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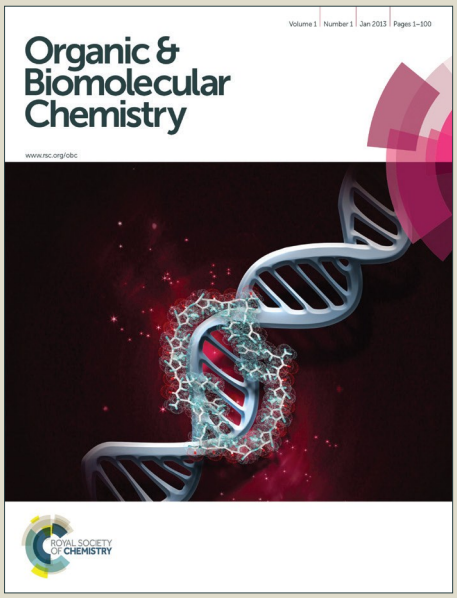

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PAPER

Asymmetric Synthesis of (+)-17-*Epi*-methoxy-kauran-3-one Through Tandem Oxidative Polycyclization-Pinacol Process

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A synthesis of (+)-17-*epi*-methoxy-kauran-3-one, an O-methylated isomer of the natural diterpene 17-hydroxy-kauran-3-one, has been achieved. The strategy is based on a diastereoselective oxidative polycyclization-pinacol tandem process consisting in transforming a functionalized phenol into a compact and complex tetracycle, which represents the main core of kaurane family members. The synthesis also includes an enantioselective Yamamoto's allylation, a diastereoselective Ru-catalyzed hydrocyanation, a ring-closing metathesis and a reductive isomerization process as key steps. The structure of our synthetic substrate was determined through comparison with an O-methylated derivative of the natural compound.

Introduction

Kauranes and their enantiomer *ent*-kauranes represent a wide family of natural diterpenes. They are isolated from numerous natural sources and have been shown to possess a variety of interesting biological properties such as antidiabetic/antiobesity, antispasmodic, antiallergic activities or immunosuppressive and platelet antiaggregating effects.[1] The main tetracyclic carbon-skeleton of kauranes **1** exhibits multiple contiguous asymmetric centers and several quaternary carbon centers, Figure 1.[1a]

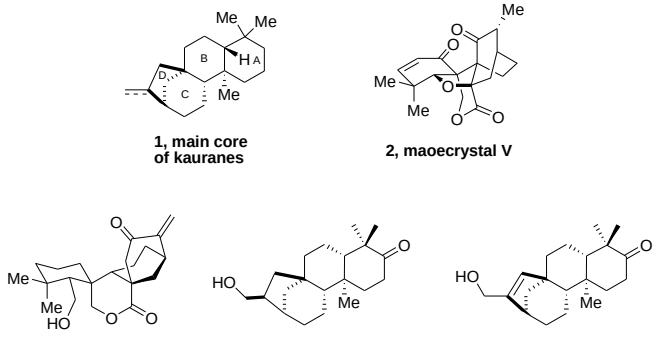

Figure 1. Main core of kauranes and representative family members.

This noteworthy structure has raised the interest of the scientific community, and during the past decades, some syntheses of *ent*-kauranes, including the unusual maoecrystal V **2** and sculponeatin N **3**, have been achieved by leading groups.[2,3,4] However, some other members of the kaurane family have received much less attention, and to the best of our knowledge, total syntheses of 17-hydroxy-kaurane-3-one **4** or 3-oxo-kaur-15-en-17-ol **5** are absent from the literature. Cationic polycyclizations of polyunsaturated compounds remain relevant transformations in the terpene-derived natural products synthesis field. Such polycyclizations have been used in biomimetic syntheses to access complex structures containing quaternary carbon centers with noteworthy diastereoselectivity.[5] In this case, selective electrophilic activation of a π-bond generates a cationic species that is trapped in an intramolecular manner by other nucleophilic π-bonds, which can subsequently react with other unsaturations. Moreover, the presence of a final electrophilic species resulting from the cyclization cascade may trigger 1,2-substituent shifts such as Wagner-Meerwein, pinacol or Prins-pinacol rearrangements to conclude the cascade. The latter, whose utility has already been demonstrated in total synthesis,[6] allows redesigning molecular structures and accessing highly functionalized compounds, also with very good stereoselectivity. Our conviction that linking these two powerful synthetic tools may provide an attractive approach to diterpene main cores combined with our interest in total synthesis of polycyclic natural compounds through oxidative dearomatization of phenols[7] led us to consider a new synthetic pathway to kaurane family members. In this paper, we describe our recent efforts toward the asymmetric synthesis of 17-hydroxy-kauran-3-one **4** *via* an oxidative polycyclization-pinacol cascade[8] as key step to yield the main core of the target and the synthesis of (+)-17-*epi*-methoxy-kauran-3-one **27**.

Results and discussion

A potential retrosynthesis of **4** includes an enantioselective Yamamoto allylation to generate the first asymmetric center of **7** from aldehyde **6**, an ozonolysis followed by a Corey-Fuchs

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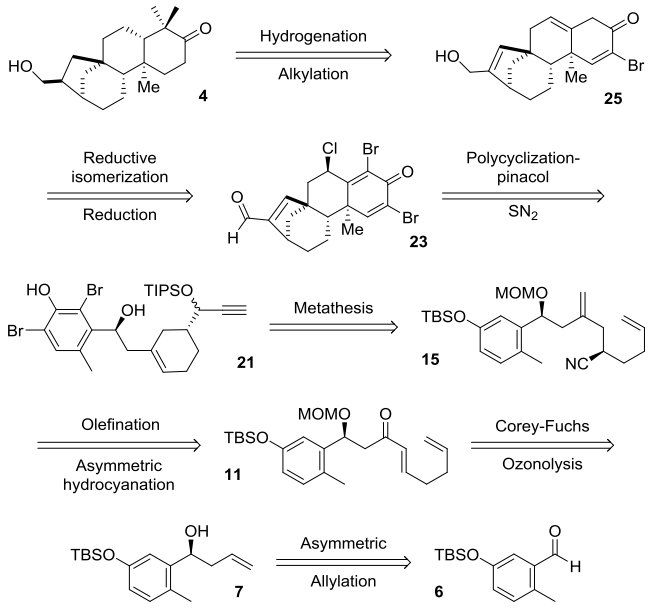
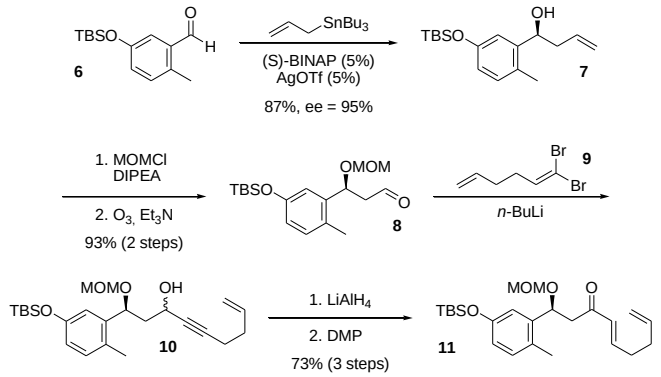
alkynylation to introduce the lateral chain of **11**, a diastereoselective hydrocyanation and an olefination to produce diene **15**, a metathesis to close the cyclohexenic ring of **21**, a S_N2 to introduce the chlorine atom stereoselectively, followed by a stereoselective oxidative polycyclization-pinacol tandem process to assemble the key tetracyclic core **23**, a selective reduction of the aldehyde of **23**, followed by a reductive isomerization to deliver enone **25** and finally, a sequence made of di-alkylation and hydrogenation to provide 17-hydroxy-kauran-3-one **4**, Scheme 1.



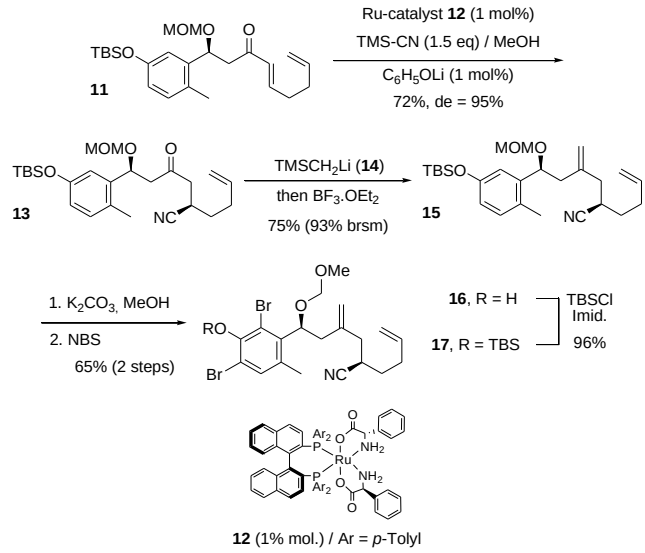
Scheme 1. Potential retrosynthesis of 17-hydroxy-kauran-3-one **4**.

The synthesis begins with the treatment of known aldehyde **6**[9] with allyltributyltin in the presence of AgOTf and (*S*)-BINAP[10] to generate allylic alcohol **7**, presenting the required first asymmetric center in 87% yield and 95% *ee*, Scheme 2. The hydroxyl group is then protected as a ketal in the presence of MOMCl, and an ozonolysis produces aldehyde **8** in 93% yield over two steps. Nucleophilic addition involving the anion resulting from a reaction between 1,1-dibromo-1,5-hexadiene **9** and BuLi[11] affords alcohol **10** as an epimeric mixture that is used to reduce the alkyne with $LiAlH_4$, thus furnishing the required *trans*-alkene moiety. Finally, oxidation of the allylic alcohols with Dess-Martin periodinane converges to Michael acceptor **11** in 73% yield over three steps.



Scheme 2. Synthesis of Michael acceptor **11**.

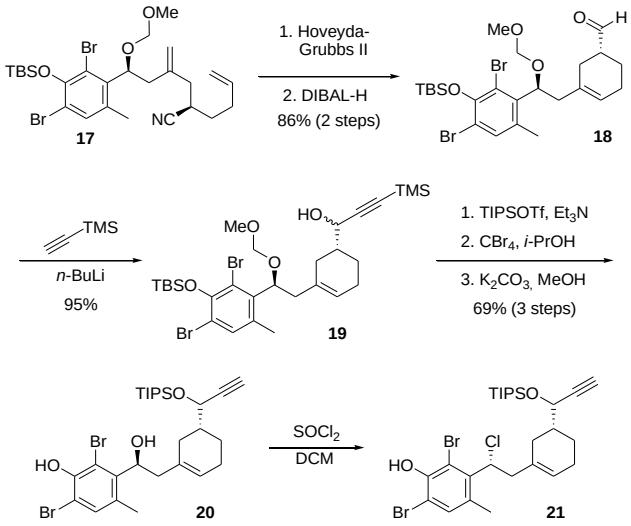
At this stage, it is necessary to prepare the molecule for the cyclohexene ring construction by a ring-closing metathesis. To this end, Michael acceptor **11** is submitted to a diastereoselective hydrocyanation process involving ruthenium-based catalyst **12** in the presence of trimethylsilyl cyanide, lithium phenoxide and methanol, as reported by the group of Ohkuma,[12] Scheme 3. Under these conditions, the second asymmetric center of **13** is installed in 72% yield and 95% *de*. The first attempt to produce the required terminal alkene of **15** through Wittig olefination mainly resulted in the degradation of the starting material. Further experiments, such as Petasis or Julia-type reactions, also failed to deliver diene **15** in good yields. However, preliminary treatment of **13** with (trimethylsilyl)methyllithium **14** followed by Lewis-acid mediated activation furnished the desired compound **15** in 75% (93% brsm). Finally, bromine atoms are introduced at the *ortho*-positions of the phenol in 62% yield over three steps. These electron-withdrawing atoms mainly serve to protect *ortho*-positions against a nucleophile attack during the "umpolung activation", thus destabilizing the formation of a cation near these positions and forcing the lateral chain to react at the required *para* position of the phenol during the polycyclization process described in Scheme 5.



Scheme 3. Synthesis of diene **17**.

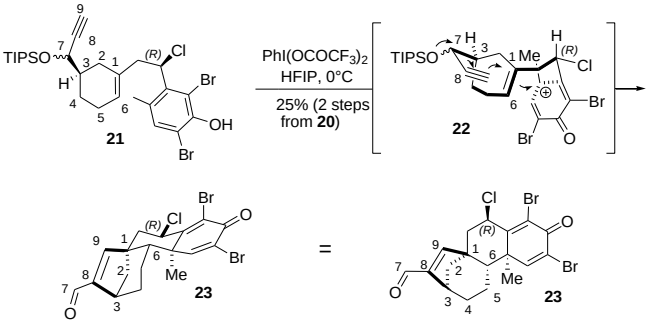
The cylohexenic ring of **18** is then closed through metathesis mediated by a 2nd generation Hoyveda-Grubb catalyst and the cyano group is transformed into an aldehyde using DIBAL-H in 86% yield over two steps, Scheme 4. The reaction between aldehyde **18** and lithium (trimethylsilyl)acetylide delivers propargylic alcohol **19** as an epimeric mixture (95% yield) which is then protected with a bulky TIPS group under standard conditions. Such protection is required to avoid possible side-reactions resulting from interactions between a free hydroxy and cationic species generated during the polycyclyzation process. Subsequent selective deprotection of the benzylic alcohol under mild acidic conditions generated by treatment of

CBr_4 in isopropanol and followed by a treatment with K_2CO_3 in methanol to furnish phenol **20** in 69% yield over three steps. Finally, the benzylic chlorine atom of **21** is installed with inversion of configuration through a SN_2 pathway involving thionyl chloride.



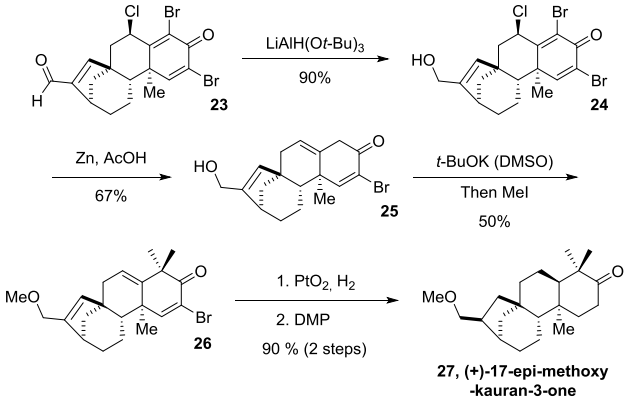
Scheme 4. Synthesis of precursor **21**.

The main tetracyclic core of kaurane family members **23** is produced through a diastereoselective oxidative polycyclization-pinacol cascade[8] from precursor **20** in 25% yield over two steps, Scheme 5. This process first implies oxidative dearomatization[13,14] or "Umpolung activation"[15] of phenol **21** mediated by phenyliodine bis(trifluoroacetate). As reported by Kita and coworker,[16] in the presence of HFIP, a highly electrophilic species **22,** known as "phenoxenium", is produced under these conditions. The latter is trapped by the π bond of the cyclohexenic ring moiety, which in turn reacts with the alkyne, and the process is ended by a pinacol transposition according to chair-like transition state **22**. It should be stressed that the diastereoselectivity of this cascade is governed by the benzylic chlorine atom, which is located equatorially in a chair-like transition state to minimize both steric and stereoelectronic interactions, and forces the lateral chain to attack on the desired top face of the phenoxenium species to control the first stereocenter of the cascade.



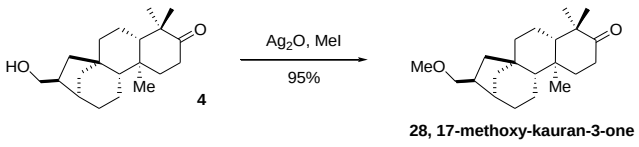
Scheme 5. Oxidative polycyclization-pinacol tandem process.

With the tetracyclic core **23** in hand, further elaborations are needed to reach the target. Selective reduction of the aldehyde in the presence of a hindered hydride generates alcohol **24** in 90% yield, Scheme 6. Reductive isomerization performed with zinc in acetic acid subsequently enables the selective reduction of both the allylic chlorine and allylic bromine generated *in situ via* double bond isomerization, thus delivering **25** in 67% yield. At this stage, the *gem*-dimethyl segment must be introduced at the *α*-position of ketone **25**. To this end, 2**5** is treated with *t*-BuOK in DMSO in the presence of methyl iodide, yielding intermediate **26** in 50% yield. It should be stressed that the unprotected primary alcohol is also methylated in this transformation, but *O*-methylation may be avoided by TBS protection if necessary. Another hydrogenation process in the presence of Adams' catalyst[17] facilitates the removal of the last bromine atom and allows for the reduction of remaining unsaturations. Under these conditions, partial reduction of the ketone to an epimeric alcohol mixture is noted. Nevertheless, further treatment with Dess-Martin periodinane produces desired compound **27** in 90% yield.



Scheme 6. Synthesis of (+)-17-*epi*-methoxy-kauran-3-one **27**.

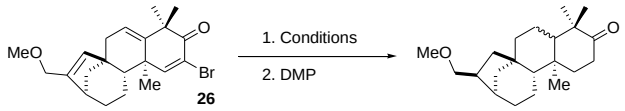
To verify the stereoselectivity of the hydrogenation process, a small amount of commercially available natural 17-hydroxy-kauran-17-one has been *O*-alkylated under mild conditions in the presence of Ag_2O and methyl iodide, yielding the *O*-methyl analog **28**, Scheme 7. The ^1H NMR spectra of **27** and **28** are very similar except for a small difference in the shift of methyl groups, which were slightly more shielded in the natural derivative.[18] Our synthetic diterpene adduct **27** is also slightly less polar by TLC. These small differences are indicative of a *cis* decalin junction,[19] meaning that during the hydrogenation process leading to **27**, the reduction is not controlled by the presence of the angular methyl group as is sometimes observed,[20] but rather by the bowl shape of the main core.



Scheme 7. O-methylation of natural 17-hydroxy-kauran-3-one.

To address the diastereoselectivity issue encountered during the hydrogenation process, other experimental conditions were tested, Table 1. Changing the pressure (Table 1, entry b) also furnished epimer **27** in 90% yield. Substitution of methanol by a more polar solvent (Table 1, entry c) once again delivered undesired isomer **27** but with a significant decrease in efficiency. Finally, using Pd/C as a catalyst in dioxane[21] (Table 1, entry d) also failed to produce the required *trans*-decalin moiety, generating **27** in 75% yield.

Table 1. Hydrogenation of **26**.



entry	Conditions	Product	Yield (%) (2 steps)
a	PtO_2, H_2 (1 atm), MeOH	**27**	90
b	PtO_2, H_2 (4 atm), MeOH	**27**	90
c	PtO_2, H_2 (1 atm), AcOH	**27**	53
d	Pd/C, H_2 (1 atm), Dioxane	**27**	75

We also considered using a less bulky diimide to invert the stereoselectivity. To this end, **26** has been treated with 2-nitrobenzenesulfonylhydrazide in the presence of triethylamine. However, under these conditions, a complex mixture of compounds was recovered.

Conclusions

In summary, we have developed a synthesis of (+)-17-*epi*-methoxy-kauran-3-one, an *O*-methylated epimer of natural 17-hydroxy-kauran-3-one. The most innovative step of our strategy is a diastereoselective oxidative polycyclization-pinacol tandem process consisting in transforming an elaborated phenol into the main tetracyclic core of kaurane family members with complete control of the stereoselectivity. The synthesis also includes an enantioselective Yamamoto allylation, a Corey-Fuchs alkynylation, a Ru-mediated diastereoselective hydrocyanation and a ring-closing metathesis as key steps. Comparing our synthetic substrate and an O-methylated derivative of extracted 17-hydroxy-kauran-3-one led us to conclude that we actually synthesized an undesired epimer derivative of the natural product. This work illustrates the potential of oxidative dearomatizations for the rapid and efficient construction of complex polycyclic structures serving as key intermediates in total synthesis of natural compounds.

Experimental

General experimental details

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), td (triplet of doublets), q (quartet), m (multiplet) and further qualified as app (apparent), br (broad), c (complex). Coupling constants, J, are reported in Hz. Mass spectra (m/e) were measured in the electrospray (ESI) mode.

(5R,6aR,9R,11aR,11bR)-2,4-dibromo-5-chloro-11b-methyl-3-oxo-3,5,6,9,10,11,11a,11b-octahydro-6a,9-methanocyclohepta[a]naphthalene-8-carbaldehyde (23). To a solution of compound **20** (105 mg, 1.00 eq, 0.175 mmol) in anhydrous DCM (3 mL) under argon atmosphere was added $SOCl_2$ (38µL, 3.00 eq, 0.525 mmol). The solution was refluxed for 8 hours and then a solution of sat. aq. $NaHCO_3$ (5 mL) was added. The aqueous phase was extracted with DCM (3 * 10 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was filtrated on a plug of silica gel (hexanes/EtOAc, 9:1) and was used without further purification. To a vigorously stirred solution of the above crude phenol in a mixture of HFIP/DCM (5:3 ; 1 mL) at room temperature was added over 5 seconds a solution of $PhI(CO_2CF_3)_2$ (83 mg, 1.10 eq, 0.192 mmol) in a mixture of HFIP/DCM (5:3, 0.6 mL). After addition of PIFA, the solution was stirred for 2 min, quenched with 1 mL of acetone and filtered over silica gel (EtOAc). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to afford 20.3 mg of tetracyclic core **23** in 25 % yield over 2 steps. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.67 (s, 1H), 7.31 (s, 1H), 6.13 (s, 1H), 5.42 (t, *J*=9.5, 1H), 3.05 – 3.00 (m, 1H), 2.46 (d, *J*=9.6, 2H), 2.18 (dd, *J*=12.9, 5.0, 1H), 2.05 – 1.98 (m, 1H), 1.90 – 1.82 (m, 1H), 1.72 (s, 3H), 1.46 – 1.40 (m, 2H), 0.96 – 0.85 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 188.9, 172.4, 158.6, 155.2, 149.9, 147.5, 127.6, 119.3, 56.4, 52.5, 51.1, 40.0, 36.9, 31.1, 29.8, 25.2, 23.0; **HRMS** (ESI) Calc. For $C_{18}H_{17}Br_2ClO_2$ $(M+Na)^+$: 482.9155, found : 482.9159; **$[\alpha]_D$** (25°C, c = (11.6 mg/ 2mL), AcOEt) = -4.3°.

(5R,6aR,9R,11aR,11bR)-2,4-dibromo-5-chloro-8-(hydroxymethyl)-11b-methyl-5,6,9,10,11,11a-hexahydro-6a,9-methanocyclohepta[a]naphthalen-3(11bH)-one (24). To a solution of aldehyde **23** (57 mg, 1.00 eq, 0.124 mmol) in dry THF (1.2 mL) at -78°C under argon atmosphere was added dropwise $LiAlH(Ot\text{-}Bu)_3$ (0.137 mL at 1.0 M, 1.10 eq, 0.137 mmol). The resulting solution was stirred at -78°C for 15 min and sat. aq. NH_4Cl (5 mL) was added. The aqueous phase was extracted with EtOAc (3 * 5 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 7:3) to afford pure alcohol **24** as a white solid (51 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 5.34 (t, *J* = 9.5 Hz, 1H), 5.04 (s, 1H), 4.12 (d, *J* = 1.3 Hz, 2H), 2.57 (m, 1H), 2.39-2.32 (d, *J* = 10 Hz, 2H), 2.12 – 2.03 (dd, *J* = 12.6, 4.8 Hz, 1H), 1.96 (dd, *J* = 10.0, 5.1 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.67 (s, 3H), 1.64 – 1.49 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.7, 159.7, 156.0, 149.2, 126.9, 123.0, 119.0, 60.7, 57.0, 52.5, 52.0, 49.9, 49.0, 41.1, 39.9, 31.0, 25.4, 23.4. **HRMS** (ESI) Calc. For $C_{18}H_{19}Br_2ClO_2$ $(M+H)^+$: 462.9492, found : 462.9463; Calc. For. $C_{18}H_{19}Br_2ClO_2$ $(2M+Na)^+$: 942.8773, found : 942.8781; **$[\alpha]_D$** (25°C, c = (18.4 mg/ 1 mL), AcOEt) = +27.8°.

(6aS,9R,11aR,11bR)-2-bromo-8-(hydroxymethyl)-11b-methyl-6,9,10,11,11a,11b-hexahydro-6a,9-methanocyclohepta[a]naphthalen-3(4H)-one (25). To a solution of alcohol **24** (20 mg, 1 eq, 0.043 mmol) in *i*-PrOH (4.7 mL) were added AcOH (0.04 mL, 15. eq, 0.65 mmol) and Zn (28 mg, 10.00 eq, 0.43 mmol). The resulting mixture was refluxed for 10 min and filtrated over silica gel (EtOAc). The residue was dissolved in $CHCl_3$ (5 mL) and washed with water (3 mL) and sat. aq. NaCl, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 85:15) to afford

pure enone **25** as a white solid (10 mg, 67%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 5.56 (dt, *J* = 6.5, 2.0 Hz, 1H), 5.39 (s, 1H), 4.21 (d, *J* = 1.2 Hz, 2H), 3.52 (d, *J* = 17.2 Hz, 1H), 3.19 (d, *J* = 17.3 Hz, 1H), 2.67 – 2.45 (m, 1H), 2.41 – 2.24 (m, 1H), 2.14 – 2.04 (m, 1H), 2.03 – 1.97 (m, 1H), 1.95 (d, *J* = 5.9 Hz, 1H), 1.92 – 1.76 (m, 3H), 1.34 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.5, 157.3, 146.9, 135.7, 127.1, 123.3, 121.9, 61.2, 52.5, 46.4, 46.3, 45.7, 44.1, 39.4, 34.0, 29.8, 25.5, 21.4; **LRMS** (ESI) : Calc. For $C_{18}H_{21}BrO_2$: 349-351, found : 349-361; **$[\alpha]_D$** (25°C, c = (6.8 mg/ 1 mL), $CHCl_3$) = - 27.7°.

(6aS,9R,11aR,11bR)-2-bromo-8-(methoxymethyl)-4,4,11b-trimethyl-6,9,10,11,11a,11b-hexahydro-6a,9-methanocyclohepta[a]naphthalen-3(4H)-one (26). To a cooled solution of enone **25** (4 mg, 1.00 eq, 0.0114 mmol) in anhydrous DMSO (0.2 mL) under argon atmosphere was added dropwise *t*-BuOK (0.046 mL at 1.0 M, 4.00 eq, 0.046 mmol). The resulting brown solution was stirred for 1 min and CH_3I (0.01 mL, 14.00 eq, 0.16 mmol) was added. The mixture was stirred for further 10 min and sat. aq. NH_4Cl (2 mL) was added. The aqueous phase was extracted with $CHCl_3$ (3 * 2 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 95:5) to afford methylated compound **26** as a colorless oil (2.4 mg, 55%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 5.88 (dd, *J* = 7.3, 2.9 Hz, 1H), 5.36 (s, 1H), 3.97 (dd, *J* = 12.9, 1.5 Hz, 1H), 3.87 (dd, *J* = 12.8, 0.8 Hz, 1H), 3.35 (t, *J* = 4.7 Hz, 1H), 3.32 (s, *J* = 6.3 Hz, 3H), 2.58 – 2.50 (m, 1H), 2.09 (dd, *J* = 16.6, 2.9 Hz, 1H), 1.99 (dd, *J* = 16.5, 7.3 Hz, 1H), 1.89 (ddd, *J* = 9.9, 5.1, 2.2 Hz, 1H), 1.85 – 1.67 (m, 2H), 1.49 – 1.44 (m, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.7, 154.4, 144.1, 143.9, 128.5, 123.2, 119.3, 70.5, 58.4, 52.2, 50.0, 49.8, 48.2, 43.6, 39.8, 34.1, 32.7, 30.0, 27.1, 24.8, 23.3. **LRMS** (ESI): Calc. For $C_{21}H_{27}BrO_2$ $(M+H)^+$: 391-393, found : 391-393; **$[\alpha]_D$** (25°C, c = (2.2 mg/ 1 mL), $CHCl_3$) = - 30.0°.

(+)-17-*epi*-methoxy-kauran-3-one (27). To a solution of compound **26** (2.4 mg, 1.00 eq, 0.0062 mmol) in methanol (0.3 mL) was added PtO_2 (1.4 mg, 1.00 eq, 0.0062 mmol). The resulting suspension was stirred for 12h under a 4 atm H_2 atmosphere. The mixture was then then filtrated over celite (EtOAc) and solvents were removed under vacuum. The crude mixture was dissolved in anhydrous DCM (0.1 mL) under argon atmosphere and Dess-Mastin periodinane (3.2 mg, 1.20 eq, 0.0074 mmol) was added. The resulting solution was stirred for 10 min at room temperature and sat. aq. $NaHCO_3$ (1 mL) was added. The aqueous phase was extracted with $CHCl_3$ (3 * 1 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford (+)-17-*epi*-methoxy-kauran-3-one **27** as a white solid (1.8 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.56 – 3.43 (m, 2H), 3.42 (s, 3H), 2.42 (m, *J* = 12.1, 8.5, 6.3 Hz, 2H), 2.31 – 2.01 (m, 3H), 1.81 – 1.26 (complex, 15H), 1.24 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.6, 73.8, 59.0, 55.3, 54.3, 51.0, 47.4, 43.4, 42.9, 39.7, 38.0, 36.5, 35.6, 34.6, 29.8, 29.5, 27.4, 25.5, 25.3, 23.7, 21.6. **HRMS** (ESI) Calc. For $C_{21}H_{35}O_2$ $(M+H)^+$: 319.2632, found : 319.2622; **$[\alpha]_D$** (25°C, c = (2.4 mg/ 1 mL), $CHCl_3$) = +10.8°.

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Notes and references

1 For a review on biological properties, see: (a) P. A. Garcia, A. B. de Oliveira and R. Batista, *Molecules* 2007, **12**, 455. For other publications, see: (b) P. R. Jeffries and R. W. Retallack, *Aust. J. Chem.* 1968, **21,** 1311; (c) G. Drager, X. A. Dominguez, H. V. Sanchez, E. G. Gomez Lopez, E. Kunst, F. Tsichritzis, F. Jeske, J. Jakupovic and A. Kirschning, *Eur. J. Org. Chem.* 2007, **72**, 5020; (d) Y. Shao, L. H. Hu, K. Y. Sim and S. H. Goh, *Helv. Chim. Acta* 2006, **89**, 64; (e) K. Mori and S. Aki, *Liebigs Ann. Chem.* 1993, **1**, 97; (f) K. Mori and M. Matsui, *Tetrahedron* 1968, **24**, 3095; (g) R. A. Britton, E. Piers and B. O. Patrick, *J. Org. Chem.* 2004, **69**, 3068; (h) S. P. Yang and J. M. Yue, *Nat. Prod. Res.* 2008, **22**, 1163; (i) Y. Li, J. Liu, S. Yu, P. Proksch, J. Gu and W. Lin, *Phytochemistry* 2010, **71**, 2124.

2 For syntheses of maoecrystal V, see: (a) J. Gong, G. Lin, W. Sun, C. C. Li and Z. Yang, *J. Am. Chem. Soc.* 2010, **132**, 16745; (b) F. Peng and S. J. Danishefsky, *J. Am. Chem. Soc.* 2012, **134**, 18860; (c) P. Lu, Z. Gu and A. Zakarian, *J. Am. Chem. Soc.* 2013, **135**, 14552; (d) P. Lu, A. Mailyan, Z. Gu, D. M. Guptill, H. Wang, H. M. Davies and A. Zakarian, *J. Am. Chem. Soc.* 2014, **136**, 17738; (e) C. Zheng, I. Dubovyk, K. E. Lazarski and R. J. Thomson, *J. Am. Chem. Soc.* 2014, **136**, 17750; (f) W. B. Zhang, F. Z. Li, J. X. Gong and Z. Yang, *Chem. – An Asian J.* 2015, **10**, 1874.

3 For syntheses of sculponeatin N, see: (a) B. J. Moritz, D. J. Mack, L. Tong and R. J. Thomson, *Angew. Chem., Int. Ed.* 2014, **53**, 2988; (b) Z. Pan, C. Zheng, H. Wang, Y. Chen, Y. Li, B. Cheng and H. Zhai, *Org. Lett.* 2014, **16**, 216.

4 For syntheses of other kaurane-derived members, see: (a) M. J. Kenny, L. N. Mander and S. P. Sethi, *Tetrahedron Lett.* 1986, **27**, 3923; (b) M. J. Kenny, L. N. Mander and S. P. Sethi, *Tetrahedron Lett.* 1986, **27**, 3927; (c) K. Mori, M. Nakahara and M. Matsui, *Tetrahedron Lett.* 1970, **11**, 2411; (d) K. Mori; Y. Nakahara and M. Matsui, *Tetrahedron* 1972, **28**, 3217; (e) F. E. Ziegler and J. A. Kloek, *Tetrahedron* 1977, **33**, 373; (f) B. B. Snider, J. Y. Kiselgof and B. M. Foxman, *J. Org. Chem.* 1998, **63**, 7945; (g) J. Y. Cha, J. T. S. Yeoman and S. E. Reisman, *J. Am. Chem. Soc.* 2011, **133**, 14964; (h) E. C. Cherney, J. C. Green and P. S. Baran, *Angew. Chem., Int. Ed.* 2013, **52**, 9019; (i) E. C. Cherney, J. M. Lopchuk, J. C. Green and P. S. Baran, *J. Am. Chem. Soc.* 2014, **136**, 12592; (j) K. E. Lazarski, B. J. Moritz and R. J. Thompson, *Angew. Chem., Int. Ed.* 2014, **53**, 10588; (k) J. T. S. Yeoman, J. Y. Cha, V. W. Mak and S. E. Reisman, *Tetrahedron* 2014, **70**, 4070; (l) L. Zhu, J. Luo and R. Hong, *Org. Lett.* 2014, **16**, 2162; (m) W. Liu, H. Li, P. J. Z. Cai, Z. Wang, Z. X. Yu and X. Lei, *Angew. Chem., Int. Ed.* 2016, **55**, 3112.

5 (a) W. S. Johnson and G. E. DuBois, *J. Am. Chem. Soc.* 1976, **98**, 1038; (b) M. B. Gravestock, W. S. Johnson, B. E. McCarry and B. E. Ratcliffe, *J. Am. Chem. Soc.* 1978, **100**, 4274; (c) H. Yamamoto, K. Ishihara and H. Ishibashi, *J. Am. Chem. Soc.* 2004, **126**, 11122 and references therein; (d) C. A. Mullen, M. A. Campbell and M. R. Gagne, *Angew. Chem., Int. Ed.* 2008, **47**, 6011; (e) K. Surendra and E. J. Corey, *J. Am. Chem. Soc.* 2009, **131**, 13928; (f) J. J. Topczewski, M. P. Callahan, J. D. Neighbors and D. F. Wiemer, *J. Am. Chem. Soc.* 2009, **131**, 14630; (g) Y. J. Zhao, B. Li, L. J. Serena Tan, Z. L. Shen and T. P. Loh, *J. Am. Chem. Soc.* 2010, **132**, 4274; (h) S. G. Sethofer, T. Mayer and F. D. Toste, *J. Am. Chem. Soc.* 2010, **132**, 8276; (i) S. Desjardins, J. A. Andrez and S. Canesi, *Org. Lett.* 2011, **13**, 3406.

6 (a) G. C. Hirst, T. O. Johnson and L. E. Overman, *J. Am. Chem. Soc.* 1993, **115**, 2992; (b) D. W. C. MacMillan and L. E.

Overman, *J. Am. Chem. Soc.* 1995, **117**, 10391; (c) L. E. Overman and L. D. Pennington, *Can. J. Chem.* 2000, **78**, 732; (d) A. D. Lebsack, L. E. Overman and R. J. Valentkovitch, *J. Am. Chem. Soc.* 2001, 123, 4851; (e) L. E. Overman, E. J. and Velthuisen, *J. Org. Chem.* 2006, **71**, 1581; (f) A. Armstrong, Y. Bhonoah and S. E. Shanahan, *J. Org. Chem.* 2007, **72**, 8019; (g) S. M. Canham, D. J. France and L. E. Overman, *J. Org. Chem.* 2013, **78**, 9.

7 (a) K. C. Guérard, A. Guerinot, C. Bouchard-Aubin, M. A. Ménard, M. Lepage, M. A. Beaulieu and Canesi, S. *J. Org. Chem.*, 2012, **77**, 2121; (b) G. Jacquemot and S. Canesi, *J. Org. Chem.*, 2012, **77**, 7588; (c) G. Jacquemot, M. A. Menard, C. L'Homme and S. Canesi, *Chem. Sci.,* 2013, **4**, 1287; (d) M. A. Beaulieu, X. Ottenwaelder and S. Canesi, S. *Chem. Eur. J.,* 2014, **20**, 7581; (e) C. L'Homme, M. A. Menard and S. Canesi, *J. Org. Chem.*, 2014, **79**, 848; (f) M. A. Beaulieu, K. C. Guérard, G. Maertens, C. Sabot and S. Canesi, *J. Org. Chem.* 2011, **76**, 9460; (g) G. Jacquemot, G. Maertens and S. Canesi, *Chem. Eur. J.*, 2015, **21**, 7713; (h) K. C. Guérard, V. Hamel, A. Guérinot, C. Bouchard-Aubin and S. Canesi, *Chem. Eur. J.*, 2015, **21**, 18068. (i) G. Maertens and S. Canesi, *Chem. Eur. J.* **2016**, 7090.

8 S. Desjardins, G. Maertens and S. Canesi, *Org. Lett.* 2014, 16, 4928.

9 W. Schwede, H. Kuenzer, L. A. Ter, B. Bader, R. Hillig, U. Moenning, A. Schmitz and D. Zopf, *Chem. Abstr.* 2006, **145**, 83325. Synthesis of compound **11** is described in the Supporting Information.

10 A. Yanagisawa, H. Nakashima, A. Ishiba and H. Yamamoto, *J. Am. Chem. Soc.* 1996, **118**, 4723.

11 See the Supporting Information for a synthesis of **13.**

12 N. Kurono, N. Nii, Y. Sakaguchi, M. Uemura and T. Ohkuma, *Angew. Chem., Int. Ed.* 2011, **50**, 5541.

13 D. G. Vanderlaan and M. A. Schwartz, *J. Org. Chem.* 1985, **50**, 743; (b) N. Lewis and P. Wallbank, *Synthesis* **1987**, 1103; (b) T. Wirth, Ed. *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. Top. Curr. Chem.,* 2003, 224; (c) M. A. Ciufolini, N. A.; Braun, S. Canesi, M. Ousmer, J. Chang and D. Chai, *Synthesis* 2007, **24**, 3759; (d) V. V. Zhdankin and P. J. Stang, *Chem. Rev.* 2008, **108**, 5299; (e) S. Quideau, M. A. Looney and L. Pouységu, *Org. Lett.* 1999, **1**, 1651; (f) B. A. Mendelsohna and M. A. Ciufolini, *Org. Lett*. 2009, **11**, 4736; (g) H. Liang and M. A. Ciufolini, *Chem. Eur. J.* 2010, ***16***, 13262; (h) M. Ousmer, N. A. Braun, C. Bavoux, M. Perrin and M. A. Ciufolini, *J. Am. Chem. Soc.* 2001, **123**, 7534; (i) S. Quideau, L. Pouységu, M. Oxoby and M. A. Looney, *Tetrahedron* 2001, **57**, 319; (j) L. F. Silva, F. A. Siqueira, E. C. Pedrozo, F. Y. M. Vieira and A. C. Doriguetto, *Org. Lett.* 2007, **9**, 1433; (k) A. Jean, J. Cantat, D. Bérard, D. Bouchu and S. Canesi, *Org. Lett.* 2007, **9**, 2553; (l) M. Peuchmaur, N. Saıdani, C. Botté, E. Maréchal, H. Vial and Y. S. Wong, *J. Med. Chem.* 2008, **51**, 4870. (m) J. Sperry, Y. C. Liu and M. A. Brimble *Org. Biomol. Chem.*, 2010, **8**, 29. (n) A. Yoshimura, V. and V. Zhdankin, *Chem. Rev.* 2016, **116**, 3328; (o) V. V. Zhdankin, Hypervalent Iodine Chemistry, Wiley, Chichester, 2013.

14 (a) T. Jen, B. A. Mendelsohn and M. A. Ciufolini, *J. Org. Chem.* 2011, **76**, 728; (b) S. Quideau, M. A. Looney and L. Pouységu, *J. Org Chem.* 1998, **63**, 9597; (c) A. Ozanne-Beaudenon and S. Quideau, *Angew. Chem., Int. Ed.* 2005, **44**, 7065; (d) L. Pouységu, S. Chassaing, D. Dejugnac, A. M. Lamidey, K. Miqueu, J. M. Sotiropoulos and S. Quideau, *Angew. Chem., Int. Ed.* 2008, **47**, 3552; (e) L. Pouységu, M. Marguerit, J. Gagnepain, G. Lyvinec, A. J. Eatherton and S. Quideau, *Org. Lett.* 2008, **10**, 5211; (f) B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh and M. A. Ciufolini, *Org. Lett.* 2009, **11**, 1539; (g) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Bufeteau, D. Cavagnat and A. Chenede, *Angew. Chem., Int. Ed.* 2009, **48**, 4605; (h) H. Liang and M. A. Ciufolini, *Tetrahedron* 2010, **66**, 5884; (i) L. Pouységu, T. Sylla, T. Garnier, L. B. Rojas, J. Charris, D. Deffieux and S. Quideau, *Tetrahedron* 2010, **66**, 5908; (j) B. T. Kelley, J. C. Walters and S. E. Wengryniuk, *Org. Lett*. 2016, **16**, 1896.

15 (a) C. Sabot, D. Bérard and S. Canesi, S. *Org. Lett*. 2008, **10**, 4629; (b) K. C. Guérard, C. Sabot, M. A. Beaulieu, M. A. Giroux and S. Canesi, *Tetrahedron* 2010, **66**, 5893; (c) L. Pouységu, D. Deffieux and S. Quideau, *Tetrahedron* 2010, **66**, 2235.

16 (a) Y. Tamura, T. Yakura, J. Haruta and Y. Kita, *J. Org. Chem.*, 1987, **52**, 3927; (b) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai and S. Oka, *J. Am. Chem. Soc.*, 1994, **116**, 3684; (c) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer and Y. Kita, *Angew. Chem., Int. Ed*., 2008, **47**, 3787; (d) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, **45**, 2073; (e) T. Dohi, M. Itob, N. Yamaokaa, K. Morimotoa, H. Fujiokab and Y. Kita, *Tetrahedron*, 2009, **65**, 10797; (f) T. Dohi, E. Mochizuki, D. Yamashita, K. Miyazaki and Y. Kita, *Heterocycles*, 2014, **88**, 245.

17 V. Voorhees and R. Adams, *J. Am. Chem. Soc.* 1922, **44**, 1397.

18 A comparison between the two spectra is provided in the supporting information.

19 G. D. Maio, L. M. Migneco, E. Vecchi and C. Iavarone, *Magn. Res. Chem.* 2000, **38**, 108.

20 (a) K. Mori and M. Waku, *Tetrahedron* 1985, **41**, 5653; (b) G. Aranda, M. Fetizon and N. Tayeb, *Tetrahedron* 1987, **43**, 4147.

21 C. Alberto, B. Giuseppe, F. Giorgio, F. Patrizia, G. Mauro, M. Giuseppe, T. Marco and C. Walter, WO2009047101(A1), 2009**.**