Diastereoselective Intramolecular Heck Reaction Assisted by an Acetate Group: Synthesis of the Decahydrobenzofluorene Derivative Dasyscyphin E

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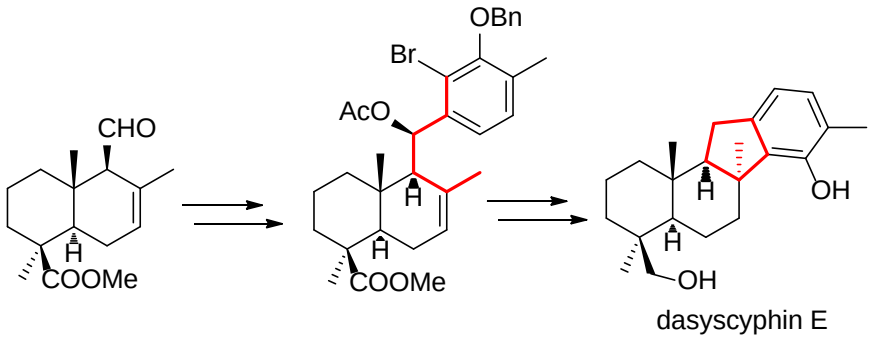


dasyscyphin E

ABSTRACT

The first synthesis of antifungal sesquiterpene quinol dasyscyphin E has been achieved, via Heck reaction conditions. The participation of an acetate group is decisive, both for the course of the reaction as for the stereoselectivity of the process.

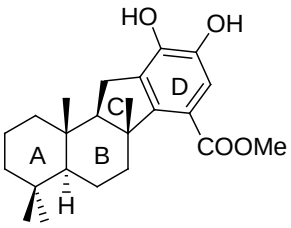
INTRODUCTION

During the last decade, a series of compounds with a tetracyclic 6/6/5/6 (decahydrobenzofluorene) skeleton exhibiting remarkable biological activity have been isolated from different natural sources. Among these two main groups of compounds can be distinguished: those presenting a *trans* B/C junction and those with a *cis* B/C union. Pelorol (**1**),[1] which can activate the inositol 5-phosphatase (SHIP),[2] belongs to the first group. Other examples of *trans* B/C fused compounds are walsucochins A (**2**) and B (**3**), with significant protective activity against H_2O_2-induced PC12 cell damage,[3] and the neuroprotective walsucochinoids A (**4**) and B (**5**).[4] Compounds with a *cis* B/C union include akaol A (**6**),[5] the cytotoxic dasyscyphin B (**7**)[6] and the antifungal dasyscyphins D (**8**) and E (**9**) (Figure 1).[7]

Only a few syntheses of this type of interesting compound have been reported, probably due to the difficulty involved in obtaining them, particularly those with a *cis* B/C junction.

In 2005, Andersen et al reported the synthesis of the *trans* B/C fused metabolite pelorol A (**1**); the construction of the C ring, a key step of the sequence, was achieved after the electrophilic cyclisation of an aryl bicyclofarnesol, derived from (+)-sclareolide, after some difficulty.[8] She et al. reported a total synthesis of dasyscyphin D (**8**) by successive Robinson annulations of an indanone prepared after a $PtCl_2$-catalysed pentannulation.[9] More recently, these authors described an enantioselective total synthesis of (-)-walsucochin B (**3**), via a cationic polyolefin cyclisation initiated by

chiral epoxide.[10] Our own group has previously reported enantiospecific syntheses for akaol A (**6**) and dasyscyphin B (**7**), utilising Diels-Alder cycloadditions.[11]



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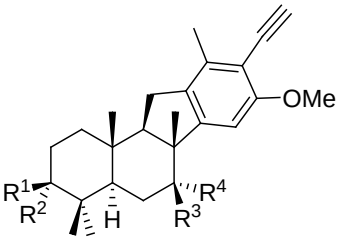
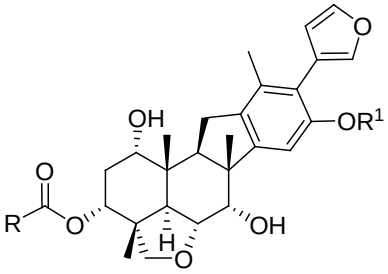
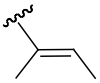
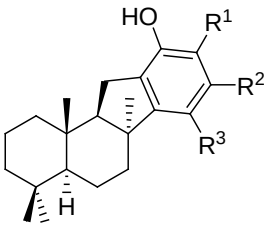


2 R^1, R^2: =O; R^3: H, R^4: OH; Δ^1
3 R^1: OH, R^2: H; R^3, R^4: =O

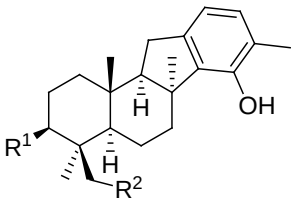


4 R: i-Pr; R^1: Me

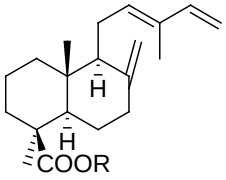
5 R:  R^1: H



6 R^1: OH, R^2:H, R^3: $MeOCH_2$
7 R^1: H, R^2:$MeOCH_2$, R^3: OH



8 R^1: OH, R^2: H
9 R^1: H, R^2: OH



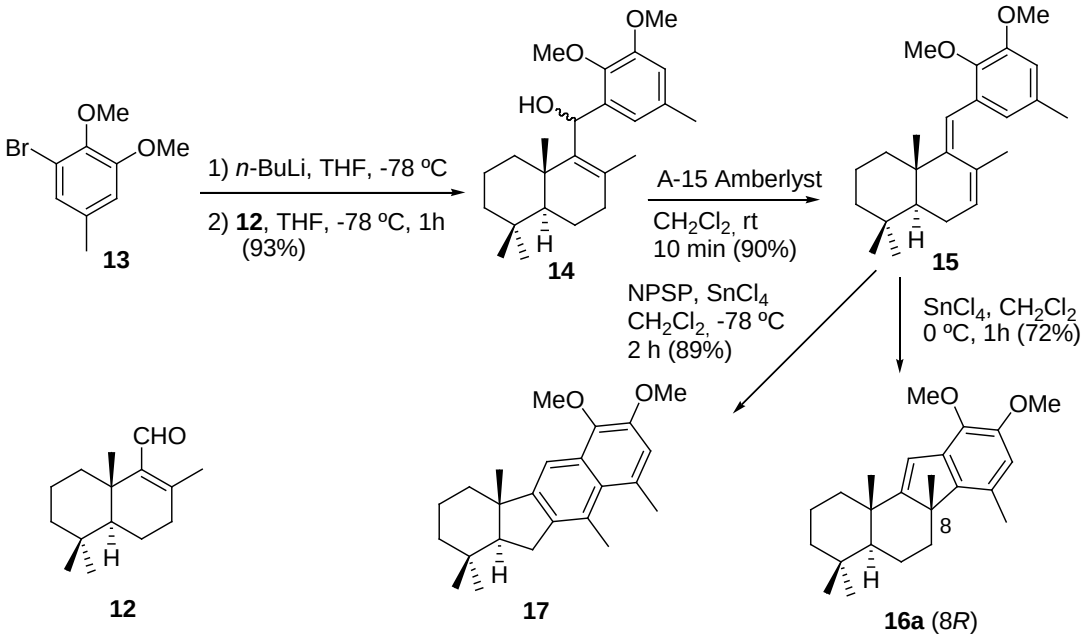
10 R: H
11 R: Me

RESULTS AND DISCUSSION

Although at first sight the cyclisation of aryl bicyclofarnesanes, as achieved by Andersen in the synthesis of pelorol (**1**), would seem to be a suitable method to access this type of benzofluorene derivative, this process has two main drawbacks that must be overcome. Firstly, constructing the cyclopentane C ring through intramolecular Friedel-Crafts processes of aryl bicyclic sesquiterpenes is a very difficult task, as Andersen et al observed, requiring the use of activated aromatic precursors. Furthermore, electrophilic

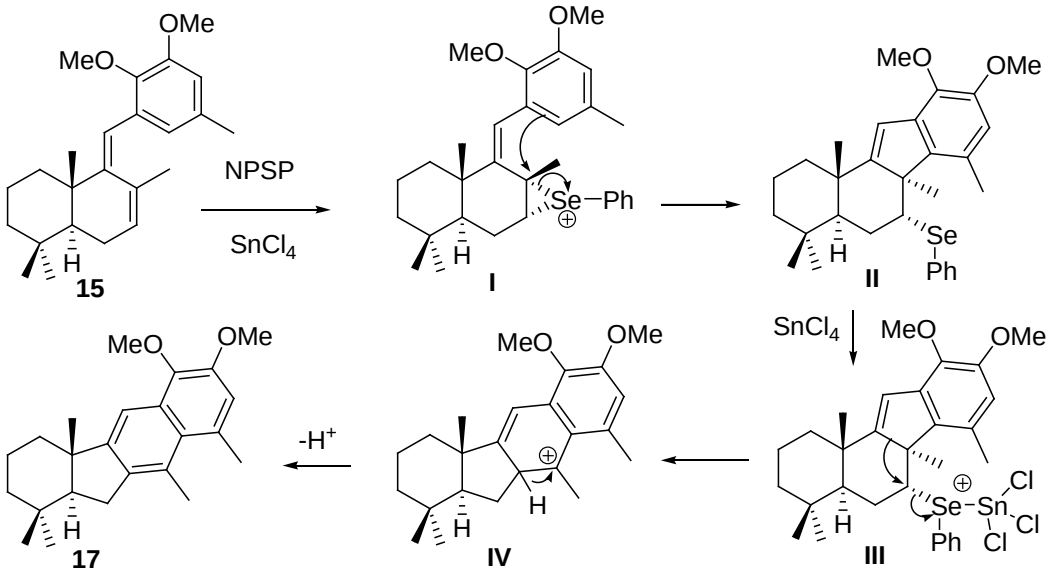
cyclisations of aryl bicyclofarnesanes afford the 8*R* diastereoisomer as the main compound, as in the case of pelorol (**1**), and do not appear to be suitable for synthesising compounds such as **6-9**. The problem of constructing the cyclopentane C ring can be circumvented by means of a highly reactive aryl allyl cation, which undergoes fast cyclisation even when non-activated aromatic rings are used. This strategy has been utilised by our group and others in the construction of the 6/5/6 taiwaniaquinoid skeleton.[12] The possibility of applying a similar procedure to the construction of the 6/6/5/6 skeleton of benzofluorene derivatives was previously explored in our laboratory. For this purpose the aryldiene **15** was prepared, starting from the sesquiterpene aldehyde **12**[13] (Scheme 1).[14] The allyl alcohol **14**,[15] was transformed into diene **15** after treatment with cationic resin. As expected, compound 15 underwent intramolecular Friede-Crafts alkylation to give the corresponding tetracyclic compound 16, with the benzofluorene skeleton characteristic of target compounds. Unfortunately, however, after assaying different acid conditions a mixture of 8-epimers, in which the unwished-for 8*R* isomer 16a was the major constituent, was obtained. When the reaction was performed with cationic resin at room temperature, a 3.1 mixture resulted; with $SnCl_4$ at 0 ºC, compound **16a** was obtained as the only stereoisomer. Recently, Bisai et al. reported similar results in the synthesis of akaol A (**6**).[15] To explore the possibility of achieving the desired 8*S* configuration through Se-induced cyclisation, the aryl diene **15** was subjected to cyclisation with $SnCl_4$ in the presence of N-phenylselenophthalimide (NPSP); however, under these conditions the tetracyclic naphthalene derivative **17** was obtained (Scheme 1).

Scheme 1. Attempts to synthesize benzofluorene derivatives.



A possible mechanism for the transformation of aryldiene **15** into the tetracyclic compound **17** is depicted in Scheme 2. The coordination of $SnCl_4$ with the Se atom in the expected intermediate **II**, resulting from diastereoselective cyclisation, promotes contraction of the B ring, leading to the benzyl cation **IV**, the deprotonation of which finally yields the aromatic compound **17**.

Scheme 2. A possible mechanism for the transformation of aryl diene **15** into compound **17.**

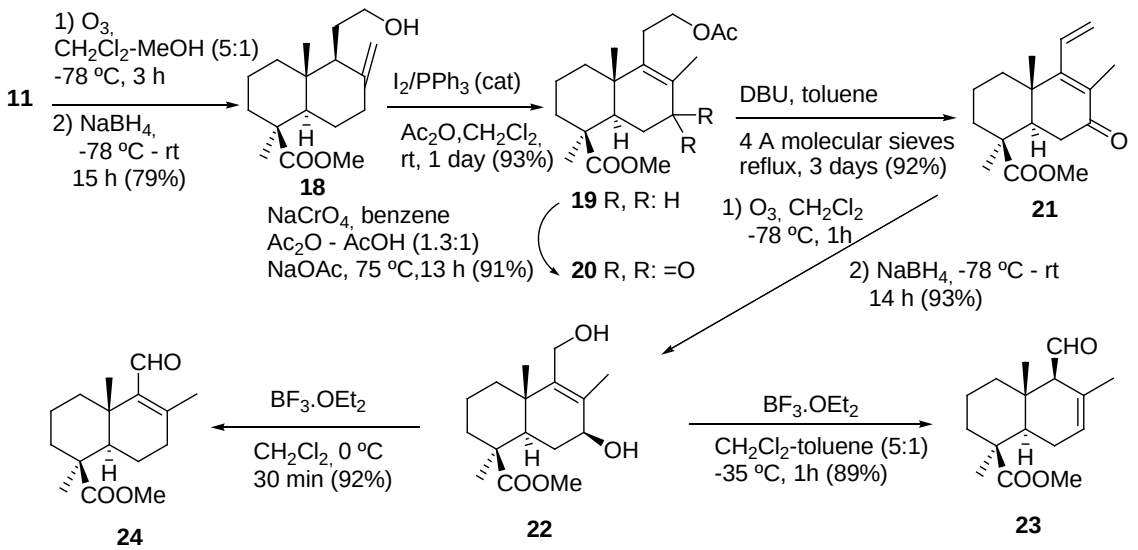


The unsatisfactory diastereoselectivity of the above cationic cyclisation of aryl sesquiterpenes prompted us to investigate new synthetic strategies towards benzofluorene derivatives with a 8*S* configuration, such as compounds **6-9**. We focus on the synthesis of dasyscyphin E (**9**), not yet synthesised. The tetracyclic carbon skeleton of target compounds with the suitable 8*S* configuration will be achieved after a Heck reaction-based cyclisation of an aryl sesquiterpene obtained from an A ring functionalised sesquiterpene aldehyde and the suitable aryllithium. A precedent could be found on the synthesis of taiwaniaquinoids, with a 6/5/6 skeleton. The cyclopentane ring of this type of compound has previously been obtained by utilising an intramolecular Heck reaction; although the reported processes were not diastereoselective. Banerjee et al cyclised a benzyl methylenecyclohexene, obtaining the desired tricyclic compound in moderate yield and low diastereoselectivity.[16] Similarly, Node et al utilised an aryldiene as the substrate, obtaining the corresponding dehydroderivative in good yield.[17] Even though the Heck cyclisation of aryldiene seems

to be more favourable, its preparation is troublesome and the stereochemistry obtained after hydrogenation of the carbon-carbon double bond remains impredictable.

In this paper, we study the use of the Heck reaction in the construction of the 6/6/5/6 skeleton of target compounds with the suitable 8*S* configuration. In a first approach, the A ring functionalised bicyclofarnesane could be prepared starting from the suitable diterpene *trans*-communic acid (**10**), after the side chain degradation. However, this process involves some difficulties, because the exocyclic carbon-carbon double bond is also affected during the oxidative degradation of the side chain, as previous studies revealed. This complication may explain why, despite its accessibility, very little use has been made of this acid as a starting product.[18,19] Scheme 3 shows the synthetic sequence we have developed for obtaining gram-scale ketoesters **23** and **24** from methyl ester **11**.

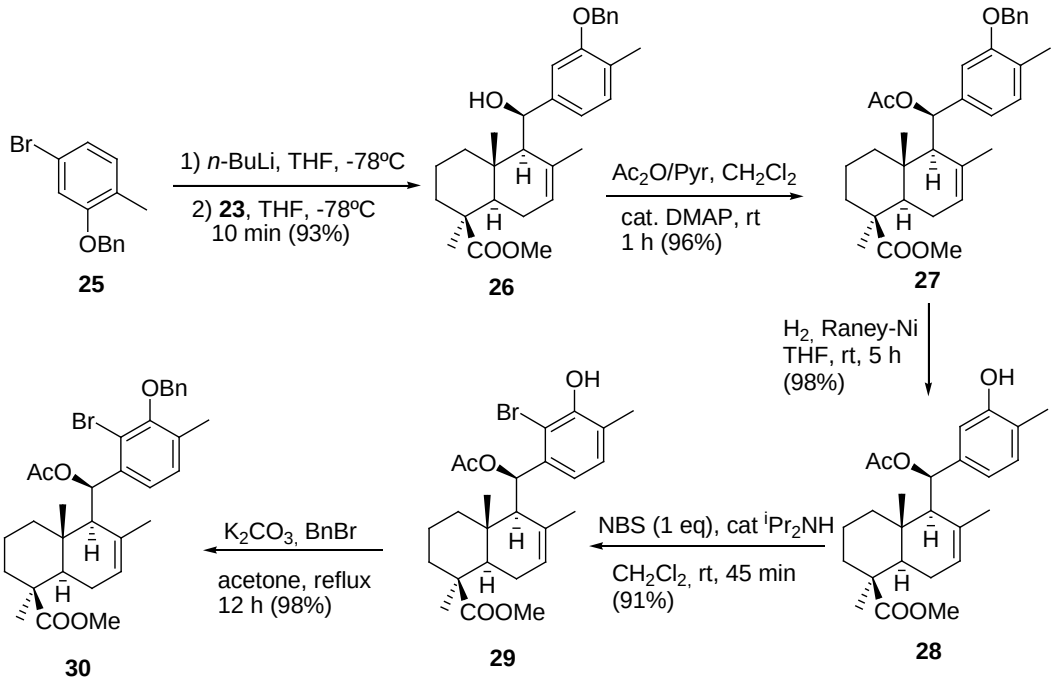
Scheme 3. Scalable synthesis of sesquiterpene ketoesters **23** and **24.**



The reductive ozonolysis of ester **11** gave hydroxy ester **18**, which was directly converted into the tetrasubstituted acetoxy alkene **19**, utilising a new acetylation procedure developed in our laboratory, which involves treatment with Ac_2O (1-2 equiv) in the presence of catalytic I_2/PPh_3 in dichloromethane. Compound **19** was then oxidised to the α,β-enone **20** and then refluxed with DBU in benzene, producing the dienone **21**, which was converted into dihydroxy ester **22**. Treatment of the latter with BF_3-OEt_2 at -35 °C finally yielded ketoester **23** as the sole regioisomer. When the reaction was carried out at 0 °C the α,β-unsaturated aldehyde **24** was obtained. Compounds **23** and **24** would seem to be suitable precursors of A ring functionalised aryl sesquiterpenes, such as adociaquinol and adociasulfate 11,[20] inhibitors of the kinesin motor protein,[21] and jaspic acid, which inhibits human 15-lipoxygenase.[22] Compound **23** is an immediate precursor of a series of metabolites recently reported.[23]

Next, aryl sesquiterpenes, such as compounds **30-32,** were synthesised starting from ester **23**. The preparation of acetoxyester **30** is depicted in Scheme 4. Alcohol **26**, after acetylation and catalytic hydrogenation, led to acetoxyphenol **28**, whose 12*R* configuration was confirmed by X ray diffraction (Fig. 2). This was further brominated and *O*-benzylated, finally affording compound **30**.

Scheme 4. Synthesis of aryl sesquiterpene **30** from ketoester **23**



The next step in the process was to construct the cyclopentane C ring. Cyclisations of aryl sesquiterpenes **30**-**32** under different Heck-reaction conditions, including $Pd(OAc)_2$ or $Pd(PPh_3)_4$ or $PdCl_2(PPh_2)_2$, in the presence of PPh_3 or $BuNCl_4$, utilising bases such as Cs_2CO_3 or K_2CO_3 or Ag_2CO_3 in DMF, acetonitrile or toluene as a solvent, were assayed. Triflate **31** was recovered unaltered under all the conditions applied, for example after treatment with $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 (entry 1, Table 1). In the view that the lack of reactivity might be caused by the bulky triflate group, bromide **32** was then assayed. This substance presented a similar behaviour to that of triflate **31**, remaining unaltered in most cases (entry 2) Interestingly, and to our great satisfaction, aryl sesquiterpene **30**, bearing an acetyloxy group at C-12, underwent the desired cyclisation with complete diastereoselectivity, thus affording the tetracyclic compound **34** under all the conditions assayed; the best results are shown in Table 1 (entry 3) (Scheme 5). The structure of compound **34** was established on the basis of 1D and 2D NMR experiments (HSQC,

gCOSY, gHMBC and NOESY). A possible explanation of the behaviour observed could be the coordination of the acetyloxy group located above the decaline carbon-carbon double bond with the palladium atom, which favours the coupling at the upper face (Fig. 3). At this point, it should be noted that in the crystal structure of acetoxyphenol **28** the phenyl group is located at some distance from the decaline carbon-carbon double bond (Fig. 2). It is significant that when the reaction was carried out in the presence of HCO_2Na, to promote the simultaneous reduction of the expected carbon-carbon double bond of the final compound, no cyclisation took place; instead, the reduction of bromide and benzyl ether occurred, and phenol **28** was obtained (entry 4) (Scheme 5). Under the latter conditions, bromide **32** was partially reduced to compound **33** (entry 5).

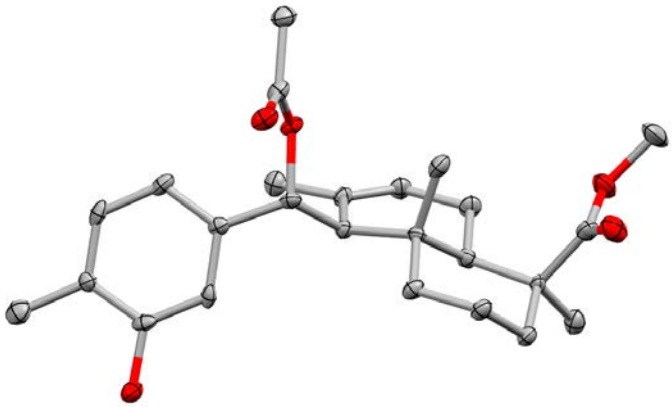
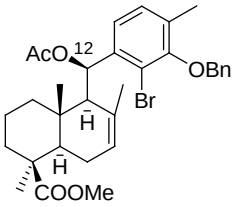


Figure 1. ORTEP for acetoxyphenol **28** (CCDC 1549031)

Table 1. Attempts to achieve the cyclisation of aryl sesquiterpenes under different Heck-reaction conditions



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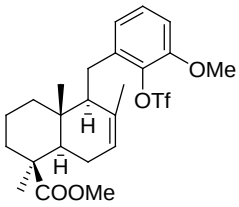
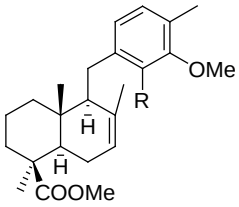


31



32 R: Br
33 R: H

Entry	Starting material	Conditions	Products
1	**31**	$Pd(OAc)_2$, PPh_3, Cs_2CO_3 DMF, 105 °C, 30 h	**31**
2	**32**	$Pd(OAc)_2$, PPh_3, Cs_2CO_3 DMF, 105 °C, 27 h	**32**
3	**30**	$Pd(OAc)_2$, PPh_3, Cs_2CO_3 DMF, 100 °C, 12 h	**34** (89%)
4	**30**	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 100 °C, 15 h	**28** (71%)
5	**32**	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 100 °C, 13 h	**32** (61%) **33** (18%)

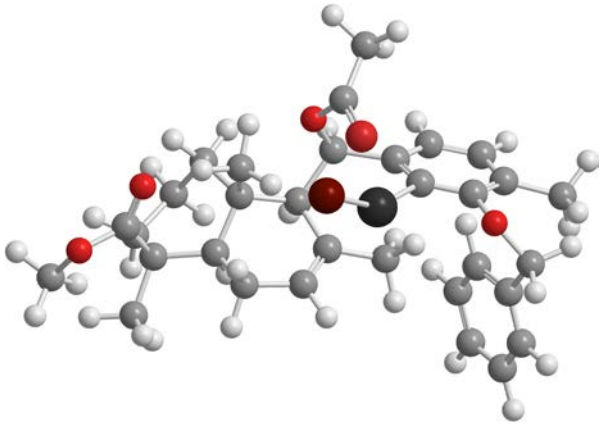
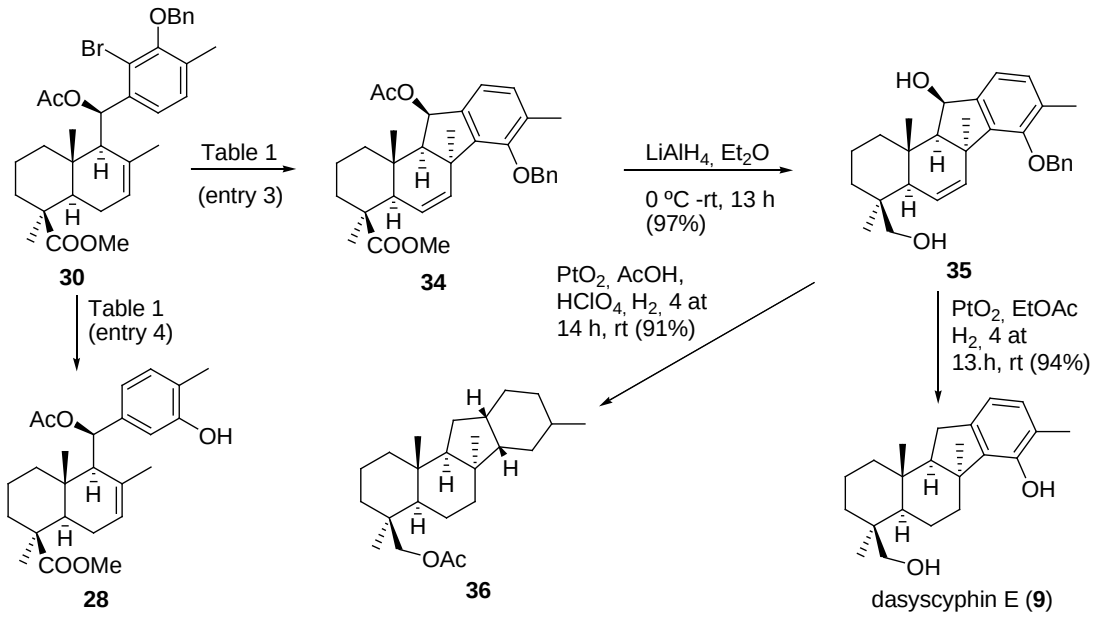


Figure 2. Possible participation of the acetyloxy group on the course of the Heck reaction

When diol **35**, resulting from the reduction of compound **34** with $LiAlH_4$, was treated with hydrogen in the presence of Pd-C, no reaction occurred. When the hydrogenation was carried out at 4 atmospheres in the presence of Adams' catalyst, the simultaneous deprotection of the phenol group and removal of benzylic alcohol took place, yielding dasyscyphin E (**5**). The over-reduction compound **36** resulted when hydrogenation was carried out in the presence of $HClO_4$ (Scheme 5). The synthetic dasyscyphin E (**9**) had identical physical properties to those previously reported.[7]

Scheme 5. Synthesis of dasyscyphin E (**9**) from ester **3.**



CONCLUSIONS

In summary, the first synthesis of dasyscyphin E (**9**) from *trans*-communic acid (**11**), *via* the versatile sesquiterpene synthon **23**, is reported. The key step of the synthesis

sequence is the diastereoselective cyclisation of a bromoaryl sesquiterpene under a Heck reaction assisted by an acetate group.

EXPERIMENTAL SECTION

General Procedures

Unless stated otherwise, reactions were performed in oven-dried glassware under an argon atmosphere using dry solvents. Solvents were dried as follows: Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene and benzene over Na-benzophenone. Dichloromethane (DCM) and methanol (MeOH) over CaH_2. Dimethylformamide (DMF) and ethyl acetate (AcOEt) were dried over 4Å molecular sieves. Thin-layer chromatography (TLC) was performed using F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching and phosphomolybdic acid solution in ethanol staining. Flash chromatography was performed on silica gel (230-400 mesh). Chromatography separations were carried out by conventional column on silica gel 60 (230-400 Mesh), using hexanes-AcOEt (AcOEt-hexane) mixtures of increasing polarity. ^{1}H and ^{13}C NMR spectra were recorded at 600, 500 and 400 MHz, and at 150, 125 and 100 MHz, respectively. $CDCl_3$ was treated with K_2CO_3. Chemical shifts (δ H) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak and tetramethylsilane. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, br d, t, q, sext and m denoting singlet, broad singlet, doublet, broad doublet, triplet, quartet, sextet and multiplet, respectively. *J* = coupling constant in Hertz (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative

to Me_4Si (δ 0.0) and the signals were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations. Infrared spectra (IR) were recorded as thin films or as solids on a FTIR spectrophotometer with samples between sodium chloride plates or as potassium bromide pellets and are reported in frequency of absorption (cm^{-1}). Only selected absorbances (ν_{max}) are reported. ($[\alpha]_D$) measurements were carried out in a polarimeter; utilizing a 1dm length cell and $CHCl_3$ as a solvent. Concentration is expressed in mg/mL. HRMS were recorded on a spectrometer, utilizing a Q-TOF analyzer, and ESI^+ ionization.

Experimental Procedures

(2,3-Dimethoxy-5-methylphenyl)((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methanol (14). To a solution of bromobenzene **13** (2.1 g, 9.54 mmol) in dry THF (20 mL) was carefully added *n*-butyllithium (9.6 mmol) at -78 °C under an argon atmosphere, and the reaction mixture was stirred at this temperature for 30 min. Then a precooled solution of aldehyde **12** (2.0 g, 9.00 mmol) in dry THF (15 mL) was syringed to the first solution and the reaction mixture was stirred for a further 1 h at which time TLC showed no starting material. The reaction was quenched with water (5 mL), the solvent was removed under vacuum, and the mixture was extracted with ether (2 x 20 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (20% ether/Hexane), affording 3.35 g of **14** (93%) (a 1:1 mixture of diastereomers) as white solid.

(4aS,8aS,E)-5-(2,3-dimethoxy-5-methylbenzylidene)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (15). To a solution of **14** (225 mg, 0.60 mmol) in dichloromethane (15 mL) was added amberlyst A-15 ion-exchange (200 mg) and the reaction mixture was stirred at room temperature for 10 min. Filtration and concentration gave 191 mg of **15** (90%) as a colorless syrup. $[\alpha]_D^{25}$= - 105.2 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.84 (m, 1H), 0.89 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.17 – 1.26 (m, 2H), 1.43 – 1.50 (m, 2H), 1.54 – 1.72 (m, 3H), 1.84 (d, *J* = 11.8 Hz, 1H), 2.01 – 2.10 (m, 2H), 2.15 (s, 3H), 2.25 (m, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 5.53 (s, 1H), 6.20 (s, 1H), 6.60 (s, 1H), 6.63 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 19.5 (CH_2), 19.7 (CH_3), 20.3 (CH_3), 22.1 (CH_3), 23.3 (CH_3), 25.3 (CH_2), 32.8 (CH_3), 34.0 (C), 38.4 (CH_2), 38.8 (C), 42.5 (CH_2), 48.5 (CH), 56.0 (CH_3), 56.3 (CH_3), 112.7 (CH), 113.4 (CH), 119.3 (CH), 128.3 (C), 128.4 (CH), 131.9 (C), 132.3 (C), 146.5 (C), 147.5 (C), 151.3 (C). IR (film): 1718, 1685, 1617, 1560, 1454, 1261, 1219, 1109 cm^{-1}. HRMS (APcl) m/z: calcd for $C_{24}H_{34}O_2Na$ ($M+Na^+$) 377.2457, found: 377.2451.

(4aS,6aR,11bS)-9,10-dimethoxy-4,4,6a,7,11b-pentamethyl-2,3,4,4a,5,6,6a,11b-octahydro-1H-benzo[a]fluorene (16a). Tin (IV) chloride (0.04 mL, 0.32 mmol) was added to a stirred solution of **15** (115 mg, 0.32 mmol) in dry dichloromethane (10 mL) cooled to 0 °C, and the reaction was further stirred for 60 min, at which time TLC showed no starting material. Then the reaction mixture was cooled to 0 °C and water (2 mL) was added dropwise. The mixture was concentrated in vacuo, ether - water (25:10

mL) was added, and the mixture was washed with brine (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (5% ether/hexanes), affording 81 mg of **16a** (72%), as white solid. $[\alpha]_D^{25}$= - 56.3 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.86 (s, 3H), 0.94 (s, 3H), 1.19 (ddd, *J* = 20.3, 8.7, 5.0 Hz, 2H), 1.26 (s, 3H), 1.49 (s, 3H), 1.53 -1.90 (m, 8H), 2.34 (s, 3H), 2.54 (ddd, *J* = 10.3, 6.8, 3.6 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 6.17 (s, 1H), 6.58 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 18.3 (CH_3), 18.8 (CH_2), 19.3 (CH_2), 19.8 (CH_3), 21.8 (CH_3), 22.8 (CH_3), 33.7 (CH_3), 33.9 (C), 37.9 (CH_2), 38.7 (CH_2), 39.4 (C), 42.5 (CH_2), 52.7 (C), 56.3 (CH_3), 56.9 (CH_3), 61.0 (CH), 112.7 (CH), 115.3 (CH), 124.6 (C), 135.0 (C), 143.5 (C), 145.9 (C), 150.5 (C), 166.4 (C). IR (KBr): 1719, 1654, 1560, 1542, 1489, 1253, 1114, 1056 cm^{-1}. HRMS (APcl) m/z: calcd for $C_{24}H_{34}O_2Na$ ($M+Na^+$) 377.2457, found: 377.24552.

(4aS,11aS)-6,7-dimethoxy-1,1,4a,9,10-pentamethyl-2,3,4,4a,11,11a-hexahydro-1H-benzo[b]fluorene (17). To a solution of *N*-(phenylseleno)phathalimide (132 mg, 0.44 mmol) and tin(IV) chloride (0.05 mL, 0.40 mmol) in dry dichloromethane (15 mL) was added **15** (128 mg, 0.36 mmol) at -78 °C and the resulting mixture was stirred for 2 h at the same temperature. The mixture was quenched by addition of sat. aq. $NaHCO_3$ and extracted by dichloromethane twice. The organic layer combined was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (5% ether/hexanes), affording 113 mg of **17** (89%), as a colorless syrup. $[\alpha]_D^{25}$= - 7.7 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 1.02 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.18 – 1.36 (m, 2H),

1.50 – 1.60 (m, 2H), 1.70 (m, 1H), 1.87 (ddt, *J* = 13.6, 7.6, 6.8 Hz, 1H), 2.18 (m, 1H), 2.62 (s, 3H), 2.71 (t, *J* = 13.8 Hz, 1H), 2.83 (s, 3H), 2.89 (dd, *J* = 14.6, 6.3 Hz, 1H), 3.84 (s, 3H), 3.95 (s, 3H), 7.06 (s, 1H), 7.32 (s, 1H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ (ppm) 19.1 (CH_3), 20.2 (CH_2), 20.6 (CH_3), 21.2 (CH_3), 22.5 (CH_3), 29.1 (CH_2), 33.3 (C), 33.5 (CH_3), 36.3 (CH_2), 41.8 (CH_2), 45.9 (C), 57.1 (CH_3), 59.2 (CH_3), 61.3 (CH), 112.3 (CH), 115.4 (CH), 127.6 (C), 128.9 (C), 129.4 (C), 130.6 (C), 141.6 (C), 144.4 (C), 148.7 (C), 152.3 (C). IR (film): 1735, 1605, 1578, 1558, 1419, 1361, 1152, 1039, 989 cm^{-1}. HRMS (APcl) m/z: calcd for $C_{24}H_{32}O_2Na$ ($M+Na^+$) 375.2300, found: 375.2307.

(1S,4aR,5S,8aR)-methyl 5-(2-hydroxyethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (18). An ozone stream was bubbled into a solution of **11** (15 g, 47.40 mmol) into a 10 : 1 mixture of CH_2Cl_2 and MeOH (400 : 40 mL) cooled at -78 ºC and the course of the reaction was monitored by TLC. When the starting material was consumed (3 h), the solution was flushed out with an argon stream for eliminating the ozone excess. Then, $NaBH_4$ (5.49 g, 142.19 mmol) was added to the cooled solution and stirred for 15 h letting the temperature increase to room temperature, at which time TLC showed no ozonide remaining. The reaction was quenched with water (60 mL) at 0 ºC, the phases were shaken and separated and the organic phase was washed with water (2 x 60 mL), brine (2 x 60 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % AcOEt/Hexane) to yield alcohol **18** (10.50 g, 79 %) as a white solid. $[\alpha]_D^{25}$= + 45.1 (c 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.52 (s, 3H), 1.01 – 1.17 (m,

2H), 1.19 (s, 3H), 1.34 (dd, *J* = 12.6, 3.0 Hz, 1H), 1.44 (s, 1H), 1.50 – 1.57 (m, 1H), 1.61 – 2.06 (m, 8H), 2.18 (d, *J* = 13.3 Hz, 1H), 2.41 (dt, *J* = 9.9, 2.4 Hz, 1H), 3.49 – 3.56 (m, 1H), 3.62 (s, 3H), 3.69 – 3.77 (m, 1H), 4.55 (s, 1H), 4.86 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 12.6 (CH_3), 19.9 (CH_2), 26.2 (CH_2), 27.2 (CH_2), 28.8 (CH_3), 38.2 (CH_2), 38.6 (CH_2), 39.1 (CH_2), 40.0 (C), 44.3 (C), 51.1 (CH), 52.1 (CH_3), 56.3 (CH), 62.4 (CH_2), 106.5 (CH_2), 148.3 (C), 177.7 (C). IR (film): 3368, 2932, 2848, 1724, 1644, 1448, 1384, 1229, 1153, 1046, 889, 774 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{17}H_{29}O_3$ ($M+H^+$) 281.2117, found: 281.2120.

(1S,4aS,8aR)-methyl 5-(2-acetoxyethyl)-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (19). To a solution of PPh_3 (1.2 g, 4.6 mmol) in dry CH_2Cl_2 (20 mL) was added I_2 (1.17 g, 4.6 mmol) and the mixture was stirred at room temperature for 5 min. After that time, the mixture was added via cannula over a solution of **18** (2.80 g, 10 mmol) in CH_2Cl_2 (60 mL) which it was previously added acetic anhydride (2 mL, 20 mmol). The resulting mixture was stirred at room temperature for 24 h, the solvent was removed under vacuum and the crude product was directly purified by flash chromatography on silica gel (95 % AcOEt/Hexane) to give the compound **19** (3 g, 93 %) as a white solid. $[\alpha]_D^{25}$= + 103.5 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.76 (s, 3H), 1.00 (ddd, *J* = 13.7, 13.6, 4.7 Hz, 1H), 1.09 (ddd, *J* = 13.4, 13.2, 4.1 Hz, 1H), 1.20 (s, 3H), 1.30 (d, *J* = 1.8 Hz, 1H), 1.47 – 1.58 (m, 1H), 1.65 (s, 3H), 1.66 – 1.77 (m, 2H), 1.83 (dt, *J* = 13.8, 3.7 Hz, 1H), 1.88 (d, *J* = 13.3 Hz, 1H), 1.92 – 2.02 (m, 2H), 2.04 (s, 3H), 2.18 – 2.29 (m, 2H), 2.38 (td, *J* = 12.3, 11.8, 5.9 Hz, 1H), 3.63 (s, 3H), 4.00 (ddd, *J* = 16.5, 10.8, 5.9 Hz, 1H) 4.01 (ddd, *J* = 16.6, 10.7, 5.8 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 17.6 (CH_3), 19.5

(CH_2), 19.9 (CH_3), 20.7 (CH_2), 21.0 (CH_3), 27.3 (CH_2), 28.4 (CH_3), 34.3 (CH_2), 37.1 (CH_2), 37.6 (CH_2), 39.2 (C), 43.9 (C), 51.1 (CH_3), 53.4 (CH), 64.0 (CH_2), 129.9 (C), 134.3 (C), 171.0 (C), 177.9 (C). IR (film): 2949, 1726, 1467, 1381, 1234, 1161, 1139, 1030 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{19}H_{31}O_4$ ($M+H^+$) 323.2222, found: 323.2216.

(1S,4aS,8aR)-methyl 5-(2-acetoxyethyl)-1,4a,6-trimethyl-7-oxo-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (20). To a solution of acetate **19** (4.0 g, 12.35 mmol) in benzene (60 mL) were added Na_2CrO_4 (3 g, 18.52 mmol), Ac_2O (13 mL), AcOH (10 mL) and AcONa (4 g). The mixture was heated to 75 ºC for 13 h until TLC showed no starting material. After cooling at 0 ºC, the reaction was quenched with water (25 mL) and the solvent was removed under vacuum. The resulting mixture was diluted with CH_2Cl_2 (70 mL) washed with water (5 x 30 mL), saturated aqueous $NaHCO_3$ solution (3 x 20 mL), brine and dried over Na_2SO_4. Removal of the solvent in vacuum afforded a crude product which was purified by flash chromatography in silica gel (15 % AcOEt/Hexane) to obtain the enone **20** (3.80 g, 91 %) as a white solid. $[\alpha]_D^{25}$= + 236.3 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.94 (s, 3H), 1.08 (ddd, *J* = 13.5, 13.5, 4.2 Hz, 1H), 1.20 (s, 3H), 1.31 (ddd, *J* = 13.1, 13.0, 4.2 Hz, 1H), 1.64 (dt, *J* = 14.6, 3.7 Hz, 1H), 1.83 (s, 3H), 1.87 (d, *J* = 3.5 Hz, 1H), 1.92 (dt, *J* = 13.9, 3.7 Hz, 1H), 1.99 – 2.04 (m, 1H), 2.06 (s, 3H), 2.27 (d, *J* = 13.5 Hz, 1H), 2.54 (ddd, *J* = 12.8, 10.3, 6.0 Hz, 1H), 2.62 (ddd, *J* = 12.8, 10.4, 6.0 Hz, 1H), 2.76 (dd, *J* = 17.5, 3.4 Hz, 1H), 2.91 (dd, *J* = 17.5, 14.7 Hz, 1H), 3.67 (s, 3H), 4.08 (ddd, *J* = 10.6, 10.5, 6.0 Hz, 1H), 4.16 (ddd, *J* = 10.6, 10.5, 5.9 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 11.8 (CH_3), 15.7 (CH_3), 19.1 (CH_2), 20.9 (CH_3), 27.7 (CH_3),

28.9 (CH_2), 36.1 (CH_2), 36.6 (CH_2), 37.3 (CH_2), 41.1 (C), 43.6 (C), 50.7 (CH), 51.5 (CH_3), 62.3 (CH_2), 132.6 (C), 160.4 (C), 170.8 (C), 177.0 (C), 199.4 (C). IR (film): 2942, 1739, 1726, 1667, 1465, 1380, 1334, 1231, 1192, 1161, 1035, 981, 773 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{19}H_{29}O_5$ ($M+H^+$) 337.2015, found: 337.2016.

(1S,4aS,8aR)-methyl 1,4a,6-trimethyl-7-oxo-5-vinyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (21). To a solution of **20** (2.00 g, 5.95 mmol) in dry toluene (40 mL) were added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.8 mL, 11.89 mmol) and 4 Å molecular sieves (2 g). The mixture was heated under reflux for 3 days, at which time TLC showed no starting material. After the mixture was cooled, and toluene was removed under vacuum resulting in a crude that was directly purified into silica gel (10 % AcOEt/Hexane) affording the unsaturated ketone **21** (1.51 g, 92 %) as a yellow syrup. $[\alpha]_D^{25}$= + 96.9 (c 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 0.94 (s, 3H), 1.03 (ddd, *J* = 13.6, 13.4, 4.1 Hz, 1H), 1.17 (s, 3H), 1.25 (ddd, *J* = 13.4, 13.2, 4.2 Hz, 2H), 1.54 (d, *J* = 14.4 Hz, 1H), 1.76 (s, 3H), 1.86 (td, *J* = 13.7, 13.0, 3.6 Hz, 2H), 2.21 (d, *J* = 13.6 Hz, 1H), 2.73 (dd, *J* = 17.7, 3.5 Hz, 1H), 2.92 (dd, *J* = 17.7, 14.6 Hz, 1H), 3.64 (s, 3H), 5.07 (d, *J* = 17.7 Hz, 1H), 5.44 (d, *J* = 11.5 Hz, 1H), 6.25 (dd, *J* = 17.8, 11.7 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 13.2 (CH_3), 16.0 (CH_3), 19.1 (CH_2), 27.7 (CH_3), 36.8 (CH_2), 37.2 (CH_2), 37.3 (CH_2), 40.0 (C), 43.6 (C), 50.5 (CH), 51.4 (CH_3), 120.8 (CH_2), 129.3 (C), 133.2 (CH), 163.6 (C), 177.0 (C), 200.3 (C). IR (film): 2938, 1724, 1664, 1441, 1379, 1323, 1233, 1191, 1162, 1136, 1088, 984, 931, 773 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{17}H_{25}O_3$ ($M+H^+$) 277.1804, found: 277.1798.

(1S,4aS,7S,8aR)-methyl 7-hydroxy-5-(hydroxymethyl)-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (22). An ozone stream was bubbled into a solution of **21** (2 g, 7.24 mmol) in CH_2Cl_2 (50 mL) cooled at -78 ºC for 1 h. The solution was flushed out with an argon stream for eliminating the ozone excess. Then, $NaBH_4$ (1.71 g, 43.44 mmol) was added to the cooled solution and stirred for 14 h letting the temperature increase to room temperature. The reaction was quenched with water (5 mL) at 0 ºC and the product was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with water (3 x 5 mL), brine (2 x 5 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % AcOEt/Hexane) to yield diol **22** (1.90 g, 93%) as a white solid. $[\alpha]_D^{25}$= + 79.1 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 0.82 (s, 3H), 1.01 (ddd, *J* = 13.4, 13.3, 4.3 Hz, 1H), 1.10 (t, *J* = 5.3 Hz, 1H), 1.19 (s, 3H), 1.36 (d, *J* = 13.3 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 2H), 1.61 (s, 1H), 1.75 (dd, *J* = 13.2, 10.3 Hz, 1H), 1.83 (s, 3H), 2.21 (d, *J* = 13.7 Hz, 1H), 2.38 (dd, *J* = 13.1, 6.5 Hz, 1H), 3.62 (s, 3H), 4.01 (dd, *J* = 11.7, 5.3 Hz, 1H), 4.04 – 4.11 (m, 1H), 4.15 (dd, *J* = 11.6, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 14.6 (CH_3), 17.9 (CH_3), 19.1 (CH_2), 28.1 (CH_3), 31.2 (CH_2), 36.6 (CH_2), 37.5 (CH_2), 39.4 (C), 43.3 (C), 50.3 (CH), 51.2 (CH_3), 58.3 (CH_2), 72.9 (CH), 135.3 (C), 142.4 (C), 177.5 (C). IR (film): 3351, 2933, 1724, 1448, 1380, 1232, 1194, 1157, 1090, 1035, 992, 899, 755, 666 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{16}H_{27}O_4$ ($M+H^+$) 283.1909, found: 283.1915.

(1S,4aS,5S,8aR)-methyl 5-formyl-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (23). To a stirred solution of diol **22** (1.2 g, 4.25

mmol) in a 5 : 1 mixture of dry CH_2Cl_2 and toluene (100 : 20 mL) cooled at -35 ºC was added dropwise $BF_3.OEt_2$ (1.1 mL, 8.50 mmol) and stirred for 1 h, at which time TLC showed no starting material. Then, saturated aqueous $NaHCO_3$ (20 mL) was added to the cooled mixture and was stirred for 10 minutes. Solvents were evaporated under vacuum and then ethyl acetate (80 mL) was added. The phases were shaken and separated. The organic layer was washed with water (3 x 20 mL), brine (2 x 20 mL), dried over Na_2SO_4 and filtered. Removal of the solvent under vacuum afford a crude product that was purified by flash chromatography on silica gel (30 % AcOEt/Hexane) to yield aldehyde **23** (1.00 g, 89%) as a white solid. $[\alpha]_D^{25}$= + 4.9 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.90 (s, 3H), 1.09 (ddd, *J* = 14.2, 12.9, 3.7 Hz, 1H), 1.21 (s, 3H), 1.32 (ddd, *J* = 13.6, 13.5, 4.2 Hz, 1H), 1.38 (dd, *J* = 12.1, 4.7 Hz, 1H), 1.46 – 1.53 (m, 1H), 1.61 (s, 3H), 1.72 (br d, *J* = 13.2 Hz, 1H), 1.86 (qt, *J* = 13.8, 3.3 Hz, 1H), 2.19 (br d, *J* = 13.5 Hz, 1H), 2.25 – 2.34 (m, 1H), 2.50 – 2.58 (m, 1H), 2.61 (s, 1H), 3.67 (s, 3H), 5.72 (br s, 1H), 9.64 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 14.6 (CH_3), 19.1 (CH_2), 21.5 (CH_3), 24.5 (CH_2), 28.7 (CH_3), 36.8 (C), 38.0 (CH_2), 40.5 (CH_2), 43.7 (C), 50.2 (CH), 51.4 (CH_3), 66.8 (CH), 125.6 (CH), 126.7 (C), 177.4 (C), 206.1 (CH). IR (film): 3351, 2933, 1724, 1448, 1380, 1232, 1194, 1157, 1090, 1035, 992, 899, 755, 666 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{16}H_{25}O_3$ ($M+H^+$) 265.1804, found: 265.1799.

(1S,4aS,8aR)-methyl 5-formyl-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (24). To a stirred solution of diol **22** (1.2 g, 4.25 mmol) in dry CH_2Cl_2 cooled at 0 ºC was added dropwise $BF_3.OEt_2$ (1.1 mL, 8.50 mmol) and stirred for 30 min, at which time TLC showed no starting material. Then, saturated

aqueous $NaHCO_3$ (20 mL) was added to the cooled mixture and was stirred for 10 minutes. Solvent was evaporated under vacuum and then ethyl acetate (80 mL) was added. The phases were shaken and separated. The organic layer was washed with water (3 x 20 mL), brine (2 x 20 mL), dried over Na_2SO_4 and filtered. Removal of the solvent under vacuum afford a crude product that was purified by flash chromatography on silica gel (30 % AcOEt/Hexane) to yield aldehyde **24** (1.03 g, 92%) as a white solid. $[\alpha]_D^{25}$= + 100.6 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.96 – 1.00 (m, 1H), 1.01 (s, 3H), 1.02 – 1.07 (m, 1H), 1.21 (s, 3H), 1.28 (dd, *J* = 12.6, 1.8 Hz, 1H), 1.50 (dt, *J* = 14.5, 3.6 Hz, 1H), 1.75 – 1.90 (m, 2H), 1.98 – 2.05 (m, 1H), 2.07 (s, 3H), 2.19 – 2.37 (m, 3H), 2.57 (d, *J* = 13.1 Hz, 1H), 3.64 (s, 3H), 10.05 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 17.4 (CH_3), 19.2 (CH_3), 19.4 (CH_2), 20.0 (CH_2), 28.6 (CH_3), 36.2 (CH_2), 37.3 (CH_2), 37.7 (CH_2), 38.1 (C), 43.6 (C), 51.2 (CH_3), 53.4 (CH), 142.2 (C), 155.0 (C), 177.6 (C), 192.3 (CH). IR (film): 2950, 2870,1724, 1670, 1610, 1465, 1376, 1229, 1191, 1161, 1140, 1037, 978, 829, 773, 701 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{16}H_{25}O_3$ ($M+H^+$) 265.1804, found: 265.1809.

2-(benzyloxy)-4-bromo-1-methylbenzene (25). Benzyl bromide (0.7 mL, 5.88 mmol) was added to a stirred suspension of 5-bromo-2-methylphenol (1.0 g, 5.35 mmol) and K_2CO_3 (0.96 g, 6.95 mmol) in acetone (50 mL) under argon atmosphere. The mixture was heated under reflux overnight. Then, the solvent was evaporated in vacuo, Et_2O (100 mL) was added and the mixture was washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was purified by flash chromatography (30 % AcOEt/hexane) to give **25** (1.4 g, 92 %) as a colorless syrup. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.24 (s,

3H), 5.07 (s, 2H), 7.03 – 7.04 (m, 2H), 7.04 (d, *J* = 1.0 Hz, 1H), 7.33 – 7.39 (m, 1H), 7.40 – 7.50 (m, 4H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 16.0 (CH_3), 70.1 (CH_2), 114.8 (CH), 119.5 (C), 123.5 (CH), 126.1 (C), 127.2 (CH x 2), 128.0 (CH), 128.6 (CH x 2), 131.7 (CH), 136.7 (C), 157.5 (C). IR (film): 3065, 3031, 2922, 1593, 1487, 1454, 1399, 1380, 1304, 1240, 1190, 1126, 1083, 1025, 879, 836, 801, 772, 736, 696, 631, 580 cm^{-1}

(1S,4aS,5S,8aR)-methyl 5-((R)-(3-(benzyloxy)-4-methylphenyl)(hydroxy)methyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (26). To a solution of bromobenzene **25** (1.3 g, 4.54 mmol) in dry THF (15 mL) was carefully added *n*-butyllitium (4.54 mmol) at -78 ºC under an argon atmosphere and the reaction mixture was stirred at this temperature for 30 min, observing the formation of a white precipitate of the aryllithium salt. Then a solution of aldehyde **23** (0.8 g, 3.03 mmol) in dry THF (10 mL) was syringed to the first solution and the reaction mixture was stirred for a further 10 min at -78 ºC, at which time TLC showed no starting material. The reaction was quenched with water (5 mL), the solvent was removed under vacuum, and the mixture was extracted with ether (2 x 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (30 % AcOEt/hexane), affording 1.30 g of alcohol **26** (93%) as a colorless syrup. $[\alpha]_D^{25}$= - 46.5 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.94 (s, 3H), 1.14 (ddd, *J* = 13.4, 13.4, 3.7 Hz, 1H), 1.24 (s, 3H), 1.35 (s, 3H), 1.45 (dd, *J* = 12.1, 4.2 Hz, 1H), 1.61 (dt, *J* = 14.2, 3.6 Hz, 1H), 1.79 (s, 1H), 2.00 (qt, *J* = 13.9, 3.3 Hz, 1H), 2.09 (d, *J* = 12.8 Hz, 1H), 2.18 – 2.26 (m, 2H), 2.29

(s, 3H), 2.40 – 2.48 (m, 2H), 3.69 (s, 3H), 5.03 (d, *J* = 4.4 Hz, 1H), 5.12 (s, 2H), 5.59 (br s, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 7.02 (s, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 14.5 (CH_3), 16.0 (CH_3), 19.7 (CH_2), 23.9 (CH_3), 24.3 (CH_2), 28.9 (CH_3), 37.0 (C), 38.2 (CH_2), 40.8 (CH_2), 43.9 (C), 51.3 (CH_3), 51.5 (CH), 61.8 (CH), 69.5 (CH), 69.9 (CH_2), 109.0 (CH), 117.0 (CH), 124.5 (C), 126.8 (CH), 127.1 (CH x 2), 127.6 (CH), 128.5 (CH x 2), 130.1 (CH), 131.4 (C), 137.6 (C), 145.7 (C), 156.5 (C), 177.8 (C). IR (film): 3500, 2927, 1721, 1611, 1582, 1506, 1453, 1413, 1380, 1237, 1196, 1172, 1150, 1127, 1026, 986, 841, 812, 755, 696, 627 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{30}H_{39}O_4$ ($M+H^+$) 463.2848, found: 463.2851.

(1S,4aS,5S,8aR)-methyl 5-((R)-acetoxy(3-(benzyloxy)-4-methylphenyl)methyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (27). To a solution of alcohol **26** (0.9 g, 1.94 mmol) in pyridine (15 mL) at room temperature were added DMAP (24 mg, 0.19 mmol) and Ac_2O (2 mL, 10.88 mmol) and stirred for 1 h at room temperature. The reaction was quenched with water (10 mL) at 0 ºC and the solution obtained was diluted with Et_2O (50 mL), washed with water (1 x 15 mL), HCl 2M (4 x 15 mL), again with water (1 x 15 mL), with saturated aqueous $NaHCO_3$ (4 x 15 mL) and brine (1 x 15 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude obtained was purified by flash chromatography (10 % AcOEt/Hexane) affording acetate **27** (942 mg, 96 %) as a colorless syrup. $[\alpha]_D^{25}$= - 9.3 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.70 (s, 3H), 1.12 (ddd, *J* = 13.5, 13.4, 3.8 Hz, 1H), 1.16 – 1.21 (m, 1H), 1.23 (s, 3H), 1.40 (s, 3H), 1.44 (dd, *J* = 12.3, 4.3 Hz, 1H), 1.61 (dt, *J* = 14.1, 3.8 Hz, 1H), 1.96

(qt, *J* = 13.9, 3.3 Hz, 1H), 2.12 (s, 3H), 2.15 – 2.24 (m, 3H), 2.26 (s, 3H), 2.34 – 2.46 (m, 2H), 3.67 (s, 3H), 5.09 (s, 2H), 5.45 (br s, 1H), 6.13 (s, 1H), 6.60 (s, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 13.2 (CH_3), 16.0 (CH_3), 19.7 (CH_2), 21.2 (CH_3), 23.7 (CH_3), 24.1 (CH_2), 28.9 (CH_3), 37.0 (C), 38.1 (CH_2), 40.7 (CH_2), 43.9 (C), 51.3 (CH), 51.5 (CH_3), 60.3 (CH), 70.1 (CH_2), 71.5 (CH), 109.0 (CH), 117.0 (CH), 124.2 (CH), 125.2 (C), 126.9 (CH x 2), 127.7 (CH), 128.5 (CH x 2), 130.2 (CH), 131.9 (C), 137.5 (C), 141.4 (C), 156.5 (C), 170.3 (C), 177.6 (C). IR (film): 2926, 1721, 1583, 1508, 1453, 1414, 1372, 1233, 1150, 1128, 1077, 1024, 814, 753, 696, 666, 626 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{32}H_{41}O_5$ ($M+H^+$) 505.2954, found: 505.2955.

(1S,4aS,5S,8aR)-methyl 5-((R)-acetoxy(3-hydroxy-4-methylphenyl)methyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (28). 70 % Raney - Nickel dispersion in water (1 mL) was added to a stirred solution of **27** (400 mg, 0.79 mmol) in THF (25 mL) with an H_2 atmosphere provided by a balloon. The mixture was stirred at room temperature for 5 h, at which time TLC showed no remaining starting material. Then, the resulting mixture was filtered through a silica gel (7.0 g) – anhydrous Na_2SO_4 (10.0 g) pad and washed with AcOEt (50 mL). The solvent was evaporated to yield phenol **28** (322 mg, 98 %) as a white solid. $[\alpha]_D^{25}$= - 6.9 (c 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.70 (s, 3H), 1.10 (ddd, *J* = 13.7, 13.4, 3.9 Hz, 1H), 1.21 (s, 3H), 1.25 – 1.32 (m, 1H), 1.35 (t, *J* = 6.1 Hz, 1H), 1.44 (s, 1H), 1.45 (s, 3H), 1.58 (br d, *J* = 14.3 Hz, 1H), 1.94 (qt, *J* = 13.9, 3.3 Hz, 1H), 2.15 (s, 3H), 2.17 (s, 3H), 2.19 – 2.29 (m, 2H), 2.32 – 2.45 (m, 1H), 2.49 (s, 1H), 3.67 (s, 3H),

5.45 (br s, 1H), 6.12 (s, 1H), 6.56 (s, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 13.3 (CH_3), 15.4 (CH_3), 19.6 (CH_2), 21.3 (CH_3), 23.7 (CH_3), 24.1 (CH_2), 28.9 (CH_3), 37.0 (C), 38.1 (CH_2), 40.6 (CH_2), 43.9 (C), 51.4 (CH_3), 51.5 (CH), 60.1 (CH), 71.6 (CH), 111.7 (CH), 116.7 (CH), 122.0 (C), 124.2 (CH), 130.5 (CH), 131.9 (C), 141.7 (C), 153.9 (C), 170.8 (C), 177.9 (C). IR (KBr): 3429, 2953, 2926, 2855, 1720, 1591, 1436, 1376, 1234, 1151, 1118, 1040, 1001, 943, 754, 667 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{25}H_{35}O_5$ ($M+H^+$) 415.2484, found: 415.2478.

(1S,4aS,5S,8aR)-methyl 5-((R)-acetoxy(2-bromo-3-hydroxy-4-methylphenyl)methyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (29). A solution of NBS (129 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) was prepared and added via cannula to a solution of phenol **28** (300 mg, 0.72 mmol) in CH_2Cl_2 (20 mL) and 2 drops of diisopropylamine. The reaction mixture was stirred for 45 min at room temperature, at which time TLC showed no starting material. Then, the solvent was removed, and the crude product was purified by flash chromatography (30 % AcOEt/Hexane) to afford bromine derivative **29** (325 mg, 91 %) as a colorless syrup. $[\alpha]_D^{25}$= - 34.3 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.77 (s, 3H), 1.12 (ddd, *J* = 13.5, 13.2, 3.8 Hz, 1H), 1.22 (s, 3H), 1.43 (s, 3H), 1.53 (dd, *J* = 12.2, 4.5 Hz, 1H), 1.60 – 1.74 (m, 2H), 1.93 (qt, *J* = 13.6, 3.5 Hz, 1H), 2.16 (s, 3H), 2.21 (br d, *J* = 13.6 Hz, 2H), 2.27 (s, 3H), 2.37 (br d, *J* = 11.8 Hz, 2H), 2.90 (s, 1H), 3.67 (s, 3H), 5.50 (br s, 1H), 6.19 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 14.2 (CH_3), 16.5 (CH_3), 19.7 (CH_2), 21.4

(CH_3), 24.4 (CH_2), 25.3 (CH_3), 29.1 (CH_3), 37.9 (CH_2), 39.1 (C), 40.8 (CH_2), 44.1 (C), 51.3 (CH_3), 51.8 (CH), 54.8 (CH), 72.5 (CH), 109.0 (C), 120.5 (CH), 124.3 (C), 125.8 (CH), 129.0 (CH), 131.8 (C), 138.5 (C), 150.2 (C), 170.0 (C), 177.8 (C). IR (film): 3448, 2952, 2930, 2856, 1720, 1448, 1406, 1370, 1228, 1171, 1149, 1123, 1040, 1010, 945, 818, 753, 667 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{25}H_{34}BrO_5$ ($M+H^+$) 493.1590, found: 493.1587.

(1S,4aS,5S,8aR)-methyl 5-((R)-acetoxy(3-(benzyloxy)-2-bromo-4-methylphenyl)methyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (30). Benzyl bromide (0.05 mL, 0.45 mmol) was added to a stirred suspension of **29** (270 mg, 0.548 mmol) and K_2CO_3 (146 mg, 1.06 mmol) in dry acetone (10 mL) under argon atmosphere. The mixture was heated under reflux overnight. Then, the solvent was evaporated in vacuo, Et_2O (40 mL) was added and the mixture was washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was purified by flash chromatography (10 % AcOEt/hexane) to give **30** (313 mg, 98 %) as a colorless syrup. $[\alpha]_D^{25}$= - 39.9 (c 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 0.76 (s, 3H), 1.09 (ddd, *J* = 13.4, 13.3, 3.8 Hz, 1H) 1.19 (s, 3H), 1.39 (s, 3H), 1.47 – 1.63 (m, 2H), 1.73 (td, *J* = 13.2, 3.7 Hz, 1H), 1.88 (td, *J* = 13.5, 3.1 Hz, 1H), 2.15 (s, 3H), 2.18 – 2.24 (m, 2H), 2.27 (s, 3H), 2.37 (t, *J* = 12.8 Hz, 2H), 3.01 (s, 1H), 3.65 (s, 3H), 4.87 (d, *J* = 10.7 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 5.47 (br s, 1H), 6.26 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 7.30 – 7.57 (m, 5H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 14.3 (CH_3), 16.6 (CH_3), 19.7 (CH_2), 21.4 (CH_3), 24.4 (CH_2), 25.4 (CH_3), 29.1 (CH_3), 37.9 (CH_2), 39.1 (C), 40.6 (CH_2), 44.1 (C), 51.3 (CH_3), 51.8

(CH), 54.6 (CH), 72.8 (CH), 74.2 (CH_2), 116.7 (C), 124.6 (CH), 125.7 (CH), 128.0 (CH x 2), 128.1 (CH), 128.4 (CH x 2), 129.0 (CH), 131.7 (C), 131.9 (C), 137.0 (C), 140.0 (C), 154.0 (C), 170.0 (C), 177.8 (C). IR (film): 2930, 1721, 1454, 1366, 1229, 1174, 1149, 1014, 941, 821, 752, 697, 667, 631 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{32}H_{40}BrO_5$ ($M+H^+$) 583.2059, found: 583.2064.

(1S,4aR,5S,8aR)-methyl 5-(3-methoxy-2-(((trifluoromethyl)sulfonyl)oxy)benzyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (31). Colorless syrup. $[\alpha]_D^{25}$= + 95.3 (c 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 0.70 (s, 3H), 0.94 (ddd, *J* = 13.5, 13.4, 4.2 Hz, 1H), 0.99 (s, 3H), 1.14 (ddd, *J* = 13.1, 13.0, 4.2 Hz, 1H), 1.21 – 1.29 (m, 2H), 1.37 – 1.53 (m, 3H), 1.65 (d, *J* = 4.4 Hz, 1H), 1.71 (s, 3H), 1.80 (qt, *J* = 14.1, 4.1 Hz, 1H), 2.11 – 2.19 (m, 1H), 2.36 (d, *J* = 9.0 Hz, 1H), 3.22 (d, *J* = 9.5 Hz, 1H), 3.57 (s, 3H), 3.88 (s, 3H), 5.11 (br s, 1H), 6.88 (t, *J* = 9.1 Hz, 2H), 7.21 (t, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 19.3 (CH_3), 19.4 (CH_2), 21.0 (CH_3), 27.3 (CH_2), 27.7 (CH_3), 34.4 (CH_2), 35.9 (C), 38.1 (CH_2), 40.0 (CH_2), 42.0 (CH_3), 43.5 (C), 50.9 (CH), 51.7 (CH_3), 55.9 (CH), 110.5 (CH), 122.9 (CH), 122.9 (CF_3, q, *J* = 320.5 Hz), 128.0 (CH), 132.4 (C), 135.3 (C), 137.2 (CH), 137.9 (C), 151.1 (C), 177.7 (C). IR (film): 2941, 1724, 1613, 1581, 1480, 1413, 1307, 1283, 1204, 1165, 1132, 1078, 965, 883, 760, 636, 607, 571, 498 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{24}H_{32}F_3O_6S$ ($M+H^+$) 505.1872, found: 505.1889.

(1S,4aR,5S,8aR)-methyl 5-(2-bromo-3-methoxy-4-methylbenzyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (32). Colorless syrup. $[\alpha]_D^{25}$=

+ 71.4 (c 1.1, $CHCl_3$). ^1H NMR (300 MHz, Chloroform-*d*) δ (ppm) 0.79 (s, 3H), 0.94 – 1.02 (m, 1H), 1.04 (s, 3H), 1.16 – 1.33 (m, 3H), 1.40 – 1.55 (m, 3H), 1.71 – 1.77 (m, 1H), 1.81 (s, 3H), 2.20 (d, *J* = 13.5 Hz, 1H), 2.36 (s, 3H), 2.37 – 2.58 (m, 2H), 3.38 (d, *J* = 11.0 Hz, 1H), 3.65 (s, 3H), 3.84 (s, 3H), 5.15 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 16.4 (CH_3), 19.5 (CH_2), 19.6 (CH_3), 21.2 (CH_3), 27.4 (CH_2), 27.9 (CH_3), 35.9 (C), 38.1 (CH_2), 40.2 (CH_2), 40.6 (CH_2), 41.8 (CH_3), 43.6 (C), 51.1 (CH), 51.9 (CH_3), 60.0 (CH), 120.1 (C), 126.6 (CH), 129.3 (CH), 130.1 (C), 133.3 (C), 136.8 (CH), 139.7 (C), 155.4 (C), 177.8 (C). IR (film): 2955, 2933, 1725, 1447, 1377, 1263, 1236, 1158, 1137, 1030, 801, 756 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{24}H_{34}BrO_3$ ($M+H^+$) 449.1691, found: 449.1687.

(1S,4aR,5S,8aR)-methyl 5-(3-methoxy-4-methylbenzyl)-1,4a,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (33). To a solution of **32** (87 mg, 0.194 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (20 mg, 0.089 mmol), PPh_3 (120 mg, 0.42 mmol) and HCO_2Na (97 mg, 1.42 mmol) and the mixture was heated at 100 ºC for 13 h. Then, the mixture was diluted with AcOEt (25 mL) and washed with HCl 2 M (2 x 10 mL), water (3 x 10 mL), brine (1 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded a crude product (135 mg) which was purified by flash chromatography (5 % AcOEt/Hexane) to obtain **33** (13 mg, 18 %) as a colorless syrup and **32** (53 mg, 61%). $[\alpha]_D^{25}$= + 31.6 (c 0.6, $CHCl_3$). ^1H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.70 (s, 3H), 1.06 (s, 3H), 1.74 (s, 3H), 2.20 (s, 3H), 3.60 (s, 3H), 3.84 (s, 3H), 5.12 (s, 1H), 6.69 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 15.8 (CH_3), 19.5 (CH_2), 19.6 (CH_3), 21.5 (CH_3), 27.6 (CH_2), 27.9 (CH_3), 35.9 (C), 38.2 (CH_2), 40.2 (CH_2 x 2), 43.5

(CH), 43.6 (C), 51.0 (CH_3), 52.0 (CH), 55.3 (CH_3), 111.0 (CH), 120.9 (CH), 123.6 (C), 130.2 (CH), 133.2 (C), 136.9 (CH), 139.9 (C), 157.4 (C), 177.8 (C). IR (film): 2934, 1727, 1510, 1465, 1220, 1133, 1043, 772 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{24}H_{35}O_3$ ($M+H^+$) 371.2586, found: 371.2591.

(4S,4aR,6aS,11R,11aR,11bS)-methyl 11-acetoxy-7-(benzyloxy)-4,6a,8,11b-tetramethyl-2,3,4,4a,6a,11,11a,11b-octahydro-1H-benzo[a]fluorene-4-carboxylate (34). To a solution of **30** (200 mg, 0.34 mmol) in DMF (10 mL) were added $Pd(OAc)_2$ (30 mg, 0.13 mmol), PPh_3 (120 mg, 0.458 mmol) and Cs_2CO_3 (90 mg, 0.277 mmol) and the mixture was heated at 100 ºC for 12 h, at which time TLC showed no **35**, Then, the mixture was diluted with AcOEt (25 mL) and washed with 2 M HCl (2 x 10 mL), water (3 x 10 mL), brine (1 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded a crude product (300 mg) which was purified by flash chromatography (10 % AcOEt/Hexane) to obtain **34** (146 mg, 89 %) as a colorless syrup. $[\alpha]_D^{25}$= + 32.1 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.46 (s, H-25), 1.05 (ddd, *J* = 13.5, 13.3, 4.1 Hz, H-3”), 1.14 (ddd, *J* = 13.4, 13.3, 4.2 Hz, H-1´), 1.26 (s, H-27), 1.34 (s, H-20), 1.43 (dt, *J* = 13.6, 3.5 Hz, H-2”), 1.79 (qt, *J* = 14.2, 4.0 Hz, H-2´), 2.00 (s, H-5), 2.12 – 2.17 (m, H-1”), 2.17 – 2.21 (m, H-3´), 2.21 (s, H-23), 2.35 (s, H-18), 2.37 (d, *J* = 7.4 Hz, H-9), 3.53 (s, H-30), 4.87 (d, *J* = 11.0 Hz, H-31”), 4.91 (d, *J* = 11.1 Hz, H-31´), 6.12 (dd, *J* = 10.5, 1.8 Hz, H-7), 6.42 (dd, *J* = 10.5, 3.0 Hz, H-6), 6.65 (d, *J* = 7.4 Hz, H-11), 6.77 (d, *J* = 7.5 Hz, H-14), 7.06 (d, *J* = 7.5 Hz, H-15), 7.38 (t, *J* = 7.3 Hz, H-35), 7.45 (t, *J* = 7.6 Hz, H-34,36), 7.55 (d, *J* = 7.2 Hz, H-33,37). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 14.5 (C-25), 16.5 (C-18), 19.2 (C-2), 21.8 (C-23), 28.4 (C-27), 30.2 (C-20), 37.5 (C-3), 38.1 (C-1), 38.2 (C-10), 43.3 (C-

4), 47.6 (C-8), 51.3 (C-30), 52.5 (C-9), 63.9 (C-5), 74.7 (C-31), 77.4 (C-11), 118.0 (C-14), 125.5 (C-7), 127.7 (C-33,37), 128.1 (C-35), 128.8 (C-34,36), 130.6 (C-15), 130.7 (C-6), 131.3 (C-16), 137.7 (C-32), 139.2 (C-13), 140.3 (C-12), 152.8 (C-17), 171.3 (C-22), 177.5 (C-26). IR (film): 2931, 1726, 1454, 1372, 1226, 1157, 1042, 1022, 823, 753 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{32}H_{39}O_5$ ($M+H^+$) 503.2797, found: 503.2800.

Treatment of 30 with $Pd(OAc)_2/PPh_3$ and HCO_2Na. To a solution of **30** (95 mg, 0.163 mmol) in DMF (6 mL) were added $Pd(OAc)_2$ (29 mg, 0.129 mmol), PPh_3 (125 mg, 0.477 mmol) and HCO_2Na (110 mg, 1.62 mmol) and the mixture was heated at 100 ºC for 15 h. Then, the mixture was diluted with AcOEt (30 mL) and washed with HCl 2 M (1 x 10 mL), water (5 x 10 mL), brine (1 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded a crude product (155 mg) which was purified by flash chromatography (15 % AcOEt/Hexane) to obtain **28** (48 mg, 71 %) as a colorless syrup.

(4S,4aR,6aS,11R,11aR,11bS)-7-(benzyloxy)-4-(hydroxymethyl)-4,6a,8,11b-tetramethyl-2,3,4,4a,6a,11,11a,11b-octahydro-1H-benzo[a]fluoren-11-ol (35). To a stirred solution of **34** (113 mg, 0.225 mmol) in dry Et_2O (15 mL) cooled at 0 ºC was added $LiAlH_4$ (40 mg, 1.05 mmol) and the resulting suspension was stirred for 13 h at room temperature. Then, the mixture was quenched with acetone (1 mL) and the mixture was diluted with Et_2O (15 mL) and water (10 mL) was added. The phases were shaken and separated and the organic phase was washed with water (2 x 5 mL), brine (2 x 5 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the crude product was purified by flash chromatography (35 %

AcOEt/Hexane) to afford diol **35** (94 mg, 97 %) as a colorless syrup. $[\alpha]_D^{25}$= + 8.9 (c 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.62 (s, 3H), 0.84 – 0.95 (m, 1H), 1.05 (s, 3H), 1.17 – 1.26 (m, 1H), 1.32 (s, 3H), 1.42 – 1.48 (m, 1H), 1.50 – 1.70 (m, 2H), 1.79 (d, *J* = 13.7 Hz, 1H), 1.95 (s, 1H), 2.25 (d, *J* = 7.6 Hz, 1H), 2.37 (s, 3H), 2.67 (d, *J* = 13.1 Hz, 1H), 3.49 (d, *J* = 11.3 Hz, 1H), 3.54 (s, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 5.67 (t, *J* = 7.0 Hz, 1H), 5.78 (d, *J* = 10.9 Hz, 1H), 6.56 (dd, *J* = 10.2, 3.1 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 16.5 (CH_3), 16.6 (CH_3), 18.1 (CH_2), 26.4 (CH_3), 30.1 (CH_3), 35.3 (CH_2), 38.1 (C), 38.3 (C), 39.3 (CH_2), 47.8 (C), 52.6 (CH), 65.4 (CH_2), 66.6 (CH), 74.6 (CH_2), 77.2 (CH), 117.8 (CH), 124.4 (CH), 127.5 (CH x 2), 127.9 (CH), 128.6 (CH x 2), 130.6 (CH), 130.8 (C), 133.8 (CH), 137.5 (C), 138.8 (C), 144.1 (C), 152.8 (C). IR (film): 3416, 2922, 2853, 1710, 1454, 1373, 1223, 1158, 1024, 909, 822, 754, 696, 666 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{29}H_{37}O_3$ ($M+H^+$) 433.2743, found: 433.2739.

((4S,4aR,6aR,11aS,11bR)-4,6a,8,11b-tetramethylhexadecahydro-1H-benzo[a]fluoren-4-yl)methyl acetate (36). To a solution of compound **35** (123 mg, 0.28 mmol) in AcOH (1 mL) were added PtO_2 (25 mg, 0.11 mmol) and $HClO_4$ (0.2 mL) and the mixture was stirred under hydrogen atmosphere (4 atm.) during 14 h at room temperature. After this time, the resulting mixture was filtered in silica gel, was washed with AcOEt (30 mL) and the filtrate was washed with water (8 x 10 mL) and brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The resulting crude was purified through silica gel (5 % AcOEt/Hexane) for

yield acetate **36** (93 mg, 91 %) as a colorless syrup. $[\alpha]_D^{25}$= + 12.3 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, Chloroform-*d*) δ (ppm) 0.85 (s, 3H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 3H), 0.91 – 1.00 (m, 6H), 1.02 (s, 3H), 1.05 – 1.80 (m, 16H), 2.04 (s, 3H), 2.11 – 2.18 (m, 1H), 4.11 (d, *J* = 10.9 Hz, 1H), 4.33 (d, *J* = 11.0 Hz, 1H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ (ppm) 17.4 (CH_3), 17.9 (CH_2), 18.4 (CH_2), 21.0 (CH_3), 23.1 (CH_3), 26.3 (CH_3), 26.4 (CH_2), 27.1 (CH_2), 29.0 (CH_2), 30.1 (CH_2), 32.5 (CH_3), 33.8 (CH_2), 33.9 (CH), 35.2 (CH), 36.0 (C), 36.5 (CH_2), 37.0 (C), 42.7 (C), 43.2 (CH_2), 49.4 (CH), 50.6 (CH), 62.8 (CH), 66.4 (CH_2), 171.4 (C). IR (film): 2932, 1725, 1667, 1601, 1535, 1464, 1412, 1372, 1248, 1219, 1194, 1136, 771 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{24}H_{41}O_2$ ($M+H^+$) 361.3107, found: 361.3103.

Dasyscyphin E (9). To a solution of compound **35** (85 mg, 0.20 mmol) in AcOEt (1 mL) was added PtO_2 (40 mg, 0.19 mmol) and the mixture was stirred under hydrogen atmosphere (4 atm.) during 13 h at room temperature. After this time, the resulting mixture was filtered in silica gel, and washed with AcOEt (20 mL) and the solvent was removed under vacuum. The resulting crude was purified by flash chromatography on silica gel (25% AcOEt/Hexane) for yield *dasyscyphin E* (**9**) (60 mg, 94 %) as a colorless syrup. $[\alpha]_D^{25}$= + 2.1 (c 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 0.46 (s, 3H), 0.83 - 0.99 (m, 2H), 1.00 (s, 3H), 1.16 (dd, *J* = 11.3, 3.7 Hz, 1H), 1.23 (s, 3H), 1.25 - 1.45 (m, 2H), 1.48 (br d, *J* = 13.6 Hz, 1H), 1.55 - 1.77 (m, 4H), 1.83 (br d, *J* = 13.6 Hz, 1H), 2.19 (s, 3H), 2.64 (d, *J* = 16.6 Hz, 1H), 2.79 (m, 1H), 3.00 (dd, *J* = 16.5, 7.7 Hz, 1H), 3.43 (d, *J* = 10.9 Hz, 1H), 3.73 (d, *J* = 10.9 Hz, 1H), 4.53 (br s, 1H), 6.61 (d, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm) 15.5 (CH_3), 16.7 (CH_3), 18.3 (CH_2), 19.7 (CH_2), 26.7 (CH_3), 31.0 (CH_3), 32.5

(CH_2), 34.8 (CH_2), 35.7 (CH_2), 37.3 (C), 38.6 (C), 41.4 (CH_2), 47.8 (C), 53.4 (CH), 62.6 (CH), 65.3 (CH_2), 116.5 (CH), 120.8 (C), 129.1 (CH), 135.7 (C), 144.1 (C), 150.3 (C). IR (film): 3390, 2923, 2852, 1714, 1585, 1471, 1366, 1262, 1215, 1012, 907, 797 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{22}H_{33}O_2$ ($M+H^+$) 329.2481, found: 329.2476.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra.

X-ray crystal structure and crystallographic table for compound **28.**

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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