PAPER

Late-stage C−H amination of abietane diterpenoids†

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This study aims at highlighting the synthetic versatility of the rhodium-catalyzed C−H amination reactions using iodine(III) oxidants for the late-stage functionalization of natural products. Inter- and intramolecular nitrene insertions have been performed from various abietane diterpenoids, leading to the amination of the C-3, C-6, C-7, C-11 and C-15 positions. Ca. 20 aminated compounds have been isolated with yields of up to 86% and high levels of regio-, chemo- and stereoselectivities.

Introduction

Catalytic C–H functionalization has emerged in the last decade as a unique tool that opens new horizons in chemical synthesis with the aim to generate a greater molecular diversity and complexity.[1] The ability to perform site-selective reactions through the development of appropriate conditions and well-designed catalysts provides rapid access to unprecedented functionalized molecules. Of particular relevance, in this context, is the late-stage C–H functionalization of natural products and bioactive compounds. Such a simple transformation allows for the modification of sophisticated molecules in a single step thereby affording new products that would be difficult to access by application of classical organic reactions relying on the manipulation of existing functionalities.[2]

The late-stage C–H functionalization strategy can be useful when the introduction of a nitrogen functionality is considered in the course of a medicinal chemistry program. A nitrogen group can indeed deeply impact either the activity or the bioavailability of a pharmaceutical, a unique feature that makes this atom present in more than 80% of the drugs approved by the U.S. FDA.[3] The C–H amination reaction, therefore, offers unique opportunities to modify a bioactive natural product and fine tune its profile; particularly, it could afford

new compounds that nature cannot produce as no known enzyme is programmed to convert a C–H into a C–N bond.[4]

Significant achievements in C(sp^3)–H amination reactions have recently been reported by application of metal-catalyzed nitrene transfers.[5] Worth mentioning are the efficient protocols that have been uncovered by combining dirhodium(II) catalysis and iodine(III) oxidants.[6] Selective inter- and intramolecular processes have been reported under these conditions allowing the introduction of a nitrogen at specific sites. Thus, intermolecular reactions preferentially occur at secondary benzylic and allylic positions or non-activated tertiary centres, whereas intramolecular reactions lead to the selective amination of C–H bonds β- or γ- to the nitrene-donor functionality. Such a set of conditions, therefore, is appropriate to derivatize any natural product to a large number of nitrogen-containing scaffolds.

In this context, abietane diterpenoids of type **A** (Fig. 1) have appeared to us as a textbook case to apply dirhodium(II)-catalyzed C–H amination reactions for the formation of a library of diversely substituted amino compounds. These naturally occurring tricyclic diterpenoids isolated from terrestrial plant sources have been the purpose of several synthetic studies that have led to the formation of a wide range of compounds displaying either antimicrobial, antifungal, antiprotozoal, or anticancer activities, to name but a few.[7]

With the aim to increase the variety of accessible analogues, recent studies have demonstrated that catalytic C(sp^3)–H functionalization reactions can be successfully applied to dehydroabietic acid analogues (Fig. 1a). Amide-directed C(sp^3)–H activation, thus, allows the introduction of alkyl,[8a] amino,[8b] boryl,[8c] chloro,[8d] or aryl[8e] substituents selectively at the C-19 position. Two isolated examples of amination at the C-7 benzylic centre have also been reported following the application of intermolecular C(sp^3)–H amination.[9] In this communication, we, therefore, wish to present the results of

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A. Abietane skeleton

1a. Previous examples of C—H functionalization products derived from abietane diterpenoids

X: alkyl, NR^{1}R^2, BPin, Cl, aryl

1b. This work
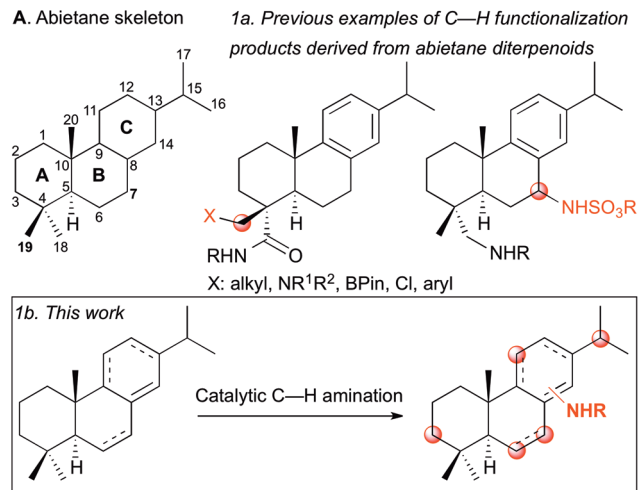
Catalytic C—H amination

Fig. 1 Background for the study.

our investigations on the application of catalytic nitrene transfers to various abietane derivatives that has led to the isolation of diversely substituted amino derivatives (Fig. 1b).

Results and discussion

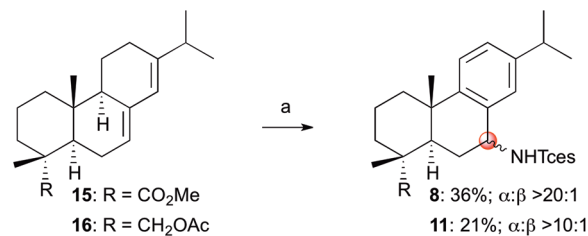### Catalytic intermolecular C(sp^3)–H amination reactions

We first investigated the application of catalytic intermolecular nitrene C(sp^3)–H insertions into various abietane derivatives (Scheme 1). All the reactions were developed under stoichiometric conditions with respect to the starting material. Substrates **1–5** are easily accessible from dehydroabietic acid, with compound **2** being prepared following a sequence of acylation–Baeyer–Villiger oxidation–saponification–methylation adapted from a synthesis of taiwaniaquinone F (see the ESI†).[10] Compounds **6–7** are directly obtained from podocarpic acid. We, then, performed the C(sp^3)–H amination reaction using the conditions previously reported by Du Bois.[11]

When applied to dehydroabietic acid derivatives **1–5**, the reaction selectively affords products resulting from the functionalization of the secondary benzylic C-7 centre. Very good yields in the 46–86% range are obtained with the α-isomer being preferentially formed, with α : β ratios around 4.5 : 1. Interestingly, starting from podocarpic acid derivatives **6** and **7**, the α-isomers **13** and **14** are exclusively isolated in 75% and 76% yields respectively. We propose to rationalize this excellent selectivity by the involvement of stereoelectronic factors. According to the dihedral angle with the adjacent aromatic ring, hyperconjugation could increase the reactivity of the α-C(sp^3)–H bond, favouring the insertion from the α-face. However, the lower selectivities observed with dehydroabietic acid substrates **1–5** might result from the increased steric hindrance provided by the C-18 substitution.

The same reaction conditions were applied to abietic acid derivatives **15** and **16** (Scheme 2). In both cases, we have isolated the same products as those obtained from the corres-
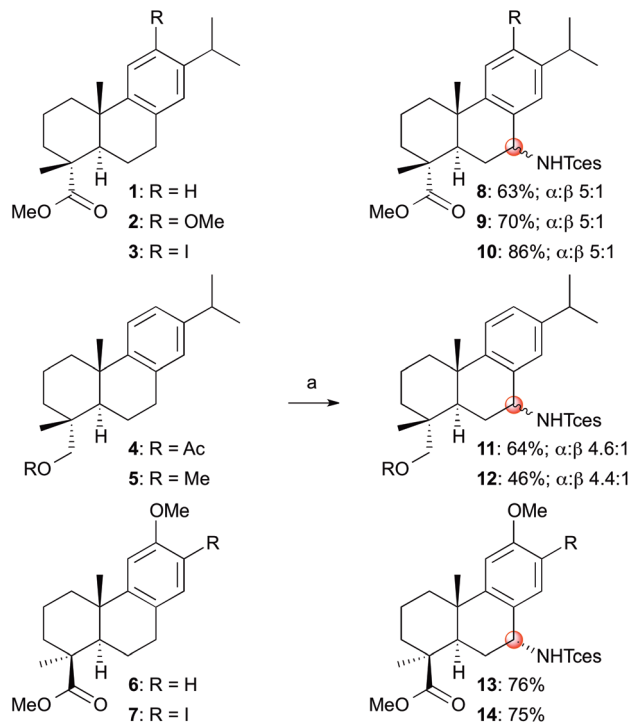

Scheme 1 Rhodium(ɪɪ)-catalyzed intermolecular C(sp^3)–H amination reaction of dehydroabietic acid and podocarpic acid derivatives. Reaction conditions: (a) Rh$_2$(esp)$_2$ 2 mol%, TcesNH$_2$ 1 equiv., PhI(OPiv)$_2$ 2 equiv., benzene, rt. Tces = 2,2,2-trichloroethoxysulfonyl.

Scheme 2 Rhodium(ɪɪ)-catalyzed intermolecular C(sp^3)–H amination reaction of abietic acid derivatives. Reaction conditions: (a) Rh$_2$(esp)$_2$ 2 mol%, TcesNH$_2$ 1 equiv., PhI(OPiv)$_2$ 2 equiv., benzene, rt.

ponding dehydroabietic acid analogues **1** and **4**, with higher selectivities in favour of the α-isomers but lower yields. These results are reminiscent of previous observations made in the total synthesis of hispidospermidin by Overman.[12] Accordingly, a possible mechanism for the formation of **8** and **11** from, respectively, **15** and **16** would involve an initial formal ene reaction followed by an aromatization of the resulting 1,3-cyclohexadiene intermediate.

Surprisingly, the application of our reported conditions for catalytic stereoselective C(sp^3)–H amination[13] led to totally different results (Scheme 3). While they proved unsuccessful from aromatic abietanes **1–6**, they afforded a single product arising from a C(sp^3)–H amination reaction at the allylic centre C-15 in the case of abietane substrates **15** and **16**. Such a switch in regioselectivity could be explained by steric
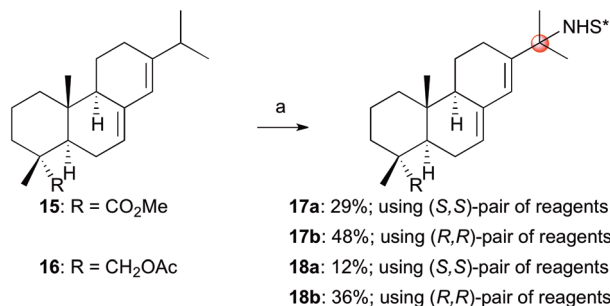
Scheme 3 Catalytic intermolecular C(sp^3)–H amination with sulfonimidamides. Reaction conditions: (a) Rh$_2$(S- or R-nta)$_4$ 3 mol%, S*NH$_2$ 1.2 equiv., PhI(OPiv)$_2$ 1.4 equiv., TCE : MeOH 3 : 1, −35 °C. S*: (S)- or (R)-(N-(p-toluenesulfonyl)-p-toluenesulfonimidoyl. TCE: 1,1,2,2-tetrachloroethane.

factors as the C-15 position is the more accessible reacting site for the sterically demanding sulfonimidamide-derived reagent. Matched and mismatched effects were also observed as higher yields are recorded by using the (R,R)-pair of reagent and catalyst.

Application of the catalytic intermolecular C(sp^3)–H amination to the synthesis of the fluorinated aminoabietane derivative 21

Increasing attention has been paid to the synthesis of fluorinated compounds as fluorine might strongly influence either the lipophilicity, the metabolic stability, or the conformation of a drug.[14] For example, the CF$_2$H group is now considered as a lipophilic H-bond donor acting as a bioisostere of a hydroxyl, thiol, or amide group.[14a] The growing impact of fluorine is demonstrated by its presence in nearly 30% of pharmaceuticals and agrochemicals, while it was absent in medicinal chemistry until 1957. This, combined with the aforementioned ubiquity of nitrogen, led us to plan the synthesis of the modified abietane diterpenoid 21 incorporating both nitrogen- and fluorine-containing functional groups (Scheme 4).

Starting from iodoarene 7, introduction of the ethyl difluoroacetate moiety proceeds efficiently via copper(0)-mediated coupling in DMSO.[15] After the selective saponification of the ethyl ester group, carboxylic acid 19 was isolated in 81% yield. A three-step sequence involving a Barton decarboxylation reaction,[16] then, affords the difluoromethyl derivative 20. Application of the rhodium(II)-catalyzed intermolecular C(sp^3)–H amination, finally, delivers the targeted molecule 21 with an excellent yield of 83%.[17] This transformation, to the best of our knowledge, highlights for the first time the compatibility of the C(sp^3)–H amination reaction with the presence of a CF$_2$H group. This is a significant result in our case because application of classical conditions for the introduction of the CF$_2$H group all proved unsuccessful in the presence of an amino function.[17]

Catalytic intramolecular C(sp^3)–H amination reactions

We, then, turned our attention to the use of intramolecular nitrene C(sp^3)–H insertions to increase the number of posi-
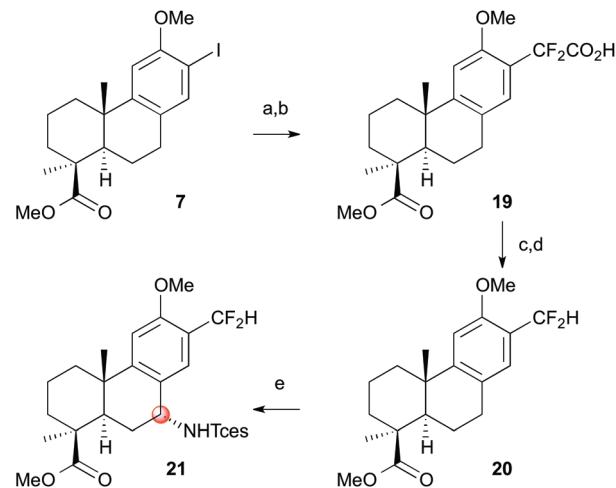

Scheme 4 Synthesis of the nitrogen- and fluorine-containing abietane derivative 21. Reaction conditions: (a) BrCF$_2$CO$_2$Et, Cu, DMSO, 60 °C, 15 h; (b) LiOH 1.25 M, THF, MeCN, rt, 2 h, 19 81% (2 steps); (c) oxalyl chloride, 10 mol% DMF, DCM, rt; (d) 2-mercaptopyridine N-oxide sodium salt, DMAP, n-Bu$_3$SnH, toluene, reflux, 2 h, 20 31% (3 steps); (e) Rh$_2$(esp)$_2$ 5 mol%, TcesNH$_2$ 1 equiv., PhI(OPiv)$_2$ 2 equiv., benzene, rt, 21 83%.

tions likely to be functionalized. The design of tethered reagents has indeed been shown to allow the modification of specific sites according to the nature of the nitrene donor.[18] To this end, sulfamates 22, 24, 26, 28, and 30[19] as well as carbamate 32 were easily prepared from abietic, dehydroabietic and podocarpic acids (Scheme 5).

Starting from sulfamate 22, the reaction delivers a single product resulting from the intramolecular C(sp^3)–H amination at the C-3 position. Compound 23 is isolated with a very good yield of 71% as a single stereoisomer arising from the selective functionalization of the axial C-3(sp^3)–H bond.[20] The same selectivity was observed from the unsaturated analogue 24 that leads to the tetracyclic derivative 25 though with a lower yield of 42%. The latter could be explained by the formation of aziridine 34 arising from a dimerization process as a result of the intermolecular alkene aziridination of the cyclic sulfamate 25 (Fig. 2). We propose that 1,3-diaxial interaction induced by the axial C-19 methyl substituent may prevent the reaction from proceeding at the equatorial C-3–H bond thereby explaining the selectivity observed for the amination of 22 and 24. The podocarpic acid-derived sulfamate 26, on the other hand, allows for the isolation of the analogous C-3 aminated compound 27 in 41% yield that arises from the amination from the β-face. Interestingly, products 23, 25, 27, and 34 are rare examples of abietane diterpenoid analogues functionalized at the A-ring.[7]

When the same reaction conditions were applied to the abietic acid derivative 28, a switch of regioselectivity was unexpectedly observed. Thus, the intramolecular C(sp^3)–H insertion takes place at the C-6 position delivering product 29 in 29% yield as a single isomer.[21] The latter is a rare example of a 7-membered ring obtained by intramolecular C(sp^3)–H amin-
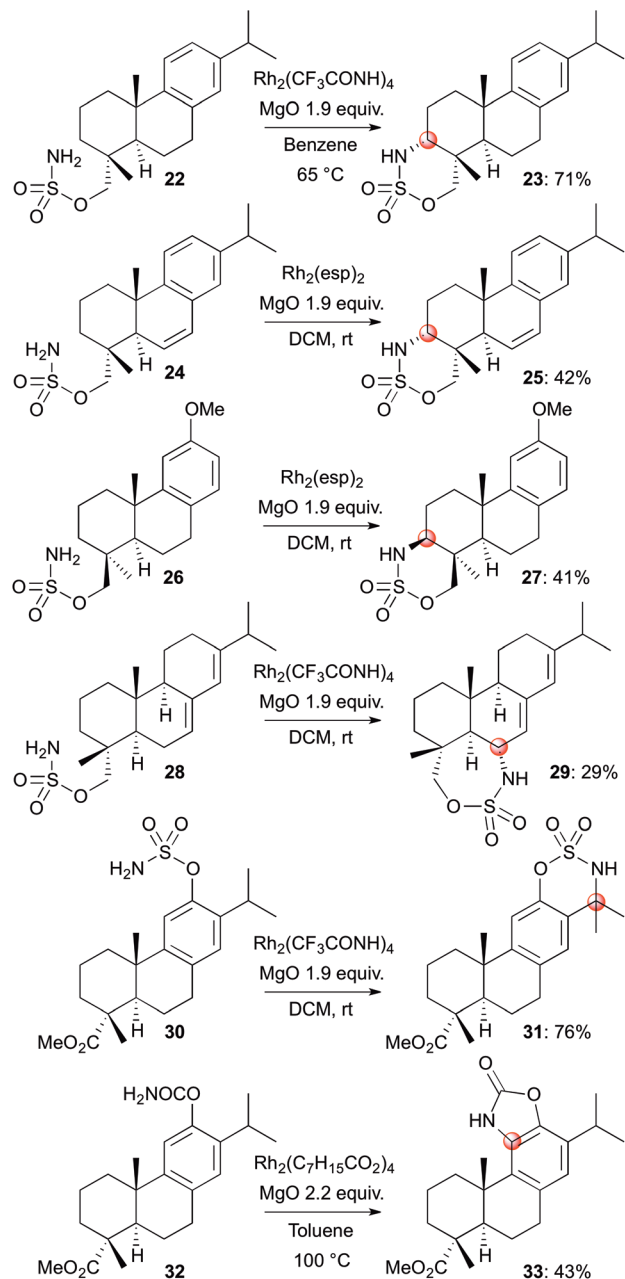
Scheme 5 Rhodium(II)-catalyzed intramolecular C(sp³)−H amination. Reaction conditions: Rh(II) complex 3 or 5 mol%, MgO, PhI(OAc)₂ 1.3 equiv.
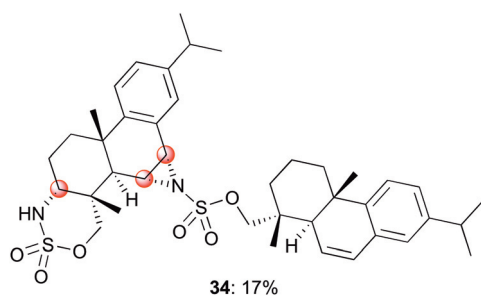

Fig. 2 Aziridine **34** resulting from a dimerization process from **24** according to an intramolecular C(sp³)−H amination followed by the intermolecular alkene aziridination.

ation,[22] the structure of which was corroborated by comparison between the NMR spectra of substrate **28** and the resulting product **29** (see the chemical shifts of H-7, C-3 and C-6 in the ESI†). The formation of the 7-membered cyclic sulfamate could be rationalized by the increased reactivity of the allylic C–H bond.

Additional intramolecular reactions have also been designed by capitalizing on the presence of the phenol ring in dehydroabietic acid derivatives. Classical reaction conditions applied to sulfamate **30**, therefore, allows for the amination of the tertiary benzylic position in 76% yield. More significantly, the use of carbamate **32** offers the opportunity to functionalize the aromatic C-ring, thereby enhancing the potential of this chemistry for late-stage amination. Following the recent protocol reported by Singh,[23] the rhodium-catalyzed electrophilic aromatic substitution, thus, proceeds at the *ortho* C(sp²)–H bond thereby leading to the functionalization of the C-11 site.[24]

Conclusions

In conclusion, we have demonstrated that the rhodium(II)-catalyzed C–H amination reaction with iodine(III) oxidants is a useful tool for the late-stage functionalization of natural compounds with the aim to produce new analogues. By application of inter- and intramolecular processes and/or screening different nitrene precursors and rhodium(II) complexes, we have been able to selectively introduce an amino functional group either at C-3, C-6, C-7, C-11 or C-15 positions of various abietane diterpenoids. *Ca*. 20 derivatives were, thus, isolated with yields ranging from 12% to 86%, but also with high levels of chemo-, regio- and stereoselectivities. Worth mentioning is the compatibility of the reaction conditions with the presence of a CF₂H group.

The difference in the regioselectivity observed between the various abietane derivatives highlights that the course of the nitrene insertion is controlled by the subtle balance of steric and stereoelectronic factors. Such a study, therefore, is likely to provide useful information with the aim to perform C(sp³)–H functionalization reactions with high levels of predictability. Work in that direction is in progress in our group through the application of catalytic nitrene transfers to other classes of natural products available at the ICSN.

Experimental

Melting points were measured in a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a PerkinElmer Spectrum BX FT-IR spectrometer and a Scientific Nicolet iS50 FT-IR. Specific rotation was measured on a PerkinElmer 343 polarimeter. Proton (¹H) and carbon (¹³C) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP-C13, P31, or Dual C13 probe), Fourier 300 MHz (Easy probe, ¹H and ¹³C standard 5 mm probe),

Avance 500 MHz (BBO-ATM probe or BBI-ATM probe), Avance II 500 MHz (BBO-ATM probe or BBI-ATM probe) and Avance Neo 500 (BBO-ATM probe or BBI-ATM probe). Fluorine (^{19}F) NMR were recorded on a Bruker Avance II spectrometer. Carbon (^{13}C) spectra were recorded at 126 or 75 MHz, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. NMR experiments were carried out in deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane (TMS) or residual solvent peaks as internal standards. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, sept: septet, m: multiplet, dd: doublet of doublets, dt: doublet of triplets, td: triplet of doublets, ddd: doublet of doublet of doublets, tdd: triplet of doublet of doublets, qt: quartet of triplets, tt: triplet of triplets, and br: broad. Coupling constants (J) are reported in hertz (Hz). Mass spectra were obtained with an LCT (Micromass) or with a Bruker MicroTOF-Q II instrument using electrospray ionization and from a time of flight analyzer for the high resolution mass spectra (HRMS). Thin layer chromatography was performed on silica gel 60 F254 on aluminium plates (Merck) and visualized under a UVP Mineralight UVLS-29 lamp (254 nm) and by staining with acidic solutions of vanillin in ethanol, *p*-anisaldehyde in ethanol, potassium permanganate or cerium molybdate. Flash chromatography was conducted on Merck silica gel 60 (40–63 μm) at medium pressure (300 mbar) or on puriFlash Spot II (Interchim) unless otherwise stated. All reagents were obtained from commercial suppliers unless otherwise stated. The rhodium catalysts $Rh_2(NHCOCF_3)_4$ and $Rh_2(S$- or R-nta)$_4$ were prepared according to the literature procedures from rhodium(II) acetate which was purchased from the Alfa Aesar company.[13,25] Sulfonimidamides were prepared following the previously published protocols.[13,26] Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. Organic extracts were dried over sodium sulfate (Na_2SO_4).

General procedure 1: Intermolecular C(sp^3)–H amination reaction with Rh$_2$(esp)$_2$ and TcesNH$_2$ (compounds 8–14 and 21)

A flask containing TcesNH$_2$ (137 mg, 0.600 mmol) and benzene (0.60 ml) was charged with $Rh_2(esp)_2$ (9.1 mg, 12 μmol) and substrate (0.600 mmol). To this bright green mixture was added a 0.83 M benzene solution of PhI(OPiv)$_2$ (1.40 ml, 1.20 mmol) *via* a syringe pump over 3 h. Following the transfer of the oxidant, the solution was stirred at 23 °C for 2–4 h. DCM (5 ml) and 2 ml of a saturated aqueous solution of thiourea were then added, and the orange biphasic mixture was stirred vigorously for 30 min. The contents were transferred to a separatory funnel, and the organic phase was collected. The aqueous layer was extracted with DCM (2 × 10 ml). The combined organic extracts were washed with a 0.1 M pH 7 Na_2HPO_4/NaH_2PO_4 buffer (2 × 10 ml), dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Purification of the isolated material by flash chromatography afforded the desired product.

General procedure 2: Intermolecular C(sp^3)–H amination with sulfonimidamides (compounds 17 and 18)

In an oven-dried tube were introduced activated 4 Å molecular sieves (100 mg), Rh$_2$[(S/R)-nta]$_4$ (7.7 mg, 6.0 μmol), (R/S)-N-(p-toluenesulfonyl)-p-toluenesulfonimidamide (77.9 mg, 0.240 mmol) and the substrate (0.200 mmol). The tube was capped with a rubber septum and purged with argon. Anhydrous and degassed 1,1,2,2-tetrachloroethane (0.75 ml) and methanol (0.25 ml) were added under argon. The tube was cooled to −78 °C, and PhI(OPiv)$_2$ (115 mg, 0.280 mmol) was added. The mixture was stirred at −35 °C for 3 days. After dilution with DCM (3 ml), the molecular sieves were removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The oily residue was purified by flash chromatography, affording the following C–H insertion products.

Methyl 7-(((2,2,2-trichloroethoxy)sulfonyl)amino)-8,11,13-abietatrien-18-oate (8)

8 was prepared following general procedure 1 starting from **1** (189 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 90 : 10), compound **8** (206 mg, 63%) was obtained as a white amorphous solid. Integration by ^{1}H NMR provides a ratio of 5 : 1 α : β isomers. The same compound was prepared as well starting from **15** (190 mg, 0.600 mmol). Purification affords **8** (114 mg, 36%). Integration by NMR provides a ratio of >20 : 1 α : β isomers.

NMR signals of the major isomer α: **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.30 (d, J = 1.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 5.48 (d, J = 8.1 Hz, 1H), 4.80–4.75 (m, 1H), 4.75 (d, J = 10.8 Hz, 1H), 4.69 (d, J = 10.8 Hz, 1H), 3.73 (s, 3H), 2.87 (sept, J = 6.9 Hz, 1H), 2.31 (dd, J = 12.6, 1.2 Hz, 1H), 2.34–2.26 (m, 1H), 2.12 (ddd, J = 14.1, 12.7, 4.9 Hz, 1H), 1.85–1.69 (m, 4H), 1.65 (td, J = 14.2, 13.5, 4.6 Hz, 1H), 1.43 (td, J = 13.0, 3.9 Hz, 1H), 1.28 (s, 3H), 1.23 (d, J = 6.9 Hz, 6H), 1.20 (s, 3H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 178.9, 147.3, 147.1, 132.8, 128.5, 127.1, 124.9, 93.9, 78.1, 54.2, 52.6, 47.1, 40.7, 38.0, 37.4, 36.9, 33.7, 29.2, 24.3, 24.1, 24.0, 18.6, 16.5. NMR signals of the minor isomer β that can be distinguished: **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.38 (d, J = 1.9 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.13 (dd, J = 8.3, 1.9 Hz, 1H), 4.92–4.82 (m, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.71 (d, J = 10.8 Hz, 1H), 3.67 (s, 3H), 1.92–1.83 (m, 2H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 178.4, 147.9, 147.2, 133.0, 126.5, 126.1, 124.8, 55.7, 52.3, 47.3, 37.3, 36.7, 33.8, 31.5, 25.6, 24.2, 18.5. **IR (ATR, neat):** ν = 3271, 2955, 2935, 1725, 1705, 1435, 1362, 1248, 1179, 1127, 1052, 980, 894, 748, 720 cm^{-1}. **HRMS ESI (+):** m/z [M + Na]$^+$ calcd for $C_{23}H_{32}Cl_3NNaO_5S^+$: 562.0959; found: 562.0959.

Methyl 7-(((2,2,2-trichloroethoxy)sulfonyl)amino)-12-methoxy-8,11,13-abietatrien-18-oate (9)

9 was prepared following general procedure 1 starting from **2** (207 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 85 : 15), product **9** (239 mg,

70%) was obtained as a white amorphous solid. Integration by ^{1}H NMR provides a ratio of 5 : 1 α : β isomers.

NMR signals of the major isomer α: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 (s, 1H), 6.67 (s, 1H), 5.37 (d, J = 7.8 Hz, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.76–4.69 (m, 1H), 4.69 (d, J = 10.8 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.22 (sept, J = 6.6 Hz, 1H), 2.33 (dd, J = 12.7, 1.3 Hz, 1H), 2.30–2.23 (m, 1H), 2.09 (ddd, J = 14.2, 12.7, 4.8 Hz, 1H), 1.85–1.71 (m, 4H), 1.67 (td, J = 13.3, 4.3 Hz, 1H), 1.47 (td, J = 13.2, 3.2 Hz, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 178.8, 157.3, 148.2, 136.2, 128.1, 124.7, 106.0, 93.9, 78.1, 55.5, 53.9, 52.6, 47.2, 40.7, 38.1, 37.7, 36.8, 29.2, 26.8, 24.3, 22.9, 22.6, 18.7, 16.5. NMR signals of the minor isomer β that can be distinguished: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30 (s, 1H), 6.68 (s, 1H), 4.86–4.79 (m, 1H), 3.67 (s, 3H), 3.28–3.19 (m, 1H), 1.29 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 178.4, 156.9, 148.9, 135.9, 125.8, 124.8, 106.1, 78.3, 55.6, 55.4, 53.8, 52.4, 47.3, 43.9, 37.6, 36.7, 31.6, 27.0, 25.5, 22.8, 22.7, 18.5. **IR (ATR, neat):** ν = 3260, 2951, 1703, 1502, 1435, 1361, 1249, 1178, 1046, 976, 957, 848, 749, 721 cm^{-1}. **HRMS ESI (+):** m/z [M + Na]$^+$ calcd for C$_{24}$H$_{34}$Cl$_3$NNaO$_6$S$^+$: 592.1065; found: 592.1042.

Methyl 7-(((2,2,2-trichloroethoxy)sulfonyl)amino)-12-iodo-8,11,13-abietatrien-18-oate (10)

10 was prepared following general procedure 1 starting from **3** (265 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 90 : 10), product **10** (345 mg, 86%) was obtained as a white amorphous solid. Integration by ^{1}H NMR gives a ratio of 5 : 1 α : β isomers.

NMR signals of the major isomer α: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (s, 1H), 7.31 (s, 1H), 5.67 (d, J = 8.1 Hz, 1H), 4.73 (d, J = 10.8 Hz, 1H), 4.75–4.70 (m, 1H), 4.68 (d, J = 10.8 Hz, 1H), 3.71 (s, 3H), 3.10 (sept, J = 6.7 Hz, 1H), 2.25 (br d, J = 12.6 Hz, 1H), 2.29–2.19 (m, 1H), 2.10 (ddd, J = 14.1, 12.7, 5.1 Hz, 1H), 1.91–1.65 (m, 4H), 1.60 (td, J = 13.2, 4.7 Hz, 1H), 1.42 (td, J = 13.1, 4.4 Hz, 1H), 1.27 (s, 3H), 1.22 (d, J = 6.7 Hz, 6H), 1.19 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 178.9, 149.1, 148.9, 136.1, 133.6, 128.0, 102.0, 93.8, 78.1, 53.6, 52.6, 46.9, 40.5, 37.9, 37.8, 37.4, 36.8, 29.0, 24.3, 23.2, 23.1, 18.5, 16.4. NMR signals of the minor isomer β that can be distinguished: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (s, 1H), 7.38 (s, 1H), 5.09 (d, J = 9.2 Hz, 1H), 4.84–4.75 (m, 1H), 3.67 (s, 3H), 3.11 (sept, J = 6.7 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 178.3, 149.9, 148.7, 136.0, 133.9, 125.6, 101.4, 93.6, 78.3, 55.3, 52.4, 47.2, 37.1, 36.6, 31.1, 25.6, 18.3, 16.5. **IR (ATR, neat):** ν = 3257, 2957, 2869, 1700, 1469, 1434, 1362, 1247, 1179, 977, 849, 752, 721 cm^{-1}. **HRMS ESI (−):** m/z [M + H]$^-$ calcd for C$_{23}$H$_{30}$Cl$_3$INO$_5$S$^-$: 663.9960; found: 663.9969.

7-(((2,2,2-Trichloroethoxy)sulfonyl)amino)-8,11,13-abietatrien-18-yl acetate (11)

11 was prepared following general procedure 1 from **4** (197 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 90 : 10), product **11** was obtained (213 mg, 64%) as a white amorphous solid.

Integration by NMR provides a ratio of 4.6 : 1 α : β isomers. The same compound was prepared as well starting from **16** (198 mg, 0.600 mmol). Purification affords **11** (71 mg, 21%). Integration by ^{1}H NMR provides a ratio of >10 : 1 α : β isomers.

NMR signals for the major isomer α: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 8.2, 2.0 Hz, 1H), 5.08 (d, J = 7.1 Hz, 1H), 4.83–4.77 (m, 1H), 4.73 (s, 2H), 3.97 (d, J = 11.3 Hz, 1H), 3.77 (d, J = 11.4 Hz, 1H), 2.87 (sept, J = 6.8 Hz, 1H), 2.33–2.26 (m, 1H), 2.25–2.19 (m, 1H), 2.06 (s, 3H), 1.99 (ddd, J = 14.1, 12.9, 4.7 Hz, 1H), 1.86 (dd, J = 12.9, 1.4 Hz, 1H), 1.88–1.65 (m, 2H), 1.53 (td, J = 13.5, 4.3 Hz, 1H), 1.45–1.32 (m, 2H), 1.23 (d, J = 7.0 Hz, 6H), 1.19 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.3, 147.7, 147.3, 132.2, 128.2, 127.3, 125.1, 93.9, 78.0, 71.4, 54.2, 39.2, 38.2, 37.8, 36.5, 35.2, 33.7, 26.2, 24.8, 24.2, 24.0, 21.1, 18.6, 17.8. NMR signals of the minor isomer β that can be distinguished: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 8.2, 2.1 Hz, 1H), 5.00–4.90 (m, 1H), 4.77 (d, J = 10.9 Hz, 1H), 4.74 (d, J = 10.9 Hz, 1H), 3.90 (d, J = 11.2 Hz, 1H), 3.75 (d, J = 11.2 Hz, 1H), 2.51–2.44 (m, 1H), 2.03 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.1, 147.1, 133.0, 126.5, 126.0, 124.9, 78.3, 72.0, 55.9, 43.2, 38.3, 36.7, 35.3, 33.8, 26.2, 25.9, 18.4, 17.6. **IR (ATR, neat):** ν = 2953, 2836, 1716, 1641, 1572, 1492, 1464, 1435, 1375, 1291, 1264, 1252, 1237, 1216, 1189, 1173, 1149, 1136, 1070, 1049, 973, 877, 802, 788, 773, 734, 771 cm^{-1}. **HRMS ESI (+):** m/z [M + NaMeCN]$^+$ calcd for C$_{26}$H$_{37}$Cl$_3$N$_2$NaO$_5$S$^+$: 617.1381; found: 617.1394.

7-(((2,2,2-Trichloroethoxy)sulfonyl)amino)-18-methoxyabieta-8,11,13-triene (12)

12 was prepared following general procedure 1 from **5** (180 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 90 : 10), compound **12** was obtained (145 mg, 46%) as a white amorphous solid. Integration by ^{1}H NMR provides a ratio of 4.4 : 1 α : β isomers.

NMR signals of the major isomer α: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, J = 2.1 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.13 (dd, J = 8.2, 2.0 Hz, 1H), 5.61 (d, J = 8.5 Hz, 1H), 4.75–4.71 (m, 1H), 4.69 (s, 2H), 3.38 (d, J = 9.2 Hz, 1H), 3.36 (s, 3H), 2.86 (sept, J = 6.9 Hz, 1H), 2.81 (d, J = 9.2 Hz, 1H), 2.27–2.20 (m, 1H), 2.12–2.01 (m, 1H), 1.99–1.92 (m, 1H), 1.91 (d, J = 12.6 Hz, 1H), 1.86–1.62 (m, 3H), 1.40–1.27 (m, 2H), 1.23 (d, J = 6.9 Hz, 6H), 1.19 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 147.7, 146.9, 133.0, 128.4, 126.8, 125.2, 93.9, 80.9, 78.1, 59.3, 54.7, 42.8, 39.1, 38.7, 37.9, 36.8, 35.5, 33.7, 26.0, 24.2 (1C + 1C), 24.0, 18.9, 18.0. NMR signals of the minor isomer β that can be distinguished: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.2, 2.0 Hz, 1H), 4.88–4.80 (m, 1H), 4.76 (d, J = 10.8 Hz, 1H), 3.30 (s, 3H), 3.21 (d, J = 9.2 Hz, 1H, 1H), 2.50–2.42 (m, 1H), 1.55 (td, J = 13.6, 4.3 Hz, 1H), 1.22 (d, J = 7.0 Hz, 6H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.4, 146.8, 133.1, 126.3, 125.8, 125.0, 81.9, 78.3, 59.4, 56.1, 42.8, 38.5, 37.7, 37.3, 35.4, 33.8, 28.7, 25.8, 18.7, 17.9. **IR (ATR, neat):** ν = 3322, 2961, 2929, 2865, 1447, 1418, 1363, 1177, 1102, 1088, 1023, 969, 874, 857, 837, 766, 753, 717 cm^{-1}. **HRMS ESI**

(−): *m/z* [M + H]⁻ calcd for C₂₃H₃₃Cl₃NO₄S⁻: 524.1201; found: 524.1215.

Methyl 7α-(((2,2,2-trichloroethoxy)sulfonyl)amino)-*O*-methyl-podocarpate (13)

13 was prepared following general procedure 1 starting from **6** (181 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 80 : 20), **13** was obtained (240 mg, 76%) as a white amorphous solid.

$[\alpha]_D^{20}$ = +77.6 (*c* = 1.00 in CHCl₃). **¹H NMR** (500 MHz, CDCl₃) δ 7.33 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.84 (d, *J* = 6.2 Hz, 1H), 4.83–4.79 (m, 1H), 4.74 (d, *J* = 10.6 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 2.63–2.57 (m, 1H), 2.38–2.30 (m, 1H), 2.26–2.17 (m, 2H), 1.98 (qt, *J* = 13.6, 3.5 Hz, 1H), 1.69 (dd, *J* = 13.0, 1.3 Hz, 1H), 1.70–1.62 (m, 1H), 1.37 (td, *J* = 13.3, 3.9 Hz, 1H), 1.31 (s, 3H), 1.13 (td, *J* = 13.6, 4.1 Hz, 1H), 0.98 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 177.6, 160.0, 150.6, 131.6, 124.7, 112.7, 111.2, 93.8, 78.1, 55.4, 54.2, 51.5, 46.5, 43.7, 39.2, 38.7, 37.6, 28.5, 27.8, 22.2, 19.9. **IR (ATR, neat):** ν = 3258, 2947, 2878, 2847, 1723, 1701, 1610, 1434, 1359, 1269, 1230, 1177, 1147, 1047, 980, 847, 752, 721 cm⁻¹. **HRMS ESI (+):** *m/z* [M + Na]⁺ calcd for C₂₁H₂₈Cl₃NNaO₆S⁺: 550.0595; found: 550.0597.

Methyl 7α-(((2,2,2-trichloroethoxy)sulfonyl)amino)-13-iodo-*O*-methylpodocarpate (14)

14 was prepared following general procedure 1 starting from **7** (257 mg, 0.600 mmol). After purification by flash chromatography (petroleum ether/EtOAc 80 : 20), compound **14** was obtained (295 mg, 75%) as a white amorphous solid.

$[\alpha]_D^{20}$ = +70.3 (*c* = 1.00 in CHCl₃). **¹H NMR** (500 MHz, CDCl₃) δ 7.82 (s, 1H), 6.68 (s, 1H), 4.88 (d, *J* = 6.4 Hz, 1H), 4.79–4.75 (m, 1H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.60–2.53 (m, 1H), 2.38–2.31 (m, 1H), 2.26–2.19 (m, 1H), 2.20 (ddd, *J* = 14.9, 13.1, 4.2 Hz, 1H), 1.99 (qt, *J* = 13.8, 3.6 Hz, 1H), 1.71–1.65 (m, 1H), 1.66 (dd, *J* = 12.9, 1.6 Hz, 1H), 1.37 (td, *J* = 13.3, 4.1 Hz, 1H), 1.31 (s, 3H), 1.13 (td, *J* = 13.6, 4.2 Hz, 1H), 0.98 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 177.5, 158.6, 151.0, 141.0, 126.8, 107.7, 93.7, 84.3, 78.1, 56.5, 53.6, 51.6, 46.3, 43.7, 39.2, 38.9, 37.5, 28.5, 27.9, 22.1, 19.8. **IR (ATR, neat):** ν = 3257, 2945, 2881, 2849, 1722, 1701, 1590, 1486, 1442, 1358, 1303, 1281, 1228, 1175, 1147, 1081, 1042, 980, 957, 846, 746, 721 cm⁻¹. **HRMS ESI (−):** *m/z* [M − H]⁻ calcd for C₂₁H₂₆Cl₃INO₆S⁻: 651.9596; found: 651.9643.

15-[*N*-(*S*)-(*p*-Toluenesulfonyl)-*p*-toluene-sulfonimidoyl]methyl-abietadien-18-oate (17a)

17a was prepared following general procedure 2 starting from **15** (63.3 mg, 0.200 mmol) and the (*S*,*S*) pair of reagents. After purification by flash chromatography (DCM/EtOAc 95 : 5), compound **17a** was obtained (37 mg, 29%) as a yellow amorphous solid.

$[\alpha]_D^{20}$ = +1.9 (*c* = 0.53 in CHCl₃). **¹H NMR** (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 9.1 Hz, 2H), 6.20 (s, 1H), 5.93–5.88

(m, 1H), 5.48–5.41 (m, 1H), 3.65 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.31–2.19 (m, 1H), 2.13–1.94 (m, 2H), 1.90–1.70 (m, 4H), 1.70–1.52 (m, 5H), 1.36 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.17–0.96 (m, 2H), 0.78 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 179.1, 144.4, 142.9, 140.6, 139.6, 138.1, 134.8, 129.6 (2C), 129.3 (2C), 128.1 (2C), 126.9 (2C), 126.3, 124.8, 61.3, 52.0, 50.5, 46.6, 45.1, 38.4, 37.4, 34.5, 27.8, 26.7, 26.0, 25.3, 22.2, 21.7 (1C + 1C), 18.2, 17.1, 14.1. **IR (ATR, neat):** ν = 3219, 2990, 2929, 2860, 1721, 1597, 1300, 1244, 1148, 1103, 1088, 1017, 975, 908, 812, 727 cm⁻¹. **HRMS ESI (+):** *m/z* [M + Na]⁺ calcd for C₃₅H₄₆N₂NaO₅S₂⁺: 661.2740; found: 661.2721.

15-[*N*-(*R*)-(*p*-Toluenesulfonyl)-*p*-toluene-sulfonimidoyl]methyl-abietadien-18-oate (17b)

17b was prepared following general procedure 2 starting from **15** (63.3 mg, 0.200 mmol) and the (*R*,*R*) pair of reagents. After purification by flash chromatography (DCM/EtOAc 95 : 5), compound **17b** was obtained (63 mg, 48%) as a yellow amorphous solid.

$[\alpha]_D^{20}$ = −70.0 (*c* = 1.00 in CHCl₃). **¹H NMR** (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.29 (s, 1H), 5.94–5.88 (m, 1H), 5.44–5.36 (m, 1H), 3.62 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H), 2.09–1.96 (m, 2H), 1.95–1.85 (m, 2H), 1.81–1.66 (m, 4H), 1.65–1.44 (m, 4H), 1.44 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.13–0.98 (m, 1H), 0.64 (s, 3H), 0.24–0.08 (m, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 179.0, 144.2, 142.9, 140.6, 137.8, 137.6, 134.6, 129.6 (2C), 129.3 (2C), 128.2 (2C), 127.3, 126.9 (2C), 124.7, 60.9, 52.0, 50.2, 46.6, 44.9, 38.3, 37.2, 34.4, 28.6, 27.1, 25.9, 25.7, 21.7 (1C + 1C), 21.4, 18.1, 17.1, 14.2. **IR (ATR, neat):** ν = 3219, 2948, 2928, 2875, 2836, 1720, 1598, 1433, 1380, 1300, 1250, 1147, 1107, 1087, 1067, 1016, 970, 906, 811, 726 cm⁻¹. **HRMS ESI (+):** *m/z* [M + Na]⁺ calcd for C₃₅H₄₆N₂NaO₅S₂⁺: 661.2740; found: 661.2756.

15-[*N*-(*S*)-(*p*-Toluenesulfonyl)-*p*-toluene-sulfonimidoyl]abietadien-18-yl acetate (18a)

18a was prepared following general procedure 2 starting from **16** (66.1 mg, 0.200 mmol) and the (*S*,*S*) pair of reagents. After purification by flash chromatography (DCM/EtOAc 95 : 5), compound **18a** was obtained (15 mg, 12%) as a yellow amorphous solid.

$[\alpha]_D^{20}$ = +8.0 (*c* = 0.34 in CHCl₃). **¹H NMR** (500 MHz, CDCl₃) δ 7.82 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.20 (s, 1H), 5.95–5.91 (m, 1H), 5.50–5.46 (m, 1H), 3.81 (d, *J* = 10.9 Hz, 1H), 3.68 (d, *J* = 11.0 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 2.28–2.21 (m, 1H), 2.06 (s, 3H), 2.09–1.95 (m, 2H), 1.87–1.79 (m, 1H), 1.79–1.70 (m, 2H), 1.69–1.62 (m, 1H), 1.62–1.52 (m, 2H), 1.49 (dd, *J* = 11.7, 5.3 Hz, 1H), 1.46–1.32 (m, 2H), 1.37 (s, 3H), 1.24 (s, 3H), 1.15–1.05 (m, 1H), 1.01–0.92 (m, 1H), 0.94 (s, 3H), 0.79 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 171.4, 144.4, 142.9, 140.6, 139.9, 138.2, 134.7, 129.6 (2C), 129.3 (2C), 128.0 (2C), 126.9 (2C), 126.2, 125.0, 72.8, 61.5, 50.3, 44.3, 38.8, 36.4, 36.3, 34.7, 27.5, 26.6, 25.3, 24.3, 22.5, 21.8, 21.7, 21.2, 18.1, 17.9, 14.2. **IR (ATR, neat):** ν = 3231, 2924, 2849, 1733, 1598, 1451, 1379, 1299, 1238,

1150, 1105, 1069, 1034, 976, 812, 749, 702 cm^{-1}. **HRMS ESI (+):** m/z [M + Na]$^+$ calcd for C$_{36}$H$_{48}$N$_2$NaO$_5$S$_2^+$:675.2897; found: 675.2918.

15-[N-(R)-(p-Toluenesulfonyl)-p-toluene-sulfonimidoyl]abietadien-18-yl acetate (18b)

18b was prepared following general procedure 2 starting from **16** (66.1 mg, 0.200 mmol) and the (R,R) pair of reagents. After purification by flash chromatography (DCM/EtOAc 95 : 5), compound **18b** was obtained (47 mg, 36%) as a yellow amorphous solid.

[α]$_D^{20}$ = −22.5 (c = 1.00 in CHCl$_3$). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 6.29 (s, 1H), 5.96–5.88 (m, 1H), 5.49–5.40 (m, 1H), 3.79 (d, J = 10.8 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 2.41 (s, 3H), 2.38 (s, 3H), 2.04 (s, 3H), 2.06–1.96 (m, 2H), 1.96–1.85 (m, 2H), 1.78–1.61 (m, 2H), 1.60–1.35 (m, 6H), 1.44 (s, 3H), 1.33 (s, 3H), 0.92 (s, 3H), 1.00–0.79 (m, 1H), 0.64 (s, 3H), 0.22–0.05 (m, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 171.4, 144.2, 143.0, 140.6, 138.0, 137.7, 134.5, 129.6 (2C), 129.3 (2C), 128.2 (2C), 127.2, 126.9 (2C), 125.0, 72.7, 61.0, 50.0, 44.1, 38.8, 36.4, 36.2, 34.6, 28.5, 27.1, 25.7, 24.2, 21.7 (1C + 1C), 21.6, 21.2, 18.1, 17.9, 14.3. **IR (ATR, neat):** ν = 3237, 2927, 1733, 1597, 1447, 1432, 1380, 1299, 1240, 1149, 1089, 1067, 1033, 976, 908, 812, 729, 697 cm^{-1}. **HRMS ESI (+):** m/z [M + Na]$^+$ calcd for C$_{36}$H$_{48}$N$_2$NaO$_5$S$_2^+$: 675.2897; found: 675.2896.

Methyl 7α-(((2,2,2-trichloroethoxy)sulfonyl)amino)-13-difluoromethyl-O-methylpodocarpate (21)

21 was prepared following general procedure 1 starting from **20** (106 mg, 0.300 mmol), TcesNH$_2$ (68.5 mg, 0.300 mmol), Rh$_2$(esp)$_2$ (11.4 mg, 15.0 μmol) and PhI(OPiv)$_2$ (244 mg, 0.600 mmol). The oxidant was added over 1.5 h. After purification by flash chromatography (petroleum ether/EtOAc 85 : 15), the desired compound was obtained as a white amorphous solid (109 mg, 83%).

[α]$_D^{20}$ = +84.8 (c = 1.00 in CHCl$_3$). **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.59 (br s, 1H), 6.86 (t, J = 55.5 Hz, 1H), 6.81 (br s, 1H), 4.96–4.91 (m, 1H), 4.85–4.80 (m, 1H), 4.74 (d, J = 10.9 Hz, 1H), 4.72 (d, J = 10.9 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.66–2.60 (m, 1H), 2.37–2.31 (m, 1H), 2.27–2.21 (m, 1H), 2.20 (ddd, J = 14.9, 13.1, 4.0 Hz, 1H), 1.99 (qt, J = 14.0, 3.7 Hz, 1H), 1.70 (dd, J = 13.0, 1.6 Hz, 1H), 1.72–1.64 (m, 1H), 1.38 (td, J = 13.3, 4.0 Hz, 1H), 1.32 (s, 3H), 1.14 (td, J = 13.6, 4.2 Hz, 1H), 0.99 (s, 3H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 177.5 (s), 157.6 (t, J = 5.5 Hz), 153.4 (d, J = 1.9 Hz), 128.5 (t, J = 5.6 Hz), 124.7 (s), 122.0 (t, J = 22.5 Hz), 111.3 (t, J = 236.0 Hz), 107.9 (s), 93.7 (s), 78.1 (s), 55.8 (s), 54.0 (s), 51.6 (s), 46.2 (s), 43.7 (s), 39.3 (s), 39.1 (s), 37.5 (s), 28.4 (s), 27.8 (s), 22.1 (s), 19.8 (s). **^{19}F NMR** (471 MHz, CDCl$_3$) δ −114.5 (d, J = 299.0 Hz), −116.0 (d, J = 299.0 Hz). **IR (ATR, neat):** ν = 3284, 3107, 2955, 2853, 1728, 1702, 1514, 1469, 1432, 1349, 1266, 1228, 1179, 1153, 1179, 1076, 1047, 1018, 965, 853, 843, 755, 144, 122, 634, 530 cm^{-1}. **HRMS ESI(+):** m/z [M + Na]$^+$ calcd for C$_{22}$H$_{28}$Cl$_3$F$_2$NNaO$_6$S$^+$: 600.0563, found: 600.0569.

(4aS,4bR,10bS,12aR)-8-Isopropyl-4a,10b-dimethyl-1,4,4a,4b,5,6,10b,11,12,12a-decahydrophenanthro-[2,1-d][1,2,3]oxathiazine 2,2-dioxide (23)

Sulfamate **22** (76.0 mg, 0.208 mmol), Rh$_2$(CF$_3$CONH)$_4$ (3.8 mg, 6.0 μmol) and MgO (15.3 mg, 0.380 mmol) were charged in a sealed tube under an argon atmosphere. Anhydrous benzene (1.0 ml) was then added, followed by PhI(OAc)$_2$ (83.7 mg, 0.260 mmol). The reaction mixture was stirred at 65 °C for 16 h, filtered through a pad of Celite and washed with EtOAc. After concentration under reduced pressure, the brown residue was purified by flash chromatography (petroleum ether/EtOAc 90 : 10) to afford **23** (54 mg, 71%) as a white amorphous solid.

[α]$_D^{20}$ = +11.3 (c = 1.00 in CHCl$_3$). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.13 (d, J = 8.2 Hz, 1H), 7.03 (dd, J = 8.2, 1.9 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 4.33 (d, J = 9.7 Hz, 1H), 4.22 (d, J = 12.6 Hz, 1H), 3.68 (dt, J = 9.6, 3.3 Hz, 1H), 3.03–2.93 (m, 2H), 2.84 (sept, J = 6.9 Hz, 1H), 2.32–2.15 (m, 2H), 2.13 (dd, J = 11.4, 3.2 Hz, 1H), 1.91–1.69 (m, 3H), 1.59 (td, J = 15.3, 3.7 Hz, 1H), 1.27 (s, 3H), 1.23 (d, J = 7.0 Hz, 6H), 0.95 (s, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 146.6, 145.8, 134.3, 127.1, 124.4, 123.9, 77.6, 59.6, 37.1, 36.6, 34.5, 33.6, 31.5, 29.5, 25.6, 24.1 (1C + 1C), 23.1, 18.2, 16.6. **IR (ATR, neat):** ν = 3288, 2957, 2869, 1498, 1563, 1413, 1356, 1173, 1054, 993, 972, 928, 884, 821, 781, 710, 664 cm^{-1}. **HRMS ESI (+):** m/z [M + H]$^+$ calcd for C$_{20}$H$_{30}$NO$_3$S$^+$: 364.1941; found: 364.1950.

(4aS,4bR,10bS,12aR)-8-Isopropyl-4a,10b-dimethyl-1,4,4a,4b,10b,11,12,12a-octahydrophenanthro[2,1-d][1,2,3]-oxathiazine 2,2-dioxide (25) and aziridine (34)

Sulfamate **24** (218 mg, 0.600 mmol), Rh$_2$(esp)$_2$ (13.6 mg, 18.0 μmmol) and MgO (45.9 mg, 1.14 mmol) were charged in a sealed tube under an argon atmosphere. Then anhydrous DCM (3.0 ml) was added and the mixture was cooled to 0 °C with an ice bath before adding PhI(OAc)$_2$ (251 mg, 0.780 mmol). The reaction mixture was stirred at r.t. for 16 h, filtered through a pad of Celite and washed with EtOAc. After concentration under reduced pressure, the brown residue was purified by flash chromatography (petroleum ether/EtOAc 90 : 10 to 80 : 20) to afford **25** (92 mg, 42%) as a white amorphous solid and **34** (74 mg, 17%) as a yellow amorphous solid.

Compound 25. [α]$_D^{20}$ = −72.0 (c = 1.00 in CHCl$_3$). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.12 (dd, J = 8.0, 1.6 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.67 (dd, J = 9.6, 3.1 Hz, 1H), 5.78 (dd, J = 9.6, 2.8 Hz, 1H), 4.42 (d, J = 9.4 Hz, 1H), 4.35 (d, J = 12.4 Hz, 1H), 4.27 (d, J = 12.4 Hz, 1H), 3.71 (dt, J = 9.5, 3.2 Hz, 1H), 2.96–2.79 (m, 2H), 2.24 (tt, J = 16.6, 4.3 Hz, 1H), 2.16–2.06 (m, 1H), 1.84 (td, J = 13.0, 3.8 Hz, 1H), 1.90–1.75 (m, 1H), 1.25 (d, J = 7.0 Hz, 6H), 1.11 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 147.1, 144.2, 132.3, 130.5, 126.5, 125.8, 125.1, 121.7, 77.1, 59.1, 38.0, 37.4, 33.8, 33.5, 28.8, 24.1 (1C + 1C), 23.0, 21.0, 17.6. **IR (ATR, neat):** ν = 3306, 2962, 2942, 2925, 2868, 1469, 1442, 1420, 1362, 1188, 1050, 1025, 994, 969, 927, 891, 823, 787, 775 cm^{-1}. **HRMS ESI (+):** m/z [M + H]$^+$ calcd for C$_{20}$H$_{28}$NO$_3$s$^+$: 362.1784; found: 362.1783.

Compound 34. ^{1}**H NMR** (500 MHz, CDCl$_3$) δ 7.36 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.1, 2.0 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.7 Hz, 1H), 6.90 (d, J = 1.7 Hz, 1H), 6.55 (dd, J = 9.6, 3.0 Hz, 1H), 5.91 (dd, J = 9.6, 2.6 Hz, 1H), 4.55 (d, J = 12.5 Hz, 1H), 4.38 (d, J = 12.5 Hz, 1H), 4.22–4.16 (m, 2H), 4.11 (d, J = 9.5 Hz, 1H), 3.85 (d, J = 7.4 Hz, 1H), 3.79–3.73 (m, 1H), 3.18 (dd, J = 7.6, 6.1 Hz, 1H), 2.93 (sept, J = 6.9 Hz, 1H), 2.85 (sept, J = 7.0 Hz, 1H), 2.40 (t, J = 2.9 Hz, 1H), 2.28–2.14 (m, 2H), 2.21 (d, J = 6.4 Hz, 1H), 2.12–2.05 (m, 1H), 1.85–1.73 (m, 4H), 1.70–1.54 (m, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.28 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 148.0, 147.1, 146.4, 145.3, 132.6, 129.1, 129.0, 127.9, 127.8 (1C + 1C), 125.9, 124.8, 122.8, 121.8, 81.2, 77.8, 58.9, 45.5, 40.3, 40.2, 39.6, 37.6, 37.0, 36.8, 35.5, 34.7, 34.1, 33.8, 33.7, 29.5, 26.0, 24.2, 24.1 (1C + 1C), 23.9, 22.7, 20.9, 18.2, 17.8, 17.2. **IR (ATR neat):** ν = 2559, 2932, 2869, 2097, 1682, 1462, 1444, 1359, 1177, 994, 974, 909, 858, 828, 773, 718 cm^{-1}. **HRMS ESI (−):** m/z [M + H]$^-$ calcd for C$_{40}$H$_{53}$N$_2$O$_6$S$_2^-$: 721.3350; found: 721.3310.

(4a*R*,4b*R*,10b*S*,12a*S*)-9-Methoxy-4a,10b-dimethyl-1,4,4a,4b,5,6,10b,11,12,12a-decahydrophenanthro-[2,1-*d*][1,2,3]oxathiazine 2,2-dioxide (27)

Sulfamate **26** (70.7 mg, 0.200 mmol), Rh$_2$(esp)$_2$ (4.6 mg, 6.0 μmol) and MgO (15.3 mg, 0.380 mmol) were charged in a sealed tube under an argon atmosphere. Anhydrous DCM (1.0 ml) was then added, followed by PhI(OAc)$_2$ (83.7 mg, 0.260 mmol). The reaction mixture was stirred at r.t. for 16 h, filtered through a pad of Celite and washed with EtOAc. After concentration under reduced pressure, the brown residue was purified by flash chromatography (petroleum ether/EtOAc 85 : 15) to afford compound **27** (29 mg, 41%) as a white solid.

M.p.: Decomposition at 265 °C. $[\alpha]_D^{20}$ = +2.9 (c = 0.75 in CHCl$_3$). ^{1}**H NMR** (500 MHz, CDCl$_3$) δ 6.97 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.6 Hz, 1H), 6.70 (dd, J = 8.4, 2.6 Hz, 1H), 5.17 (d, J = 11.7 Hz, 1H), 4.87 (d, J = 5.9 Hz, 1H), 4.10 (dd, J = 11.8, 2.2 Hz, 1H), 3.78 (s, 3H), 3.06–2.99 (m, 1H), 2.98–2.91 (m, 1H), 2.88–2.78 (m, 1H), 2.76 (qd, J = 13.9, 3.4 Hz, 1H), 2.42 (dt, J = 13.3, 3.6 Hz, 1H), 2.08–1.94 (m, 2H), 1.71–1.60 (m, 1H), 1.59 (d, J = 13.0 Hz, 1H), 1.51 (td, J = 13.7, 3.6 Hz, 1H), 1.42 (s, 3H), 1.28 (s, 3H). ^{13}**C NMR** (126 MHz, CDCl$_3$) δ 158.1, 149.0, 130.1, 126.3, 111.7, 110.1, 75.2, 64.1, 55.5, 49.8, 37.5, 37.0, 36.1, 29.5, 25.5, 24.7, 24.3, 19.0. **IR (ATR, neat):** ν = 3349, 3318, 3254, 2985, 2951, 2916, 2162, 1607, 1575, 1503, 1434, 1357, 1251, 1185, 1039, 973, 928, 833, 760, 552, 540, 532 cm^{-1}. **HRMS ESI (+):** m/z [M + Na]$^+$ calcd for C$_{18}$H$_{25}$NNaO$_4$S$^+$: 374.1396; found: 374.1392.

(3a*R*,3a1*R*,7a*S*,12a*R*,12b*R*)-10-Isopropyl-3a,12b-dimethyl-2,3,3a,3a1,7,7a,11,12,12a,12b-decahydro-1*H*,4*H*-phenanthro-[10,1-*de*][1,2,3]oxathiazepine 6,6-dioxide (29)

Compound **28** (147 mg, 0.400 mmol), Rh$_2$(CF$_3$CONH)$_4$ (7.6 mg, 12 μmol) and MgO (30.6 mg, 0.760 mmol) were charged in a round bottom flask under an argon atmosphere. Then anhydrous DCM (2.4 ml) was added and the mixture was

cooled to 0 °C with an ice bath before adding PhI(OAc)$_2$ (168 mg, 0.520 mmol). The mixture was stirred at r.t. for 19 h (until the disappearance of the starting material by TLC), filtered through a pad of Celite and washed with EtOAc. After concentration under reduced pressure, the brown residue was purified by flash chromatography (petroleum ether/EtOAc 85 : 15) to afford **29** (42 mg, 29%) as a slightly yellow solid.

M.p.: 123–125 °C. $[\alpha]_D^{20}$ = −40.0 (c = 1.00 in CHCl$_3$). ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 5.78 (s, 1H), 5.25 (t, J = 2.7 Hz, 1H, H-7), 4.39 (d, J = 10.3 Hz, 1H), 4.12 (d, J = 12.1 Hz, 1H), 4.14–4.02 (m, 1H, H-6), 3.61 (d, J = 12.2 Hz, 1H), 2.26 (sept, J = 6.8 Hz, 1H), 2.18–1.97 (m, 2H), 1.94–1.74 (m, 4H), 1.74–1.55 (m, 1H), 1.37 (d, J = 10.0 Hz, 1H), 1.37–1.28 (m, 1H), 1.25 (s, 3H), 1.32–1.18 (m, 1H), 1.17–1.06 (m, 2H), 1.03 (d, J = 6.7 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.85 (s, 3H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 149.8, 138.9, 121.5, 118.7, 82.3, 60.3, 50.8 (C-6), 49.4, 38.6, 38.3, 37.8, 35.4 (C-3), 35.2, 27.2, 22.0, 21.3, 20.8, 18.2, 17.7, 14.0. **IR (ATR, neat):** ν = 3828, 2921, 2851, 1712, 1655, 1446, 1424, 1338, 1178, 1036, 971, 951, 931, 890, 850, 779 cm^{-1}. **HRMS ESI(+):** m/z [M + H]$^+$ calcd for C$_{20}$H$_{32}$NO$_3$S$^+$: 366.2097; found: 366.2097.

Methyl(4*R*,4a*R*,12b*S*)-4,8,8,12b-tetramethyl-1,2,3,4,4a,5,6,8,9,12b-decahydrophenanthro[2,3-][1,2,3]-oxathiazine-4-carboxylate 10,10-dioxide (31)

Compound **30** (80.0 mg, 0.195 mmol), Rh$_2$(CF$_3$CONH)$_4$ (3.8 mg, 5.9 μmol), and MgO (14.9 mg, 0.371 mmol) were charged in a round bottom flask under an argon atmosphere. Then anhydrous DCM (2.4 ml) was added and the mixture was cooled to 0 °C with an ice bath before adding PhI(OAc)$_2$ (81.7 mg, 0.254 mmol). The mixture was stirred at r.t. until the disappearance of the starting material by TLC, filtered through a pad of Celite and washed with EtOAc. After concentration under reduced pressure, the brown residue was purified by flash chromatography (petroleum ether/EtOAc 85 : 15) to afford **31** (62 mg, 76%) as a slightly pink solid.

M.p.: Decomposition at 230 °C. $[\alpha]_D^{20}$ = +49.5 (c = 0.92 in CHCl$_3$). ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 6.86 (s, 1H), 6.85 (s, 1H), 4.55 (s, 1H), 3.67 (s, 3H), 2.92–2.81 (m, 2H), 2.26–2.16 (m, 1H), 2.17 (dd, J = 12.3, 2.1 Hz, 1H), 1.92–1.62 (m, 5H), 1.69 (s, 3H), 1.68 (s, 3H), 1.47 (td, J = 12.3, 4.7 Hz, 1H), 1.49–1.38 (m, 1H), 1.27 (s, 3H), 1.20 (s, 3H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 179.0, 151.4, 147.7, 132.8, 126.7, 125.1, 114.8, 60.1, 52.2, 47.6, 44.5, 37.9, 37.4, 36.7, 31.0, 30.9, 29.4, 25.0, 21.5, 18.5, 16.7. **IR (ATR, neat):** ν = 3219, 2999, 2940, 2926, 2873, 2846, 1694, 1496, 1437, 1401, 1384, 1358, 1254, 1155, 1110, 1020, 991, 905, 853, 845, 756 cm^{-1}. **HRMS ESI (+):** m/z [M + H]$^+$ calcd for C$_{21}$H$_{30}$NO$_5$S$^+$: 408.1839; found: 408.1851.

Methyl(7a*R*,8*R*,11a*S*)-4-isopropyl-8,11a-dimethyl-2-oxo-1,2,6,7,7a,8,9,10,11,11a-decahydrophenanthro[4,3-*d*]oxazole-8-carboxylate (33)

In a sealed tube equipped with a magnetic bar under an argon atmosphere, carbamate **32** was added (224 mg, 0.600 mmol) followed by MgO (53.2 mg, 1.32 mmol), PhI(OAc)$_2$ (251 mg, 0.780 mmol), 4 Å MS (200 wt%), and Rh$_2$(octanoate)$_4$ (23.4 mg,

30.0 μmol) and anhydrous toluene (4.0 ml). The reaction vessel was sealed and was stirred at 100 °C until the disappearance of the starting material (12 h). The reaction mixture was then filtered through a pad of Celite and the residue obtained after the concentration under reduced pressure was dissolved in DCM and 5 ml of a saturated solution of thiourea were added. The orange biphasic mixture was stirred vigorously for 30 min. The content was transferred to a separatory funnel, and the organic phase was collected. The aqueous layer was extracted with DCM (2 × 15 ml). The combined organic extracts were washed with brine (2 × 15 ml), dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Purification of the isolated material by flash chromatography (petroleum ether/EtOAc 8 : 2) afforded the desired product (95 mg, 43% yield) as a pale yellow solid.

M.p.: Decomposition at 241 °C. $[\alpha]_D^{20}$ = +99.4 (c = 1.00 in $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.68 (s, 1H), 3.69 (s, 3H), 3.18 (sept, J = 6.9 Hz, 1H), 2.95 (ddd, J = 16.4, 12.0, 6.3 Hz, 1H), 2.86 (ddd, J = 16.8, 6.2, 1.4 Hz, 1H), 2.43–2.36 (m, 1H), 2.27 (dd, J = 12.2, 1.8 Hz, 1H), 1.93–1.84 (m, 1H), 1.81 (td, J = 12.6, 3.3 Hz, 1H), 1.81–1.70 (m, 2H), 1.70–1.64 (m, 1H), 1.58 (td, J = 12.6, 3.5 Hz, 1H), 1.43–1.37 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.0, 156.3, 140.3, 131.9, 130.2, 129.1, 125.7, 121.2, 52.2, 48.0, 46.3, 37.8, 36.9, 36.3, 31.5, 28.3, 22.6, 22.4, 22.0, 21.8, 18.5, 16.8. **IR (ATR, neat):** ν = 3248, 3228, 2964, 2945, 2929, 2875, 1745, 1731, 1716, 1637, 1590, 1430, 1414, 1386, 1332, 1247, 1206, 1175, 1134, 1113, 1084, 1053, 936, 882, 813, 792, 762, 727 cm^{-1}. **HRMS ESI (+):** m/z $[M + H]^+$ calcd for $C_{22}H_{30}NO_4^+$: 372.2169; found: 372.2168.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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20 Use of Rh$_2$(esp)$_2$ as the catalyst proved less efficient as **23** was isolated only in 52% yield. In the presence of Rh$_2$(OAc)$_4$, the yield drops to 45%.

21 The Rh$_2$(esp)$_2$ complex, again, does not allow for the improvement of the result as **29**, in this case, was isolated in 17% yield.

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