Enantioselective Total Syntheses of Cassane Furanoditerpenoids and their Stimulation of Cellular Respiration in Brown Adipocytes

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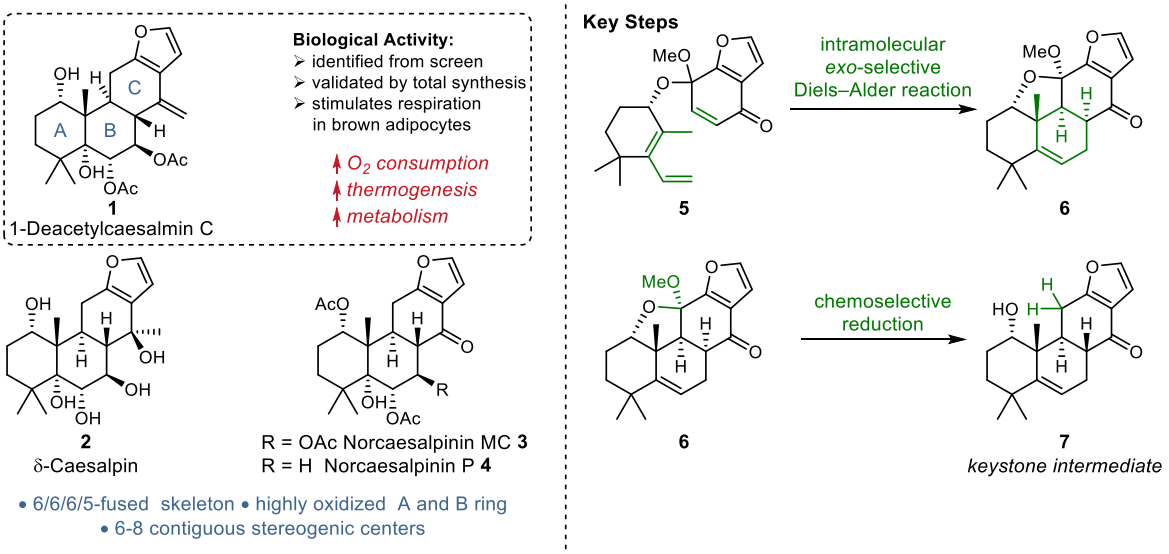
Abstract

We report the first and enantioselective total syntheses of (+)-1-deacetylcaesalmin C, (+)-δ-caesalpin, (+)-norcaesalpinin MC, and (+)-norcaesalpinin P. Salient features of the synthetic strategy are *exo*-selective intramolecular Diels–Alder reaction of a furanoquinone monoketal and subsequent chemoselective reduction of the resulting pentacyclic furfuryl ketal furnishing a keystone intermediate. The latter enables access to the collection of natural products through implementation of stereoselective oxidations. Having accessed the cassane furanoditerpenoids, we unveil previously unknown bioactivity: (+)-1-Deacetylcaesalmin C stimulates respiration in brown adipocytes, which has been suggested to play a central role in treatment of obesity.

As part of our ongoing research program on metabolic disorders, specifically obesity, we have screened a library of natural products[1] to assess their effects on brown adipocyte metabolism through quantification of coupled and uncoupled cellular respiration rates. Among the more than 5000 secondary metabolites included in the screen, (+)-1-deacetylcaesalmin C (**1**)[2] stood out based on its ability to increase oxygen consumption (Scheme 1). The natural product belongs to the class of cassane-type furanoditerpenoids, which feature a 6/6/6/5-fused skeleton. (+)-1-Deacetylcaesalmin C (**1**) has seven contiguous stereogenic centers, one of which is quaternary. To date, no syntheses of cassane furanoditerpenoids with highly oxidized A and B rings have been documented.[3,4] Herein, we report the first and enantioselective total synthesis of (+)-1-deacetylcaesalmin C (**1**) and data indicating stimulation of coupled and uncoupled respiration in brown adipocytes (Scheme 1). Highlights of the synthesis include *exo*-selective intramolecular Diels–Alder (DA) reaction of a furanoquinone monoketal and chemoselective Birch reduction. Elaboration of keystone intermediate **7** leads to the natural products (+)-1-deacetylcaesalmin C (**1**), (+)-δ-caesalpin (**2**),[5, 6, 7] (+)-norcaesalpinin MC (**3**)[8] and (+)-norcaesalpinin P (**4**).[9]

Scheme 1. 1-Deacetylcaesalpin (1), δ-Caesalpin (2), Norcaesalpinin MC (3), Norcaesalpinin P (4) and Key Steps

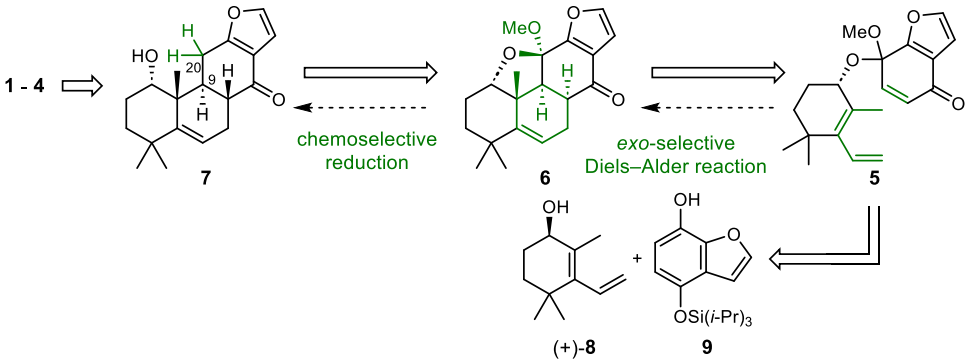


Obesity has been associated with several co-morbidities including type 2 diabetes, cardiovascular disease, musculoskeletal disorders such as osteoarthritis, and certain types of cancer.[10] Thus, its prevention and treatment is of high importance. Pharmacological approaches are limited and several anti-obesity drugs have been developed but not approved due to side effects.[11,12] An approach for treatment of obesity involves changes in lifestyle, but long-term compliance is poor.[13] The adipose organ is a multi-depot endocrine organ that can be divided into white and brown adipose tissue.[14] White adipose tissue (WAT) constitutes the major storage depot of excess energy in the form of

triacylglycerols. The primary function of brown adipose tissue (BAT) is non-shivering thermogenesis, or heat production. BAT is a promising therapeutic target to ameliorate obesity based on its increased number of mitochondria which upon stimulation can consume high levels of energy.

We designed a general, enantioselective strategy to access various cassane furanoditerpenoids, enabling the exploration of their biological activity. The retrosynthetic analysis of the targets leads back to **7** as a versatile keystone intermediate (Scheme 2). The ketone in **7** was anticipated to stabilize the otherwise oxidation-prone furan[15] and suggests a Diels–Alder disconnection. The *anti*-relationship between the C20 methyl group and the proton at C9 implicates *exo*-selective Diels–Alder reaction. For related substrates *exo*-selectivities were only observed in intramolecular DA cycloadditions. Synthetic studies towards (±)-forskolin described DA reaction of the ester of (±)-**8** and maleic acid to afford the product in an *endo*:*exo*-selectivity of 1:3 in 56% yield.[16] In addition, intramolecular DA reactions of simple, acyclic dienes tethered to protected *p*-benzoquinones have been described with *endo*:*exo*-selectivity of up to 1:1.[17] We envisioned tethering a furanoquinone to enantioenriched allylic alcohol (+)-**8**[18] via a ketal as shown in **5** and sought to evaluate its feasibility in a DA reaction. Although this transformation would provide rapid access to the tetracyclic carbon skeleton common to all cassane furanoditerpenoids, we were cognizant of a number of challenges. 1) Allylic alcohol **8** is prone to elimination resulting in a triene.[19] 2) The presence of a *gem*-dimethyl group renders the diene sterically encumbered. 3) The rigidity imposed by the system might impede adoption of the necessary *S-cis* conformation. 4) While the ketal tether could enable *exo*-selectivity its subsequent removal requires chemoselective reduction.

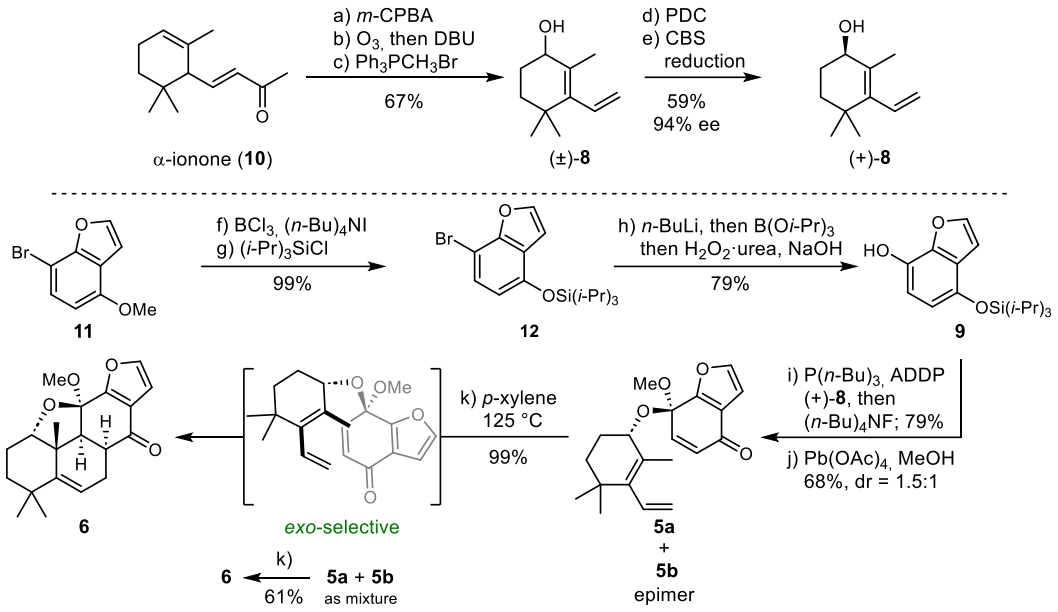
Scheme 2. Retrosynthetic Analysis



The synthesis commenced with preparation of enantioenriched allylic alcohol **8** via an adapted literature procedure (Scheme 3).[18,20] Epoxidation of α-ionone (**10**) and subsequent ozonolysis gave the corresponding aldehyde, which was treated with DBU to afford the enal in one pot. Wittig olefination provided diene (±)-**8** in an overall yield of 67% over 3 steps. Oxidation with pyridinium dichromate (PDC) followed by Corey–Bakshi–Shibata (CBS) reduction yielded (*R*)-diene (+)-**8** in 59% yield and 94% ee over two steps.

Commercially available bromide **11** was demethylated with BCl_3 in the presence of $(n\text{-Bu})_4NI$ and the resulting phenol was protected as the silyl ether using $(i\text{-Pr})_3SiCl$ and imidazole (99% yield over 2 steps). Lithium-bromine exchange and subsequent transmetallation with $B(Oi\text{-Pr})_3$ gave the boronic ester. Oxidation to the corresponding alcohol with H_2O_2·urea and aq. NaOH provided alcohol **9** in 79% yield in one pot. Alcohols **8** and **9** were coupled using Tsunoda's modification of Mitsunobu reaction[21] and the adduct subsequently desilylated in situ with $(n\text{-Bu})_4NF$ to afford the corresponding phenol in 79% yield. Oxidative dearomatization with $Pb(OAc)_4$ gave enone **5** as a diastereomeric mixture of 1.5:1 (analyzed by ^1H NMR of the unpurified reaction mixture) in 68% yield and set the stage for the key Diels–Alder reaction.

Scheme 3. Synthesis of Diene 9, Phenol 8, and Key Intramolecular Diels–Alder Reaction

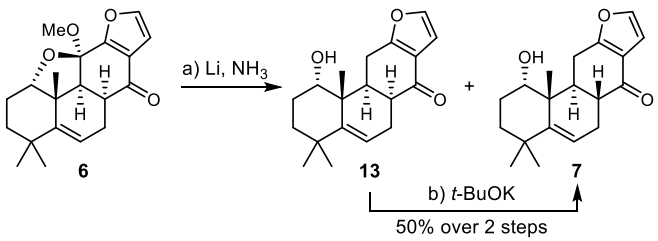


Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) O_3, CH_2Cl_2, –78 °C, then Me_2S, –78 °C to rt, then DBU; (c) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C to rt (67% over 3 steps); (d) PDC, CH_2Cl_2, 4 Å MS (99%); (e) (*S*)-CBS catalyst, $BH_3{\cdot}SMe_2$, PhMe–THF (1.1:1), 35 °C (58%, 94% ee); (f) BCl_3, $(n\text{-Bu})_4NI$, CH_2Cl_2, –78 °C to rt; (g) $(i\text{-Pr})_3SiCl$, imidazole, CH_2Cl_2 (99% over 2 steps); (h) *n*-BuLi, $B(Oi\text{-Pr})_3$, THF, –78 °C to rt, then $H_2O_2{\cdot}$urea, aq. NaOH (79%); (i) (+)-**8**, $P(n\text{-Bu})_3$, ADDP, THF, 0 °C, then $(n\text{-Bu})_4NF$ (79%); (j) $Pb(OAc)_4$, MeOH, –78 °C (68%, dr = 1.5:1); (k) *p*-xylene, 125 °C (99%); **5a** + **5b** as mixture (61%) ; ADDP = 1,1'-(azodicarbonyl)dipiperidine.

Heating the diastereomeric mixture of **5** to 125 °C in *p*-xylene led to formation of DA product **6** as a single diastereomer in 61% yield whose configuration was determined as *exo* on the basis of NOESY experiments (Scheme 3). To understand the stereochemical course of the reaction and its outcome, diastereomers of **5** (**5a** and **5b**) were separated by preparative TLC and subsequently submitted to the DA reaction conditions independently. Interestingly, under the reaction conditions **5b** decomposed to a complex mixture of products, while **5a** quantitatively afforded **6**. Given the moderate selectivity in previous substrates for simple acyclic dienols, the observed stereochemical outcome in our study can be understood to arise from the constraints imposed by the *gem*-dimethyl substituted cyclohexene in combination with the methyl ketal stereogenic center.[22]

Following successful DA cycloaddition reaction the next challenge was conversion of **6** to keystone intermediate **7** (Scheme 4). It is important to note that chemoselective reduction of ketal → CH_2 adjacent to furans, in the presence of ketones has not been investigated. [23,24] We hypothesized that such a transformation could conceivably be conducted under dissolving metal conditions. Initial attempts under reported conditions (15 min, –78 °C)[24] resulted in formation of traces (<5%) of product. Increasing the reaction time to 30 min led to isolation of the corresponding product **13** (29%) and its epimer **7** (4%). We were pleased to observe epimerization of **13** to desired *trans*-decalin **7** under the reaction conditions. Treatment of isolated **13** with *t*-BuOK furnished **7** in 94% yield. Extensive optimization studies (see SI) revealed conditions prescribing warming to –33 °C over a period of 35 minutes and a subsequent quench at –78 °C. Under these conditions **7** was obtained after epimerization in 50% yield over 2 steps.

Scheme 4. Chemoselective Birch Reduction

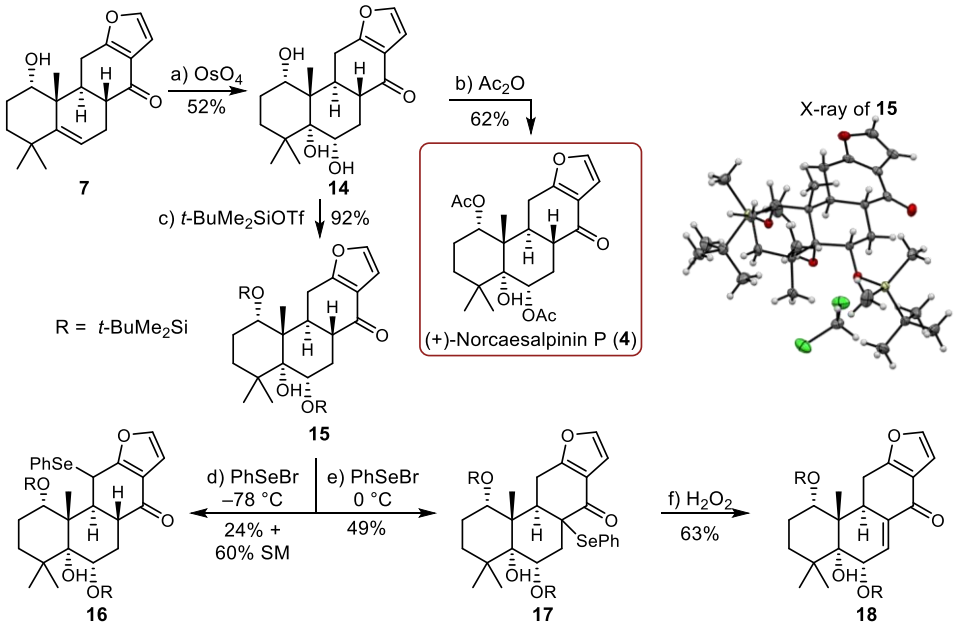


Reagents and conditions: (a) Li, NH_3 (l), –78 to –33 °C; (b) *t*-BuOK, *t*-BuOH (50% over 2 steps).

With a scalable route to keystone intermediate **7**, we turned our attention to the stereoselective introduction of the hydroxy and acetate groups contained in **1** - **4**. Initial attempts at allylic oxidation/dihydroxylation (CrO_3 or SeO_2 or CuBr) failed due to a number of side reactions: 1) elimination, 2) fragmentation, 3) aromatization.[25] The order of steps was reversed by first introducing the γ,δ-*syn*-diol followed by introduction of β-hydroxy group. Dihydroxylation of **13** with OsO_4, NMO and DABCO gave **14** in 52% yield as a single diastereomer as indicated by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture (Scheme 5). Acetylation of **14** afforded **4**, whose analytical data (^{1}H NMR, ^{13}C NMR, IR, CD) matched those reported for (+)-norcaesalpinin P.[9,26] Silylation of triol **14** afforded the disilyl ether **15** in 92% yield as crystalline compound (X-ray). Selenylation of **15** using $KN(SiMe_3)_2$ and PhSeBr at –78 °C gave γ-selenide **16** in 24% yield. We hypothesized that γ-enolate formation is kinetically controlled. Accordingly, in a subsequent experiment the enolization was conducted at 0 °C followed by the addition of PhSeBr and α-selenide **17** was isolated in 49% yield. Treatment of **17** with H_2O_2 induced selenoxide elimination to afford enone **18** in 63% yield.

We considered 1,4-addition to enone **18** to access various organo -boranes and -silanes, that could be transformed oxidatively into a hydroxy group. 1,4-Addition with Lipshutz cyanocuprate $(Me_2PhSi)_2Cu(CN)Li_2$[27] afforded silane **19** in 84% yield as a single diastereomer (determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture) (Scheme 6). The relative configuration was assigned by NOESY experiments (for details see SI). The major product of a one-pot Fleming–Tamao oxidation (AcOOH, KBr, AcOH) was enone **18**. We speculated that acidic conditions lead to the elimination of the newly formed alcohol in β-position to the ketone.

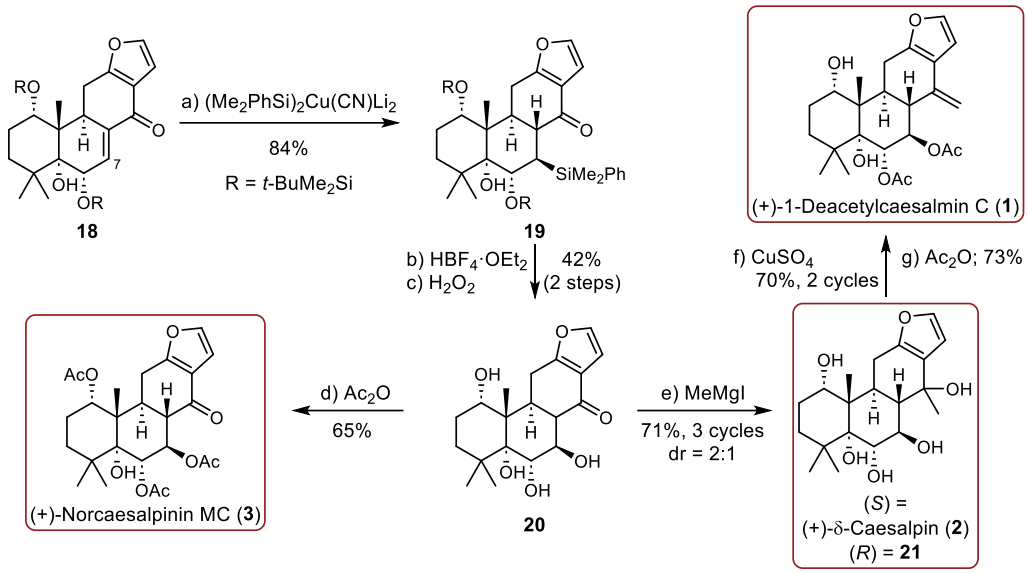
Scheme 5. Synthesis (+)-Norcaesalpinin P (4) and Enone 18



Reagents and conditions: (a) OsO_4, DABCO, NMO, acetone–H_2O (2:5:1), 90 °C (52%); (b) Ac_2O, py, DMAP (61%); (c) *t*-Bu Me_2SiOTf, 2,6-lutidine, CH_2Cl_2 (92%); (d) $KN(SiMe_3)_2$, –78 °C then PhSeBr –78 to 0 °C (24% + 60% SM); (e) $KN(SiMe_3)_2$, –78 to 0 °C then PhSeBr, THF, 0 °C (49%); (f) aq. H_2O_2, CH_2Cl_2–H_2O (20:1), 0 °C (63%).

Consequently, the conditions were changed to a two-step Fleming–Tamao oxidation procedure where the second step involves mildly alkaline oxidizing conditions. Treatment of silane **19** with $HBF_4{\cdot}OEt_2$ led to silyl fluorination and concomitant desilylation of the alcohols. Keeping the temperature at –35 °C was crucial because at higher temperatures Peterson elimination was observed. The silyl fluoride was then subjected to oxidation in the presence of KF, $KHCO_3$ and $H_2O_2{\cdot}$urea to afford tetraol **20** in 42% yield over 2 steps. Acetylation with DMAP, Ac_2O and pyridine gave (+)-norcaesalpinin MC (**3**) in 65% yield. The spectroscopic data obtained of **3** (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, HRMS, IR) were in agreement with the reported data.[8,28] 1,2–Addition of MeMgI to tetraol **20** afforded the corresponding pentaol in 35% yield and 2:1 dr along with 62% starting material. Resubjecting the starting material to the reaction conditions two more times gave the pentaol in 71% yield over 3 cycles. The major diastereomer was identified as (+)-δ-caesalpin (**2**), whose analytical data (^{1}H NMR, ^{13}C NMR) matched with literature precedent.[6,7,29] Based on derivatization studies of Canonica and co-workers[5], the mixture of **21** and **2** was dehydrated with $CuSO_4$ and gave the *exo*-methylene in 53% yield along with 45% starting material. Resubjecting the starting material to the reaction conditions gave the product in 70% yield over 2 cycles. The analytical data of the product (^{1}H NMR, ^{13}C NMR, HRMS) matched with the literature[30]. Final regioselective acetylation with Ac_2O and pyridine afforded (+)-1-deacetylcaesalmin C (**1**) in 73% yield. The obtained analytical data (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, IR) were in agreement with the literature.[2,31]

Scheme 6. Synthesis of (+)-1-Deacetylcaesalmin C (1), (+)-δ-Caesalpin (2) and (+)-Norcaesalpinin MC (3)



Reagents and conditions: (a) $(Me_2PhSi)_2Cu(CN)Li_2$, THF, 0 °C to rt (84%); (b) $HBF_4{\cdot}OEt_2$, CH_2Cl_2, –35 °C; (c) KF, $KHCO_3$, $H_2O_2{\cdot}$urea, THF–MeOH (1:1), 0 °C to rt (42% over 2 steps); (d) Ac_2O, py, DMAP (65%); (e) MeMgI, Et_2O (35%, dr = 2:1, 62% SM, 71% over 3 cycles); (f) $CuSO_4$, 1,4-dioxane (53%, 45% SM, 70% over 2 cycles); (g) Ac_2O, py (73%).

We next set out to investigate the effect of **1 – 4** on the metabolism in brown adipocytes. Cellular oxygen consumption rates (OCRs) are directly linked to mitochondrial electron transfer and thus serve as useful measure for quantification.[32] The mitochondrial electron transfer is coupled to proton transfer across the inner membrane, creating a proton gradient, which is utilized for ATP synthesis (coupled respiration) or for heat production (uncoupled respiration) mediated by Uncoupling Protein 1 (UCP1).[33,34,14] OCRs can be assessed using the Seahorse XF96 method (Figure 1).[32] Murine brown adipocytes (iBAs) were treated with DMSO (black) as a control and synthetic **1** (10 μM, red) for three days, respectively. Then, OCR was measured over a period of 18 min to yield 273 ± 17 – 248 ± 17 pmol/min for cells treated with synthetic **1** and 227 ± 4 – 203 ± 3 pmol/min for cells treated with DMSO (Figure 1A). These values represent the sum of basal mitochondrial (+ for **1** and for control) and non-mitochondrial respiration ( ). Basal mitochondrial respiration (and) in turn is the sum of ATP synthesis-coupled and -uncoupled respiration processes. To determine the OCR of each process, the cells were then treated with 2.5 μM oligomycin (Oligo), which suppresses ATP-synthesis. This led to a reduction of OCR by 74 ± 10 – 70 ± 9 pmol/min for **1** and 61 ± 3 –52 ± 3 pmol/min for control, which corresponds to the contribution of ATP synthesis-coupled respiration. The remaining OCR of 93 ± 12 – 89 ± 12 pmol/min for **1** (+), 74 ± 3 –70 ± 3 pmol/min for control ( ), accounts for uncoupled respiration. Next, the maximal uncoupled capacity was determined, which represents activation of UCP1. Isoprotenerol (Iso) is a β-adrenoceptor agonist known to activate UCP1.[35] At time = 40 min, iBAs were treated with 1 μM Iso, which resulted in increased OCR of 332 ± 17 – 408 ± 18 pmol/min for cells treated with synthetic **1** (+) and 293 ± 11 – 352 ± 13 pmol/min for control ( ). At time = 62 min, the maximal overall respiration capacity was measured by complete chemical uncoupling of all mitochondria through the addition of trifluoromethoxy carbonylcyanide phenylhydrazone (FCCP, 3.9 μM), leading to OCR values of 650 ± 13 – 648 ± 7 pmol/min for **1** ( ) and 710 ± 8 – 657 ± 10 pmol/min for control (+). Finally at time = 84, non-mitochondrial respiration ( ) was determined to be 86 ± 2 pmol/min for **1** and 77 ± 1 pmol/min for control following complete chemical inhibition of mitochondrial respiration induced by the addition of a combination of rotenone (3 μM) and 3.6 μM antimycin A (Rot/Ant).

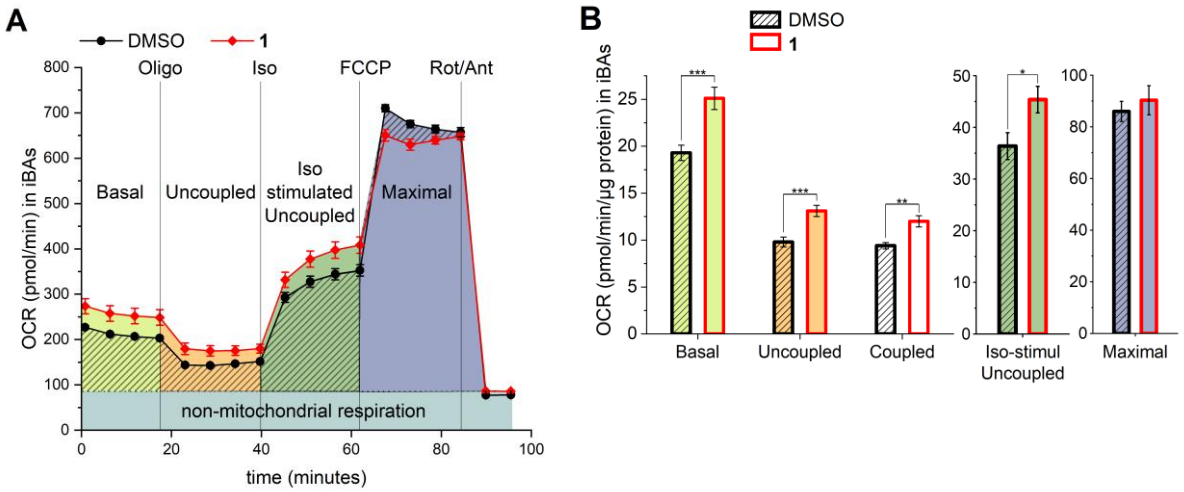


Figure 1: 1-Deacetylcaesalmin C (**1**) treatment stimulates mitochondrial respiration levels in immortalized murine brown adipocytes. Cells were treated with 10 µM of (+)-1-deacetylcaesalmin C (**1**) for 3 days. Data are presented as mean ± SEM. Statistical analysis was performed by two-sided Student´s t-test. Significance is indicated as $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$. Oligo = oligomycin; Iso = isoproterenol; FCCP = trifluoromethoxy carbonylcyanide phenylhydrazone; Rot/Ant = rotenone and antimycin.

The comparison between the normalized OCRs of iBAs treated with **1** and the OCRs of DMSO controls is shown in Figure 1B at the different stages of the Seahorse XF96 experiment. A significant increase in basal oxygen consumption was observed in the presence of **1** ( ) (25.1 ± 1.2 pmol/min/µg) compared to control ( ) (19.3 ± 0.8 pmol/min/µg). The contribution of uncoupled respiration was 13.1 ± 0.6 pmol/min/µg for **1** ( ) and 9.8 ± 0.5 pmol/min/µg for control ( ), whereas the one of coupled respiration was 12 ± 0.6 pmol/min/µg for **1** and 9.4 ± 0.3 pmol/min/µg for control . Additionally, we found an increase in Iso-stimulated uncoupled respiration of 45 ± 2.3 pmol/min/µg for **1** ( ) and 36 ± 1.8 pmol/min/µg for control ( ). In contrast, maximal overall respiration was not significantly altered (86 ± 4.3 and 90 ± 4.5 pmol/min/µg). In parallel experiments, cells treated with **2** – **4** displayed no relative increase compared to control (for details see SI). These results demonstrate that **1** stimulates uncoupled respiration and increases the maximal uncoupling capacity of brown adipocytes. Maximal overall respiration is not altered after treatment of iBAs with **1**, indicating that **1** is not causing changes in mitochondrial mass. The effect of 1-deacetylcaesalmin C (**1**) on uncoupled respiration is comparable to that of the state-of-the-art natural uncoupler capsaicin, which was shown to be neurotoxic.[36,37] Stimulation of uncoupled respiration in brown adipocytes is a potential therapeutic target for obesity, because it leads to thermogenesis or release of excess energy as heat.[14] All in all, these results suggest that **1** is a promising lead compound for further development to tackle obesity.

In conclusion, we report the first and enantioselective total syntheses of (+)-1-deacetylcaesalmin C (**1**), (+)-δ-caesalpin (**2**), (+)-norcaesalpinin MC (**3**) and (+)-norcaesalpinin P (**4**), enabled by a common keystone intermediate. Key steps include *exo*-selective Diels–Alder reaction and chemoselective Birch reduction to access the 6/6/6/5 carbon skeleton of cassane furanoditerpenoids. Study of oxygen consumption rates showed that (+)-1-deacetylcaesalmin C (**1**) upregulates uncoupled respiration and maximal Iso-stimulated uncoupled capacity in brown adipocytes. These findings could be useful for the development of future anti-obesity drugs. Further syntheses of related natural products and evaluation of their biological activity are ongoing and will be reported in due course.

Acknowledgements

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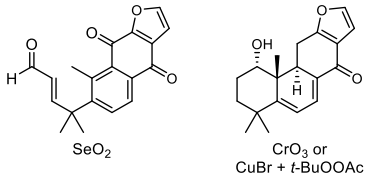

(26) A ^{1}H NMR signal (1.12 ppm) did not match with the reported tabular value (2.11 ppm). However, ^{13}C NMR spectral data were in full agreement. In addition the αD value for synthetic **4** (+68.5) did not match with the reported value (–58). CD measurements and X-ray analysis of **15** suggest a typing error in the isolation report. For further discussion see SI.
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(29) ^{1}H NMR signal (1.92 ppm (dd), 1.97–2.04) did not match with the reported value (2.02 ppm, 1.61 ppm) and a ^{13}C NMR signal (48.7 ppm) did not match with the reported value (35.1 ppm). X-ray analysis of **14** and 2D NMR analysis of **2** suggest a typing error in the isolation report. For further discussion see SI.
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(31) ^{1}H NMR signals (1.90–2.05 ppm, 1.10 ppm) did not match with the reported value (2.89 ppm, 1.00 ppm). X-ray analysis of **15** and 2D NMR analysis of **1** suggest a typing error in the isolation report. For further discussion see SI.
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