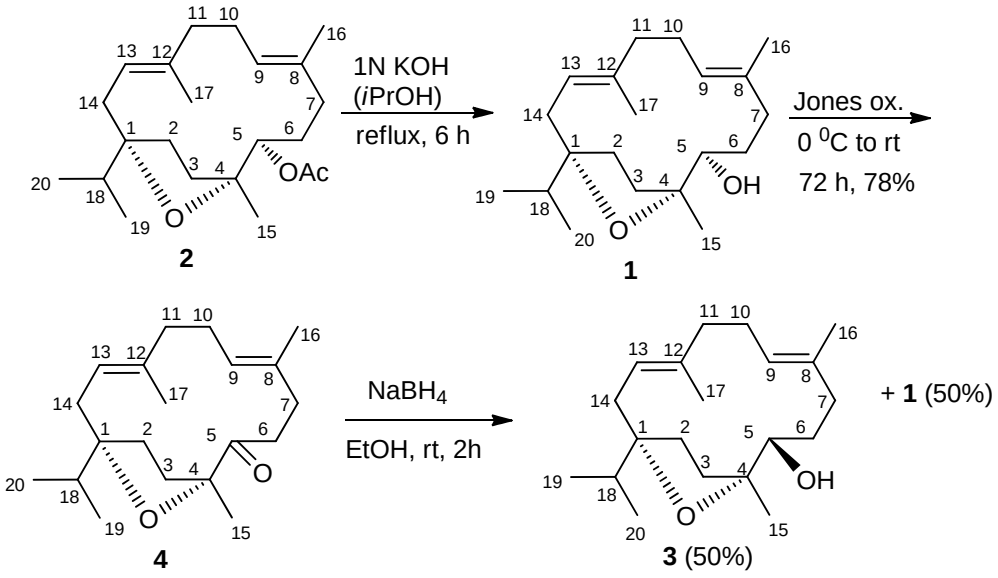
compared to other *Boswellia* species. The semi-synthetic Jauch route,[11] allowed for the conversion of a mixture of incensole (**1**) and incensole acetate (**2**) to incensole acetate (**2**) through acetylation with Ac_2O, pyridine and DMAP. Incensole acetate (**2**) was purified through conventional flash column chromatography and obtained as a pure compound from a mixture of (**1**) and (**2**) together with an array of other co-extracted compounds.



Scheme 1: Large-scale preparation of incensole acetate (**2**)[11]

Deacetylation of incensole acetate (**2**) by hydrolysis with 0.5 N KOH in *i*PrOH provided pure incensole (**1**) (Scheme 2). In order to obtain 5-*epi*-incensole (**3**), incensole (**1**) was oxidized at C-5 with Jones reagent (CrO_3/aq. H_2SO_4) in acetone to afford incensone (**4**)[3] in an acceptable 78% yield. Incensone (**4**) was then reduced with $NaBH_4$ in EtOH to incensole (**1**) and its C-5 epimer (**3**) (5-*epi*-incensole)[3] and both compounds were purified through column chromatography. Interestingly, incensole (**1**) is oily in nature while its C-

5 epimer (**3**) (5-*epi*-incensole) is solid. Initial attempts to grow crystals in different solvents (viz., CH_2Cl_2, $CHCl_3$, and mixture of CH_2Cl_2 and $CHCl_3$) proved unsuccessful. However, suitable crystals were grown in a mixture of CH_2Cl_2 and EtOH (1:1) which allowed for a single crystal X-ray diffraction analysis (Figure 1).



Scheme 2: Synthesis of 5-*epi*-incensole (**3**)

5-*Epi*-incensole (**3**) (Scheme 2) of molecular formula $C_{20}H_{34}O_2$, has IR absorptions for a) an hydroxyl (3620 cm^{-1}), b) double bond (1670 cm^{-1}) and c) an ether (1060 cm^{-1}). Comparison of the IR and ^1H NMR data of (**3**) with those of *epi*-incensole, previously synthesized by Corsano and Nicoletti[3] in 1967, confirmed the structure of the current compound. Corsano and Nicoletti[3] reported only ^1H NMR data, but not ^{13}C NMR data. The basic structure of 5-*epi*-incensole (**3**) was confirmed by 1D (^1H, ^{13}C-NMR) and 2D (COSY, HSQC and HMBC) spectral investigations.

2.2. Determination of absolute configuration

The relative configuration of 5-*epi*-incensole (**3**) was determined by single crystal X-ray diffractometry (Figure 1) and NOESY NMR (Figure 2). To assign the absolute configuration of 5-*epi*-incensole (**3**), we used the so-called solid-state CD/TDDFT approach.[14] This approach is based on a comparison between the ECD spectrum measured in the solid state as a microcrystalline KBr or KCl pellet, and that of a spectrum calculated by TDDFT. In the latter calculations the geometry derived from the X-ray structure (after optimization of only the hydrogen atoms) was used as input data. This method avoids all the uncertainties related to the molecular conformation and to the generation of input structures for TDDFT calculations, because it skips the conformational search and the optimizations of geometry as well as an estimation of the different populations is necessary as for the most common different approaches as described below. It is therefore especially useful for flexible medium-size natural products.[15] The main limitation of the method is that crystals suitable for X-ray analysis must be available. This is the case for 5-*epi*-incensole (**3**) but not, for example, for incensole (**1**) and its acetate (**2**). In Figure 3, the experimental ECD spectra of 5-*epi*-incensole (**3**) measured in solution (dotted red line) and in the solid-state as KCl pellet (solid black line) are reported which both display a negative band with a minimum at λ = 205 nm, followed (in the solution spectrum) by a positive tail at higher energy. In Figure 4, the ECD spectrum calculated at CAM-B3LYP/aug-cc-pVDZ level using the X-ray geometry with the (1*S*,4*R*,5*R*) configuration is shown (solid black line). The agreement with the experimental solid-state ECD spectrum allowed to establish the absolute configuration of 5-*epi*-incensole as (+)-(1*S*,4*R*,5*R*)-**3**. Thus, we confirm that our semi-

synthetic *epi*-incensole is the C-5 epimer of incensole, while the configuration at C-1 and C-4 is the same as incensole.[16]

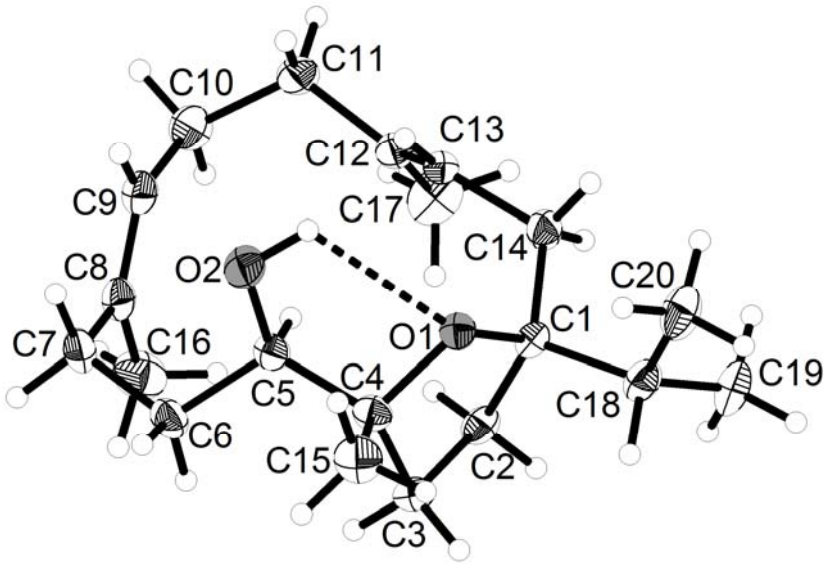


Figure 1.
Molecular structure of compound **3** in the crystalline state. Thermal elipsoids with 30% probability. The methyl groups C16 and C17 are disordered over two positions.

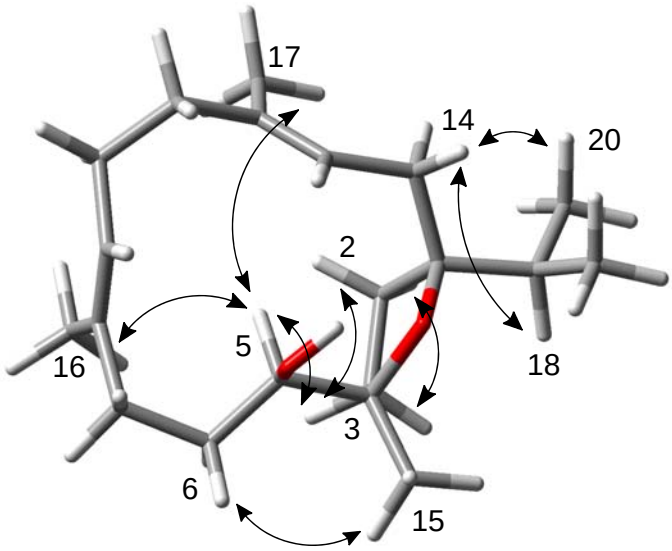


Figure 2. Important NOESY (H↔H) correlations of 5-*epi*-incensole (**3**)

Because of the presence of only two alkene chromophores the ECD spectra of 5-*epi*-incensole (**3**) showed only a weak single band Therefore, we decided to support the above assignment by calculating also the solution ECD spectrum, as well as the vibrational CD spectrum (VCD).[17] The latter technique is particularly useful in the presence of weak or negligible ECD spectra.[18] For both solution ECD and VCD calculations, we first run a thorough conformational analysis with molecular mechanics (Merck Molecular Force Field, MMFF) followed by DFT geometry optimizations; the latter of which was performed firstly at the B3LYP/6-31G(d,p) level and then at the B3LYP/6-311+G(d,p) level. Ten different conformers with a Boltzmann population of ≥1% at 300K were obtained. All of them are required to be considered in the following calculations. The large number of low-energy conformers further demonstrates how useful is the solid-state method discussed above, where only a single structure needs to be calculated. The lowest-energy DFT structure is practically completely coincident with the X-ray geometry (Figure 5). The remaining low-energy conformers (Table S1; Supporting Information) feature large variations in the conformation of the macrocycle, especially in the region ranging from C-6 to C-14, while the region from C-1 to C-6 is more rigid because of the presence of both the oxygen bridge between C-1 and C-4 and the intramolecular hydrogen bond between 5-OH and the endocyclic oxygen (also detected in the X-ray geometry, see Figure 5).

ECD and VCD calculations were applied to the 10 low-energy conformers at the CAM-B3LYP/aug-cc-pVDZ and B3LYP/6-311+G(d,p) levels, respectively. The Boltzmann-averaged ECD spectrum of (1*S*,4*R*,5*R*)-**3**, shown in Figure 4 (dotted red line), is consistent with the experimental spectrum of (+)-**3** in solution (Figure 3, dotted red line)

and confirms the assignment as previously obtained with the solid-state technique. The experimental IR and VCD spectra of *epi*-incensole (**3**) in $CDCl_3$ solution are shown in Figure 6. The spectra are almost negligible in the functional group region (not shown) because of the lack of strong oscillators. However, the comparison with the calculated Boltzmann-average spectra in the fingerprint region is quite satisfactory (Figure 6). The independently assigned absolute configuration is again (+)-(1*S*,4*R*,5*R*)-**3**.

It is noteworthy how the solid-state ECD/TDDFT approach demonstrated its validity even in the presence of two non-conjugated alkene moieties as the only chromophores present in the skeleton of **3**.[19] This is also remarkable in view of the limited amount of sample (<0.2 mg in the present case) required to measure a significant solid-state ECD spectrum. In comparison, VCD spectroscopy requires, in general, a much larger amount of sample (ca. 10 mg were employed in the current case). Moreover, an approach similar to the solid-state ECD/TDDFT, i.e. based on the X-ray geometry as input structure for calculations, is prevented in the case of VCD spectroscopy.[20]

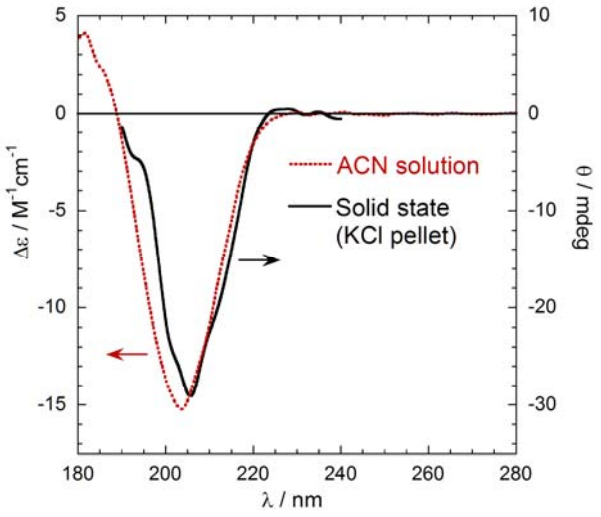


Figure 3. Experimental ECD spectra of (+)-(1*S*,4*R*,5*R*)-5-*epi*-incensole (**3**) measured in the solid state as KCl pellet (solid black line) and in acetonitrile solution (red dotted line, 4.2 mM, 0.01 cm path-length).

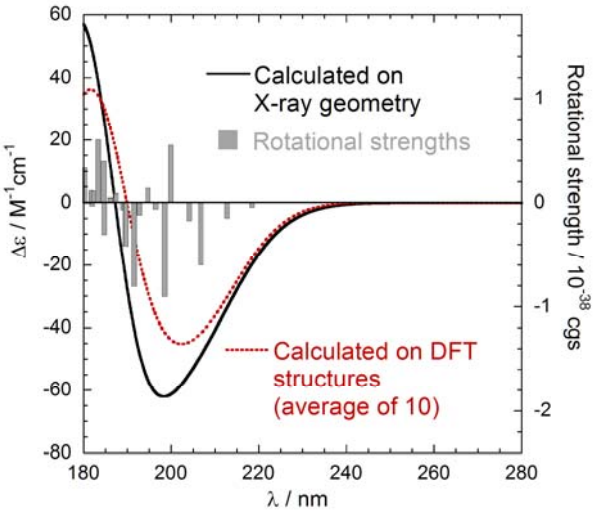


Figure 4. Calculated ECD spectra for (1*S*,4*R*,5*R*)-5-*epi*-incensole (**3**) at CAM-B3LYP/aug-cc-pVDZ level of theory. Solid black line: calculated on the X-ray geometry. Red dotted line: calculated as Boltzmann average over 10 DFT-optimized structures. Vertical bars represent calculated rotational strengths on the X-ray geometry. Spectra red-shifted by 10 nm, Gaussian band-width 0.3 eV.

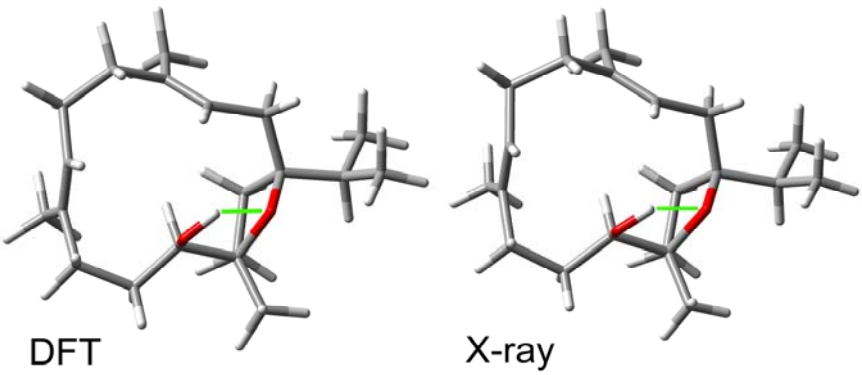


Figure 5. Comparison between the lowest-energy DFT structure calculated at B3LYP/6-311+G(d,p) and the X-ray structure of (1*S*,4*R*,5*R*)-5-*epi*-incensole (**3**). The intramolecular hydrogen bond is shown with a green line.

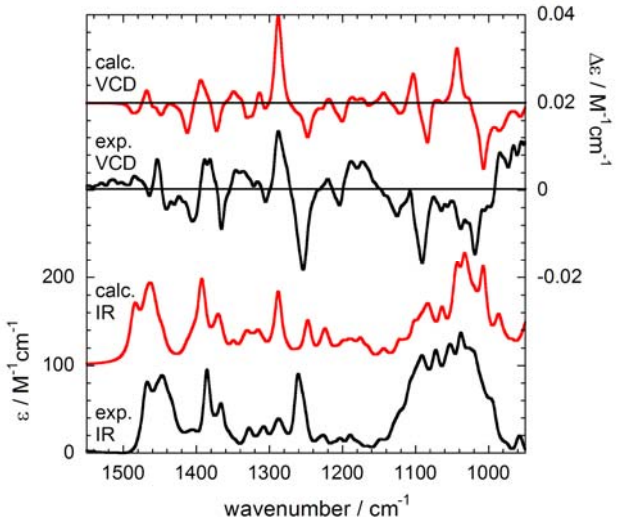


Figure 6. Calculated (red lines) and experimental (black lines) IR (bottom) and VCD (top) spectra for *epi*-incensole (**3**). Calculated spectra are shown with a vertical offset for clarity. Calculations run at B3LYP/6-311+G(d,p) level as Boltzmann average over 10 conformers; frequencies scaled by a factor 0.98; band-width σ= 6 cm^{-1}. Experimental spectra measured in 0.19 M $CDCl_3$ solution, 100 μm path-length.

Conclusion

Incensole acetate (**2**) was synthesized on large-scale employing the Paul and Jauch protocol[11] and 5-*epi*-incensole (**3**), obtained as colorless crystals, was prepared from incensole acetate (**2**) via three steps. Moreover the structure of 5-*epi*-incensole (**3**) was confirmed by means of spectroscopic data analysis viz., 1D (^{1}H and ^{13}C NMR spectra) and 2D (COSY, HSQC, and HMBC) spectra. The relative and absolute configuration of 5-*epi*-incensole (**3**) was established as (+)-(1*S*,4*R*,5*R*)-**3** by single crystal X-ray analysis in combination with electronic and vibrational circular dichroism. Therefore, we determine that our semi-synthetic *epi*-incensole (**3**) is the C-5 epimer of incensole. Most

importantly, applicability of the solid-state ECD/TDDFT protocol to a compound endowed with only two non-conjugated alkene chromophores was verified.

3. Experimental

3.1. General

Optical rotations were measured on a KRUSS P P3000 polarimeter (A. Kruss Optronic, Germany). IR spectra were recorded on a Bruker, ATR-Tensor 37 spectrophotometer. ESI–MS were recorded on a Waters Quattro Premier XE Mass Spectrometer (Waters, Milford, MA). The ^{1}H and ^{13}C NMR spectra were recorded on Bruker NMR spectrometers operating at 600 MHz (150 MHz for ^{13}C). The chemical shift values are reported in ppm (δ) units and the coupling constants (*J*) are given in Hz. ECD spectra were measured with a Jasco (Tokyo, Japan) J-715 spectropolarimeter. Solid-state ECD spectra were recorded on KCl pellets using the technique described in ref.[14] Solution spectra were recorded on a 4.2 mM acetonitrile solution using a 0.01 cm quartz cell. VCD spectra were recorded using a Jasco (Tokyo, Japan) FVS 6000 VCD spectrometer (10000 scans). The samples were measured as a 0.19 M $CDCl_3$ solution using a 100 μm BaF_2 cell. The spectra displayed in Figure 4 were obtained by subtracting the $CDCl_3$ spectrum recorded in the same conditions to the raw spectrum. For TLC, pre-coated aluminum sheets (silica gel 60 F-254, E. Merck) were used. Visualization of the TLC plates was achieved under UV light at 254 and 366 nm and by spraying with ceric sulfate reagent. Elemental analysis was performed using a Vario EL machine. The crystallographic data of compound **3** were collected with a STOE IPDS 2 diffractometer at –60 °C using graphite monochromated Mo-K_α radiation. The structural data have been deposited at the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ,

UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC 1472586. (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

3.2. Experiment procedures and spectroscopic data

3.3. Plant Material and isolation

The *B. papyrifera* frankincense was donated by Dr. Saifeldin Elnegrabi from Sudan. All these samples were authenticated by Dr. *Mustafa Mansi* (botanist), Department of Biological Sciences and Chemistry, University of Nizwa, the Sultanate of Oman and voucher specimen (No: BSHR-01/2012) was deposited with the Herbarium of the Chair of Oman's Medicinal Plants and Marine Natural Products. The air-dried ground material of *B. papyrifera* frankincense resin was exhaustively extracted by stirring with 100% MeOH at 24 ^{o}C. The extract was evaporated to yield a yellow semi-solid residue.

3.3.1. Acetylation of the crude mixture.

Crude extract of *B. papyrifera* (50 g) was dissolved in CH_2Cl_2 (100 mL) in a 500 mL three-necked flask followed by the addition of pyridine (36 mL), Ac_2O (40.8 mL) and DMAP (3 g). The reaction mixture was heated and stirred under reflux for 6 h, allowed to cool and quenched with 1 N HCl (500 mL). The organic and aqueous phases were separated and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic phases were dried with Na_2SO_4, filtered, and the filtrate was evaporated under reduced pressure to yield an orange oil that was subjected to column chromatograpy using EtOAc-*n*-hexane (2:98) as eluent; six sub-fractions F_{1-6} were obtained. Investigation demonstrated that F_2 contained incensole acetate (**2**) in large quantities. Re-chromatography of this fraction using EtOAc-*n*-hexane (2:98) afforded pure incensole

acetate (**2**) whose structure was confirmed by comparison of its NMR data with published data.[3,21]

3.3.2. Deacetylation of incensole acetate (2)

The mixture of incensole acetate (250 mg, 0.718 mmol), 1 N KOH (12 mL) in *i*PrOH (20 mL) was heated and stirred under reflux for 4 h. After cooling, most of the *i*PrOH was removed in vacuo, and the residue was acidified with 1 N HCl and extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, and the solvent was evaporated in vacuo to give a colorless oil of incensole (**1**). The structure of incensole (**1**) was confirmed by comparison of the NMR data with published data. [3,21]

3.3.3. Oxidation of incensole (1)

Jones reagent (0.4 mL) was added dropwise to a stirred solution of incensole (0.28 g, 0.915 mmol) in acetone (5 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. After cooling to 0 °C, *i*PrOH (5 ml) was added, and the solution was stirred for 30 min. The reaction was diluted with water and extracted with CH_2Cl_2 (3x30 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated to dryness and purified by column chromatography to obtain incensone (**4)** (78%); yellow liquid; $[\alpha]_D^{25}$ = -20 (*c* = 2, in CH_2Cl_2); IR (KBr): 1715, 1454, 1382, 1053, 978 and 841 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.8 Hz, 3H, H-19), 0.93 (d, *J* = 6.8 Hz, 3H, H-20), 1.27 (s, 3H, 15-Me), 1.46 (s, 3H, 17-Me), 1.54 (s, 3H, 16-Me), 1.61 (m, 1H, H-7b), 1.81 (m, 2H, H-3b, H-14b), 1.86 (m, 1H, H-11b), 1.88 (m , 1H, H-18), 1.92 (dd, *J* = 6.3, 15.7 Hz, 1H, H-2b), 1.96 (m, 2H, H-10b, H-11a), 2.08 (m, 1H, H-3a), 2.10 (m, 2H, H-10a, H-14a), 2.18 (dd, *J* = 6.3, 15.7 Hz, 1H, H-2a), 2.26 (m, 1H, H-7a), 2.33 (m, 1H, H-6b), 3.13 (dd, *J* = 11.4, 16.2 Hz, 1H, H-6a), 4.96 (m, 2H, H-9, H-13); ^{13}C

NMR (150 MHz, $CDCl_3$): δ 210.5 (C-5), 134.6 (C-12), 134.5 (C-8), 125.2 (C-9), 121.4 (C-13), 90.0 (C-1), 87.9 (C-4), 38.6 (C-11), 36.1 (C-18), 34.9 (C-6), 32.7 (C-7), 31.7 (C-14), 31.4 (C-2), 31.2 (C-3), 26.4 (C-15), 24.7 (C-10), 18.2 (C-16), 17.7 (C-19), 17.2 (C-20), 16.2 (C-17); ESIMS: *m/z* (rel. int.): *m/z* 327 $[M+Na]^+$ ($C_{20}H_{32}O_2$).

3.3.4. Reduction of incensone (4) with $NaBH_4$

In a round-bottomed flask (25 ml) equipped with a magnetic stirrer, a solution of incensone (**4**) (238 mg, 0.78 mmol) in EtOH (10 mL) was prepared. $NaBH_4$ (44 mg, 1.17 mmol) was added, and this mixture which was stirred at 24 ^oC for 4 h after for completion (as checked by TLC). Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried (anhydrous Na_2SO_4), filtered, and the filtrate was evaporated to afford a residue consisting of incensoles (**1**) and (**2**) which were easily separated by column chromatography (silica gel, eluent; *n*-hexane/EtOAc: 9/1) to yield incensole (**1**) (117 mg, 50%, as an oil) and pure 5-*epi*-incensole (**3**) (117 mg, 50%, as slightly beige yellow crystals). M.p: 77.6 ^oC; $[\alpha]_D^{25}$ = -11.8 (*c* = 0.06, in CH_2Cl_2); IR (KBr): 3583, 2957, 2305, 1053, 874 and 756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.6 Hz, 3H, H-19), 0.92 (d, *J* = 6.6 Hz, 3H, H-20), 1.10 (s, 3H, 15-Me), 1.51 (s, 3H, 17-Me), 1.53 (m, 2H, H-7b, H-18), 1.54 (s, 3H, 16-Me), 1.67 (m, 1H, H-6b), 1.71 (m, 1H, H-7a), 1.74 (m, 2H, H-3a, H-6a), 1.87 (m, 1H, H-3b), 2.07 (m, 1H, H-14b), 2.09 (m, 1H, H-10b), 2.10 (m, 1H, H-2a), 2.12 (m, 1H, H-14a), 2.27 (m, 1H, H-2b), 2.13 (m, 1H, H-11a), 2.16 (m, 1H, H-11b), 2.17 (m , 1H, H-10a), 3.70 (br s, 1H, H-5), 5.12 (t, *J* = 5.8 Hz, 1H, H-9), 5.18 (t, *J* = 6.0 Hz, 1H, H-13); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.3 (C-12), 133.0 (C-8), 127.7 (C-9), 122.8 (C-13), 89.5 (C-1), 86.1 (C-4), 72.6 (C-5), 40.4 (C-11), 38.6 (C-3), 35.6 (C-18), 34.3 (C-7), 33.2 (C-14), 31.0 (C-6), 26.6 (C-2), 25.5 (C-

10), 20.3 (C-15), 18.7 (C-16), 17.8 (C-19 & C-20), 15.6 (C-17); ESIMS: *m/z* (rel. int.): *m/z* 329 $[M+Na]^{+\cdot}$ (85) ($C_{20}H_{34}NaO_2$); analysis calcd. for $C_{20}H_{34}O_2$ (306.48): C 78.38, H 11.18; found: C 78.21, H 11.29.

3.4. Computational Section

Merck Molecular Force Field (MMFF) calculations and preliminary DFT calculations were effected with the Spartan'14 (Wavefunction, Irvine CA), with standard parameters and convergence criteria. DFT and TDDFT calculations were run with Gaussian'09 (Revision D.01. Gaussian, Inc: Wallingford, CT; 2013), with default grids and convergence criteria. Conformational searches were run with the Monte Carlo algorithm implemented in Spartan'14 using MMFF. All structures thus obtained were optimized with the DFT method using B3LYP functional and 6-31G(d,p) or 6-311G+(d,p) basis sets in vacuo. Frequency calculations were run at the B3LYP/6-311+G(d,p) level of theory on all conformers with a Boltzmann population of >1% at 300 K. IR and VCD spectra were obtained as sums of Lorentzian functions with a half-width at half height of 6 cm^{-1}, and a frequency scale factor of 0.98, and Boltzmann-averaged at 300 K using internal energies. ECD calculations were run at the CAM-B3LYP/aug-cc-pVDZ level of theory in vacuo. ECD spectra were obtained as sums of Gaussian functions with an exponential half-width of 0.3 eV, using rotational strengths calculated in the dipole-length gauge, and Boltzmann-averaged at 300 K using internal energies. Average spectra were generated with the software SpecDis, v. 1.64.[22]

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