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Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp^3)−H Activation Strategy

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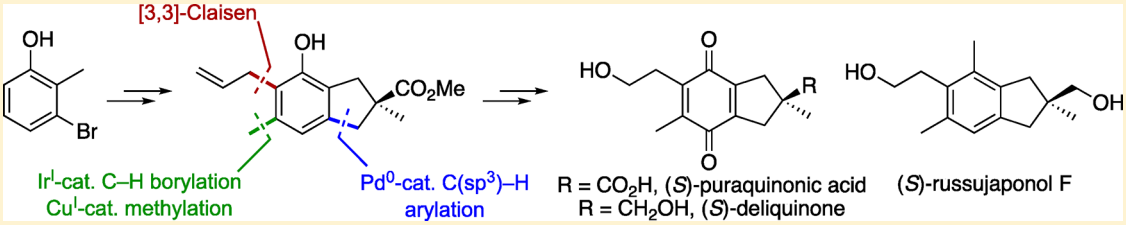


ABSTRACT: Three (nor)illudalane sesquiterpenes were synthesized from a common intermediate in racemic and enantioenriched forms using Pd^0-catalyzed C(sp^3)−H arylation as a key step. The configuration of the isolated, highly symmetric quaternary stereocenter of the target molecules was controlled through a matched combination of chiral substrate and catalyst. Moreover, the recently developed Ir-catalyzed C−H borylation/Cu-catalyzed methylation method was employed to install the methyl group on the benzene ring. This strategy allowed the efficient synthesis of both racemic and (*S*)-configured puraquinonic acid, deliquinone, and russujaponol F.

INTRODUCTION

Illudalane and norilludalane sesquiterpenes are a large family of bioactive natural products isolated from mycelial cultures of woody mushrooms.[1] These compounds usually contain a geminal dimethyl group on a cyclopentane ring fused with diverse scaffolds (Figure 1a). However, some members of this family possess a quaternary stereocenter, resulting from the oxidation of one of the geminal methyl groups to a hydroxymethyl or a carboxylic acid group, such as the benzoquinones puraquinonic acid (**4**)[2] and deliquinone (**5**),[3] and the indane russujaponol F (**6**)[4] (Figure 1b). The former, isolated from cultures of *Mycena pura*, showed a mild differentiation-inducing activity toward HL-60 cells.[2]

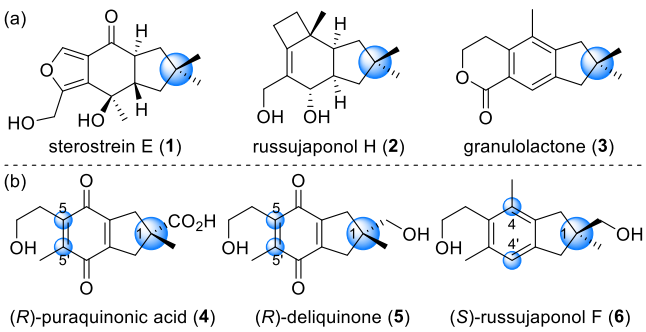
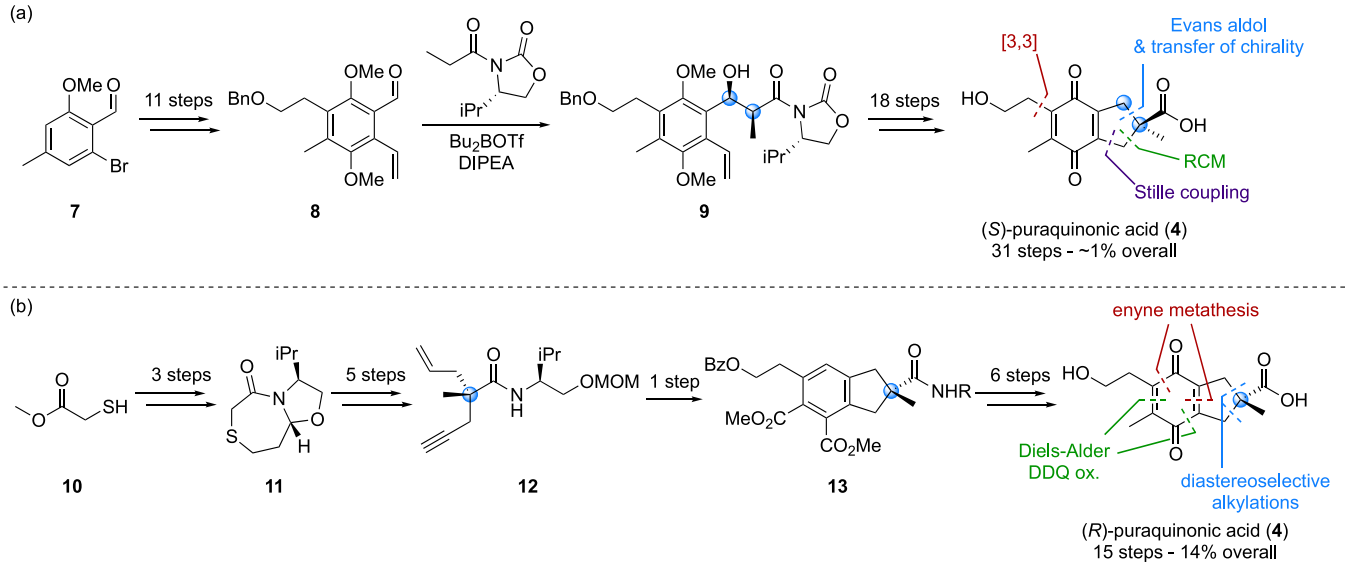


Figure 1. (a) Examples of (nor)illudalanes with a gem-dimethyl group. (b) (Nor)illudalane targets featuring a highly symmetric quaternary stereocenter.

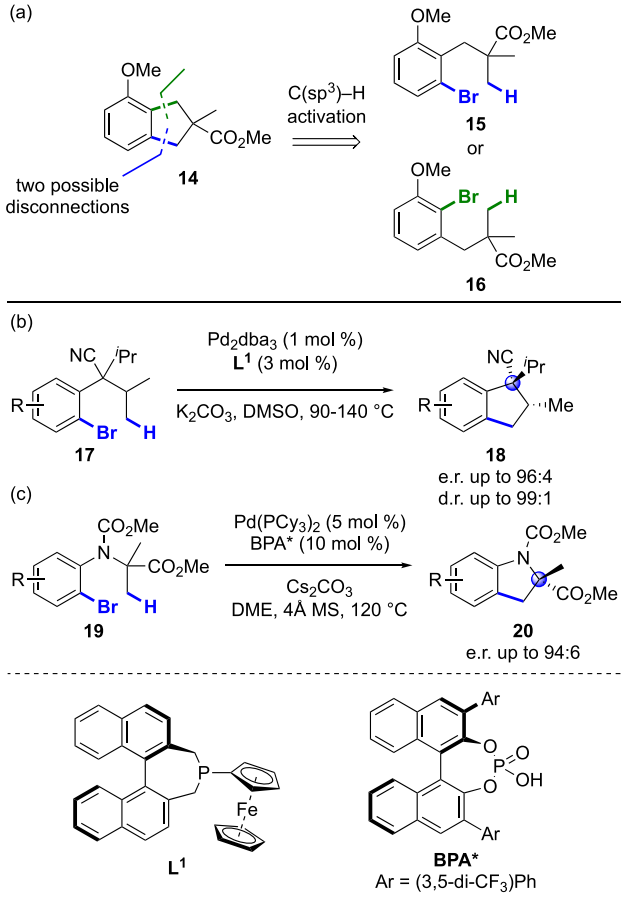
In addition to a polysubstituted aromatic or benzoquinone core, the most intriguing part of molecules **4**−**6** is probably the highly symmetric quaternary stereocenter resulting from different substituents three or four carbons away (Figure 1b). Such quaternary stereocenters constitute an interesting challenge in organic synthesis.[5] Indeed, despite a moderate structural complexity, only two enantioselective syntheses of puraquinonic acid have been reported before our work,[6,7] and none for russujaponol F and deliquinone. Clive and co-workers reported the first synthesis of (*S*)-puraquinonic acid in 31 steps using an Evans aldol reaction as the enantio-determining step (Scheme 1a, **8** → **9**).[6c,d] This strategy required a large number of functional group interconversions and manipulations. In addition, this work established the absolute configuration of natural puraquinonic acid as (*R*) upon comparison with a natural sample. More recently, Gleason and co-workers disclosed a much more efficient synthesis of (*R*)-puraquinonic acid (Scheme 1b).[7] The quaternary stereocenter was constructed at the beginning of the synthesis via sequential diastereoselective alkylations using a valine-derived chiral auxiliary (**11**). Then, the indane core was built using an elegant and effective combination of enyne metathesis and Diels−Alder cycloaddition, followed by oxidation with DDQ in a one-pot procedure (**12** → **13**). After functional group manipulations, cleavage of the chiral auxiliary and oxidation of the aromatic ring to the benzoquinone, this approach yielded enantiopure (*R*)-puraquinonic acid in 12 steps and 20% overall yield from the in-house auxiliary,[8] or 15 steps and 14% from (*S*)-valinol.

Scheme 1. Previous Enantioselective Total Syntheses of Puraquinonic Acid



In light of our longstanding interest in this field,[9] we considered a different approach to access these molecules, using Pd^0-catalyzed $C(sp^3)$–H activation as the key step (Scheme 2a). Our retrosynthetic analysis is based on a disconnection at one of the two $C(sp^2)$–$C(sp^3)$ bonds of the indane **14**, which would be constructed via asymmetric $C(sp^3)$–H arylation.[10] The quaternary stereocenter would arise from the desymmetrization of the two enantiotopic methyl groups in **15** or **16**.

Scheme 2. Retrosynthetic Analysis and Previous Work on the Generation of Tetrasubstituted Stereocenters via Pd^0-Catalyzed $C(sp^3)$–H Activation

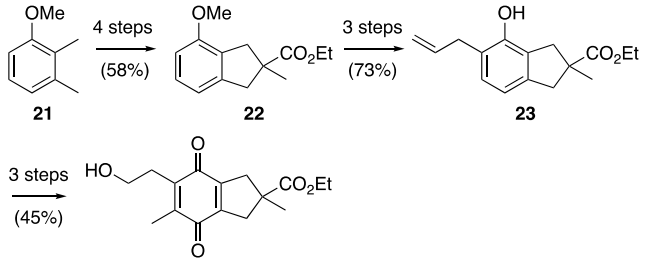


Previously, we reported the synthesis of enantioenriched indanes using $C(sp^3)$–H arylation in the presence of a chiral binepine ligand $\mathbf{L^1}$ (Scheme 2b).[11] In this case, a quaternary stereocenter was generated via desymmetrization of two isopropyl groups. More recently, we achieved the generation of tetrasubstituted stereocenters in the context of indoline synthesis using a chiral phosphate catalyst.[12] In this case, the stereocenter arose from the desymmetrization of two methyl groups on a tetrasubstituted carbon (Scheme 2c), which proved to be more challenging than desymmetrizing methyl groups on a trisubstituted carbon.[13] Moreover, in both examples the intramolecular C–H arylation was likely favored by strong Thorpe–Ingold effects. These precedents suggested that the asymmetric $C(sp^3)$–H arylation of substrates **15** and **16** leading to the formation of the all-carbon stereocenter in **14** would be particularly challenging. Herein, we report our efforts to synthesize target molecules **1**–**3** in racemic and enantioselective manner.[14]

RESULTS AND DISCUSSION

Racemic Synthesis: First Route. We first explored the feasibility of our strategy with the synthesis of racemic puraquinonic acid. Our synthetic plan was inspired from previous work by Kraus and co-workers on the synthesis of (±)-puraquinonic acid ethyl ester (**24**) (Scheme 3) and (±)-deliquinone.[15] They prepared the indane ethyl ester **22**, analogous to our putative C–H activation product **14**, through a four-step sequence from 2,3-dimethylanisole. Hence, we initially intended to follow the same sequence to complete our total synthesis. From **22**, the phenol methyl group was replaced with an allyl group, and an aromatic Claisen rearrangement led to compound **23**. The terminal alkene was cleaved via reductive ozonolysis to give the corresponding alcohol, and the phenol was oxidized to the corresponding benzoquinone in the presence of salcomine and oxygen. Finally, the missing methyl group was introduced by radical methylation using acetic acid and silver nitrate. Of note, Kraus

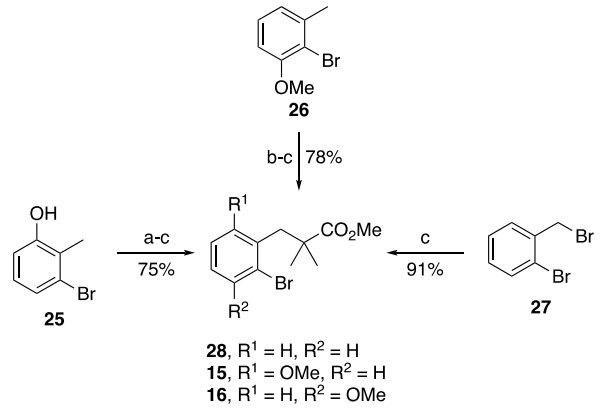
Scheme 3. Total Synthesis of Puraquinonic Acid Ethyl Ester by Kraus



and co-workers did not report the saponification of **24** to puraquinonic acid.

We selected aryl bromide **28** to test conditions for the key C(sp^3)–H arylation (Scheme 4). It was readily prepared by

Scheme 4. Preparation of C–H Arylation Substrates[a]

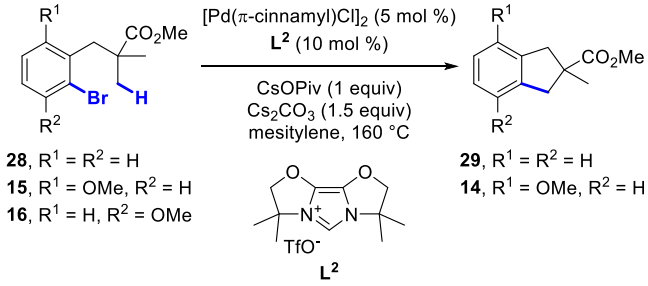


[a]Reagents and conditions: (a) K_2CO_3, MeI, DMF, 50 °C; (b) NBS, $(BzO)_2$, CCl_4, reflux; (c) ^{i}PrCO$_2$Me, LDA, 0 °C, then benzyl bromide, 0 → 25 °C.

alkylation of the lithium enolate of methyl isobutyrate with 2-bromobenzyl bromide. After some optimization, we obtained the best results using IBioxMe$_4$ (**L^2**), an *N*-heterocyclic carbene (NHC) ligand developed by Glorius and co-workers,[16] which provided a full conversion and ca. 95% of product (Table 1, entry 1).

Then, we synthesized aryl bromide **15** from 3-bromo-2-methylphenol **25** (Scheme 4). The latter is commercially available, but can be prepared on a large scale via Sandmeyer reaction from 3-bromo-2-methylaniline.[17] Phenol **25** was then methylated with K_2CO_3 and methyl iodide to yield the corresponding anisole. The benzylic position was brominated, and the corresponding benzyl bromide was employed in the alkylation of the lithium enolate of methyl isobutyrate, in a similar fashion to **28**. This robust sequence led to substrate **15** in 75% overall yield and with only one column chromatography. Substrate **16** was prepared in a similar manner from commercial 2-bromo-1-methoxy-3-methylbenzene **26**. Both substrates were engaged in C(sp^3)–H activation under the same conditions as above. Compound **15** reacted cleanly and the indane product **14** was isolated in 92% yield (Table 1, entry 2). In contrast, the isomer **16** gave a very low conversion, and ca. 90% of the starting material was recovered (entry 3). The lack of reactivity of **16** can be explained by the sterically

Table 1. C(sp^3)–H Arylation of Substrates 15, 16, and 28



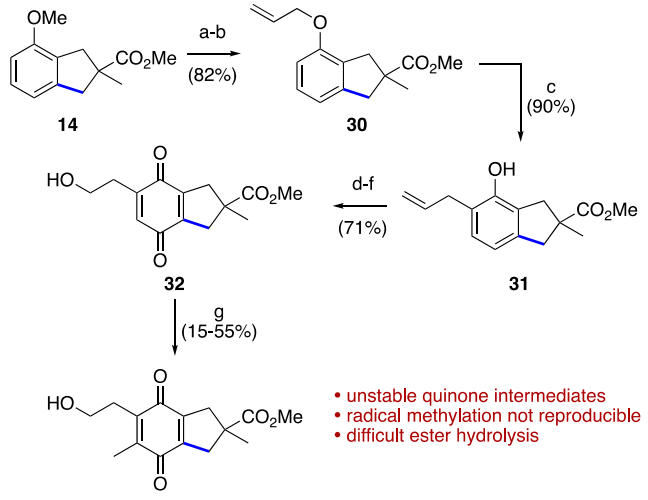
entry	reactant	product	conv. (%)[a,b]
1	**28**	**29**	95
2	**15**	**14**	96 (92)
3	**16**	**14**	6

[a]Conversion of the aryl bromide to the indane product estimated by GC–MS analysis. [b]Yield of isolated product in parentheses.

difficult oxidative addition of the di-*ortho*-substituted bromide to palladium(0).

Then, we continued our synthesis as initially planned (Scheme 5). The two methoxy groups of indane **14** were

Scheme 5. First Route for the Synthesis of (±)-Puraquinonic Acid[a]



[a]Reagents and conditions: (a) HBr aq., AcOH, reflux; (b) $KHCO_3$, MeI, DMF, 40 °C, then NaH, allyl bromide; (c) PhNEt$_2$, 200 °C; (d) OsO_4 (5 mol %), $NaIO_4$, AcOEt/H_2O, 25 °C; (e) $NaBH_4$, MeOH, 0 °C; (f) salcomine hydrate, O_2 atm., MeCN, 25 °C; (g) AcOH, $AgNO_3$, $(NH_4)_2S_2O_8$, MeCN/H_2O, 70 °C.

cleaved using hydrobromic acid in refluxing acetic acid to obtain the corresponding phenol-carboxylic acid. The crude mixture was alkylated with $KHCO_3$/MeI and NaH/allyl bromide in a one-pot fashion[18] to give compound **30** in 82% yield over 2 steps. The latter was engaged in the aromatic Claisen rearrangement. After screening a few solvents, the best yield (90%) was achieved with *N*,*N*-diethylaniline at 200 °C.

At this stage, we encountered reproducibility issues in the ozonolysis of **31**, with low yields (ca. 20%) and starting material decomposition. We assume that the free phenol undergoes oxidation to the benzoquinone and further degradation. This ozonolysis problem was already observed

by Clive and co-workers on a similar intermediate, and they found that the Lemieux–Johnson oxidation gave better results.[6a] Accordingly, **31** was oxidized to the corresponding aldehyde using OsO_4 and sodium periodate, and further reduced with sodium borohydride. This two-step sequence afforded the corresponding primary alcohol in 87% yield. Then, the phenol was oxidized to the corresponding benzoquinone using the same conditions as Kraus and co-workers,[15] i.e., with 40 mol % of salcomine under an oxygen atmosphere, hence furnishing the unstable benzoquinone **32** in 82% yield.

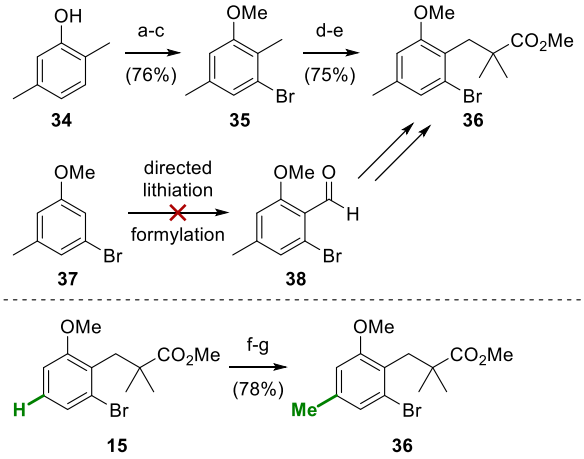
Unfortunately, the radical methylation of **32**[15,19] gave irreproducible yields in the range of 15–55%. We anyway isolated some methylated benzoquinone **33** and attempted its saponification. Unfortunately, we never succeeded to isolate puraquinonic acid despite numerous attempts, due to the sensitivity of the benzoquinone ring, and hence we decided to opt for a different strategy. Nevertheless, these results gave us important information to design a more effective plan. Indeed, we encountered three major problems during this synthesis: (1) instability of benzoquinone intermediates; (2) low yield and irreproducibility of the radical methylation; (3) impossibility to hydrolyze the ester on the benzoquinone. These problems led us to conclude that the saponification has to be performed prior to the oxidation to benzoquinone. This also precludes the introduction of the methyl group via radical methylation, which would be likely incompatible with the carboxylic acid moiety. Therefore, this methyl group has to be installed earlier in the synthesis. Besides, a late-stage oxidation of the phenol to the benzoquinone would be more adapted in light of stability issues.

Racemic Synthesis: Second Route. For this second route, we decided to start with the methyl group already present at the beginning. The global strategy remains unchanged until the end, where the ester would be cleaved first, followed by phenol oxidation to benzoquinone. This new synthetic plan led us to consider the possibility of preparing two other natural products, deliquinone and russujaponol F. Indeed, a common indane intermediate (**40**, see Scheme 7), would be the divergent point to prepare these three natural products.

Compound **36** was first prepared from 2,5-xylenol **34** (Scheme 6, top). The phenol was perbrominated using bromine and aluminum tribromide, followed by selective debromination with hydroiodic acid and phenol methylation with K_2CO_3 and MeI as described.[20] This sequence yielded the anisole **35** in 76% overall yield with one distillation as the only purification. Then selective radical benzylic bromination,[21] and enolate alkylation furnished **36** in 75% yield over two steps and 57% over 5 steps from phenol **34**. We envisaged another strategy to prepare the same benzyl bromide intermediate via directed lithiation of aryl bromide **37** and formylation to give aldehyde **38**, then reduction and Appel reaction.[22] Unfortunately, we never succeeded to achieve an efficient lithiation/formylation, probably due to the generation of the unstable benzyne intermediate.

More recently, we considered a C–H activation approach to **36** based on recent work of Hartwig and co-workers.[23] Indeed, a sequence of iridium-catalyzed C–H borylation and copper-catalyzed methylation would allow to bridge our first and second synthetic routes. The C–H borylation of ester **15** should be selective for the less hindered position, as demonstrated by Hartwig and co-workers for di- and

Scheme 6. Preparation of Methylated Aryl Bromide 36[a]

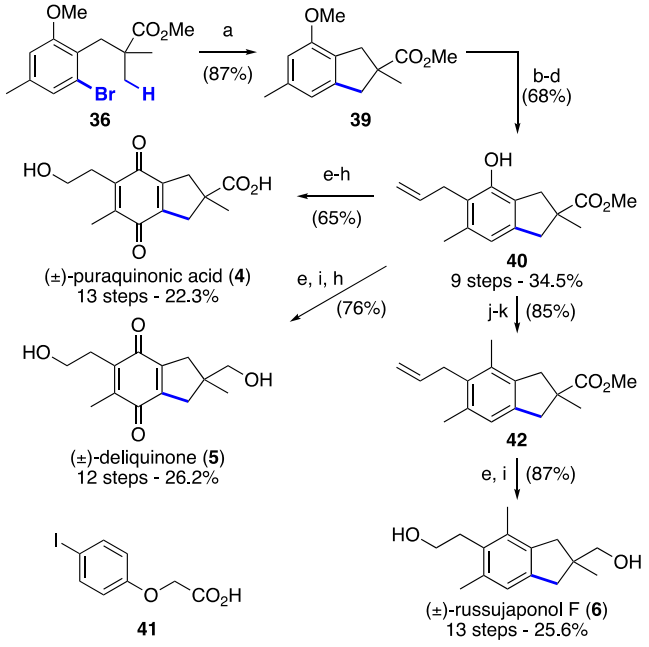


[a]Reagents and conditions: (a) Br_2, $AlBr_3$, CH_2Cl_2, 0 °C; (b) HI aq., reflux; (c) K_2CO_3, MeI, acetone, reflux; (d) *N*-bromosuccinimide, AIBN, CCl_4, reflux; (e) $^iPrCO_2Me$, LDA, THF, 0 °C, then benzyl bromide, 0 → 25 °C; (f) $[Ir(COD)OMe]_2$ (1.25 mol %), dtbbpy (2.5 mol %), B_2Pin_2, THF, 50 °C; (g) CuI (10 mol %), LiI (20 mol %), ^tBuOLi, $PO(OMe)_3$, DMI, 50 °C. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; DMI = 1,3-dimethyl-2-imidazolidinone.

trisubstituted arenes,[24] and the Cu-catalyzed methylation of the corresponding boronate would lead to the desired aryl bromide **36**. We applied this method to aryl bromide **15** and were pleased to obtain the corresponding borylated intermediate in 97% yield in a highly regio- and chemoselective manner (Scheme 6, bottom). The subsequent methylation worked well too, providing a yield of 80%. The global sequence from 3-bromo-2-methylphenol **25** (see Scheme 4) is as effective as the previous one from 2,5-xylenol **34**, with an overall yield of 58% for the same number of steps. However, the C–H borylation approach is arguably more elegant, since it avoids both harsh reaction conditions in the perbromination and debromination steps and a difficult separation of the undesired benzyl bromide isomer after radical bromination. Moreover, the borylated intermediate could be potentially useful to prepare analogues via different reactions.[25]

Next, **36** was engaged in the previously optimized C(sp^3)–H arylation in the presence of IBiox ligand $\mathbf{L^2}$, to give the indane **39** in 87% yield (Scheme 7). Then, similarly to the first route, both methoxy groups were cleaved under acidic condition (87% yield), the corresponding phenol-carboxylic acid was alkylated and allylated (89% yield) and the aromatic Claisen rearrangement furnished indane **40** (88% yield). The latter, obtained in 34.5% overall yield over 9 steps from phenol **25**, was used as a common intermediate to prepare the three target racemic natural products. Compound **40** was first engaged in the Lemieux–Johnson oxidation, followed by reduction with sodium borohydride to yield the corresponding alcohol in 75% yield over two steps. The saponification of this product proceeded well and the corresponding carboxylic acid was directly engaged in the oxidation step without purification. The benzoquinone formation failed under previous conditions with salcomine and oxygen. Gratifyingly, we found that this oxidation proceeded cleanly using conditions developed by Yakura and Konishi,[26] whereby a catalytic hypervalent iodine reagent is generated from iodophenoxyacetic acid **41** and Oxone. Under these mild conditions, (±)-puraquinonic acid was obtained in 82% yield over two steps and an overall yield

Scheme 7. Divergent Synthesis of (±)-Puraquinonic Acid, (±)-Deliquinone, and (±)-Russujaponol[a]



[a]Reagents and conditions: (a) [Pd(π-cinnamyl)Cl]$_2$ (5 mol %), L^2 (10 mol %), CsOPiv, Cs_2CO_3, mesitylene, 160 °C; (b) HBr aq., AcOH, reflux; (c) $KHCO_3$, MeI, DMF, 40 °C, then NaH, allyl bromide; (d) $PhNEt_2$, 200 °C; (e) OsO_4 (5 mol %), $NaIO_4$, AcOEt/H_2O, 25 °C; (f) $NaBH_4$, MeOH, 0 °C; (g) LiOH aq., dioxane, reflux; (h) **41** (10 mol %), Oxone, CF_3CH_2OH/H_2O, 25 °C; (i) $LiAlH_4$, THF, 0 → 25 °C; (j) Tf_2O, pyridine, CH_2Cl_2, 0 → 25 °C; (k) [Pd_2dba_3·$CHCl_3$] (2.5 mol %), XPhos (5 mol %), DABCO·2$AlMe_3$, THF, reflux. DABCO = 1,4-diazabicyclo[2.2.2]octane; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

of 22.3% over 13 steps. (±)-Deliquinone was obtained in a similar fashion. The double bond of **40** was oxidized under Lemieux–Johnson conditions and both aldehyde and ester groups were reduced using lithium aluminum hydride. Phenol oxidation under the same conditions as puraquinonic acid provided racemic deliquinone in 76% yield over three steps and an overall yield of 26.2% over 12 steps. To prepare russujaponol F, phenol **40** was triflated under classic conditions (87% yield). The corresponding triflate was engaged in a Pd^0-catalyzed cross-coupling under conditions developed by Woodward and co-workers, using the air-stable DABAL-Me_3 [DABCO-bis(trimethylaluminum)] complex.[27] These efficient and convenient conditions furnished **42** in excellent yield (98%). Finally, racemic russujaponol F was obtained by Lemieux–Johnson oxidation and reduction of both carbonyl groups in 87% yield over two steps and an overall yield of 25.6% over 13 steps. The current syntheses of (±)-puraquinonic acid and deliquinone are more efficient than the best previously reported syntheses by Clive and co-workers and Kraus and co-workers, respectively. Moreover, (±)-russujaponol F was synthesized for the first time.

Enantioselective Synthesis. After having completed the racemic syntheses, we directed our efforts toward the development of enantioselective versions. Investigations of the asymmetric C(sp^3)–H activation of the model aryl bromide **15** (see Table 1), which were detailed earlier,[14] led us to opt for a chiral substrate/chiral ligand combination. We prepared the L-proline amide **43** in 84% yield via saponification and amide formation under Schotten–Baumann conditions (Scheme 8). This substrate was engaged in the asymmetric C(sp^3)–H activation using ligand L^3, a chiral bulky NHC developed by Kündig and co-workers,[28] which furnished indane **44** in 87% yield and 85:15 diastereomeric ratio. Then, the proline and methoxy groups were cleaved with hydrobromic acid to provide the corresponding phenol-carboxylic acid **45** in 92% yield. After significant experimentation, we found that this intermediate slowly recrystallized in a mixture of chloroform and cyclohexane. The crystalline material was racemic, and the recovered mother liquor showed an enantiomeric ratio of 96:4. Despite this loss of material in the crystallization, this global sequence of deprotection and recrystallization occurred in 57% yield. At this point, we tried to determine the absolute configuration of the generated quaternary stereocenter using X-ray diffraction analysis, but unfortunately, despite numerous attempts, neither the enantioenriched compound **45**, nor any derivative that we synthesized[29] furnished suitable crystals. The configuration was finally ascribed as (*S*) by NOESY NMR of a Mosher derivative and vibrational circular dichroism,[14] and this assignment was later confirmed by the specific rotation values of the target products. With the enantioenriched intermediate **45** in hand, we employed the same sequence as for the racemic synthesis, and obtained comparable yields. In this manner, (*S*)-puraquinonic acid ($[\alpha]_D^{20}$ + 1.4, lit. for the (*R*) enantiomer: − 2.2)[6c,d] was obtained in 15 steps, 9.8% overall yield, (*S*)-deliquinone ($[\alpha]_D^{20}$ + 0.9, lit. for the (*R*) enantiomer: − 0.5)[3] in 14 steps and 9.9% overall yield, and (*S*)-russujaponol F ($[\alpha]_D^{20}$ + 2.1, lit. + 1.3)[4] in 15 steps and 12.3% overall yield. These specific rotations confirmed the configuration assignment of intermediate **45**. Therefore, we prepared natural russujaponol F, *ent*-puraquinonic acid, and *ent*-deliquinone.

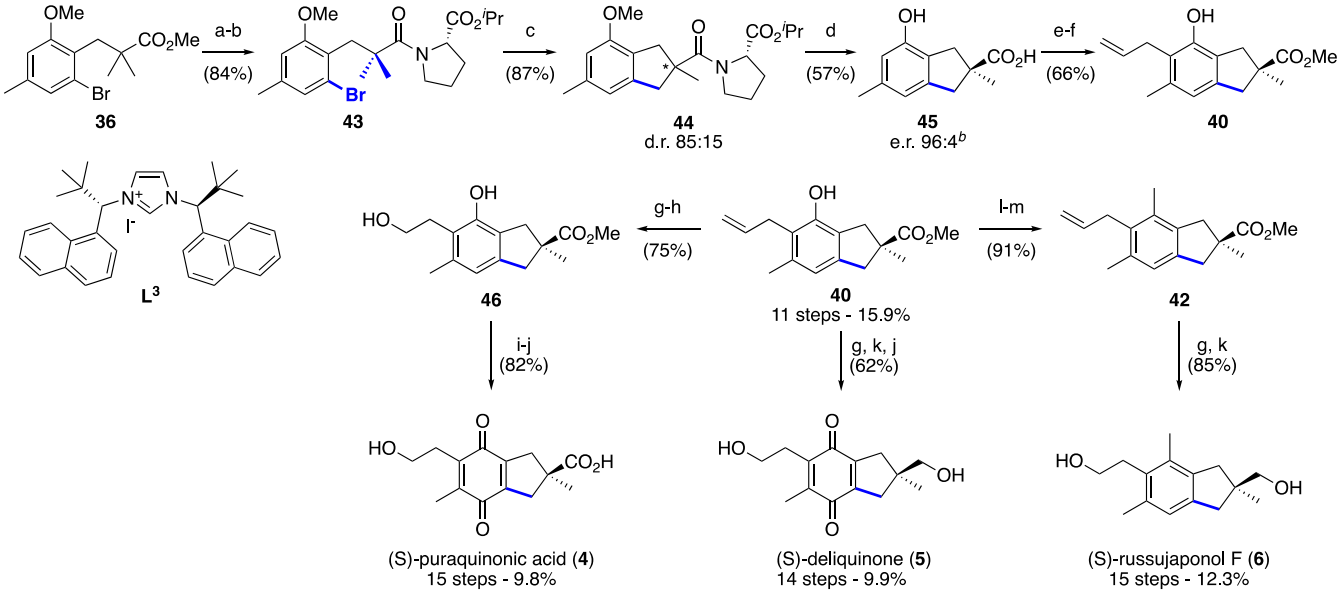
CONCLUSION

In conclusion, three (nor)illudalane sesquiterpenes were synthesized in racemic and enantioenriched forms from a common indane intermediate. The latter was obtained by Ir-catalyzed C–H borylation and Pd^0-catalyzed C(sp^3)–H arylation as key steps, and an asymmetric version of the C–H arylation allowed the construction of the isolated, highly symmetric quaternary stereocenter. This work, representing the first application of Pd^0-catalyzed enantioselective C(sp^3)–H activation to natural product synthesis, highlights the challenges and potential of this transformation for the synthesis of chiral bioactive molecules.

EXPERIMENTAL SECTION

General Methods. All reactions involving air-sensitive material were carried out in predried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glovebox. An oil bath was used as heating source unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using precoated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains ($KMnO_4$ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230–400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases. Anhydrous solvents were purchased from Acros Organics or Sigma-Aldrich. The solvents were degassed by three cycles of freeze–pump–thaw and storing in single-necked flasks equipped with a JYoung PTFE valve when necessary. Palladium complexes were purchased from Sigma-Aldrich or Strem. All other chemical reagents

Scheme 8. Divergent Synthesis of (*S*)-Puraquinonic Acid, (*S*)-Deliquinone, and (*S*)-Russujaponol[a]



[a]Reagents and conditions: (a) LiOH aq., THF/MeOH, 80 °C; (b) $(COCl)_2$, DMF cat., CH_2Cl_2, 25 °C, then L-Pro-O^{i}Pr; (c) $[Pd(\pi\text{-cinnamyl})Cl]_2$ (5 mol %), **L**^{3} (10 mol %), CsOPiv, Cs_2CO_3, mesitylene, 160 °C; (d) HBr aq., AcOH, reflux, then recrystallization from $CHCl_3/C_6H_{12}$ 3:1; (e) $KHCO_3$, MeI, DMF, 40 °C, then NaH, allyl bromide; (f) $PhNEt_2$, 200 °C; (g) OsO_4 (5 mol %), $NaIO_4$, AcOEt/H_2O, 25 °C; (h) $NaBH_4$, MeOH, 0 °C; (i) LiOH aq., dioxane, reflux; (j) **41** (10 mol %), Oxone, CF_3CH_2OH/H_2O, 25 °C; (k) $LiAlH_4$, THF, 0 → 25 °C; (l) Tf_2O, pyridine, CH_2Cl_2, 0 → 25 °C; (m) $[Pd_2dba_3{\cdot}CHCl_3]$ (2.5 mol %), XPhos (5 mol %), DABCO·2$AlMe_3$, THF, reflux. [b]Measured by HPLC on a chiral stationary phase using the racemic compound as reference.

were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Apollo scientific and Fluorochem and used as received without further purification unless otherwise stated. GC−MS analyses were performed with a Shimadzu QP2010SB GC−MS apparatus on a Rtx-5 ms-LowBleed column lined with a mass (EI) detection system. HPLC analyses was performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU20A3 degasser and SPD-M20A Diode Array or UV/vis detector. The following chiral columns from Daicel Chemical Industries were used: OJ-H (Chiralcel), IA (Chiralpak) in 4.6 × 250 mm size. Melting points were obtained on a Büchi melting point M-565, and are uncorrected.

IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 400 (400 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual peaks ^1H δ 7.26 ppm, ^{13}C δ 77.16 ppm) unless otherwise noted. ^{19}F NMR spectra were referenced to external $CFCl_3$. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and brs = broad singlet), coupling constant in Hz and integration. High resolution mass spectra were recorded by Dr. H. Nadig, Dr. M. Pfeffer and S. Mittelheisser (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotations were measured on a PerkinElmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100 mm) with NaD-Line (λ = 589 nm). The concentration (c) was given in g/100 mL.

3-Bromo-2-methylphenol (25)..[14,17] Freshly distilled 3-bromo-2-methylaniline (70 g, 376 mmol) was added to an aqueous 1 M solution of sulfuric acid (451 mL, 451 mmol) at 0 °C under vigorous stirring (formation of a white suspension of anilinium). Then a saturated solution of sodium nitrite (31.1 g, 451 mmol) in water was added dropwise at −5 °C. After stirring at −5 °C for 20 min (most of the solid is dissolved at this point), concentrated sulfuric acid (14 mL, 258 mmol) was added and the solution was heated at 100 °C for 1 h. The mixture was then diluted with water, extracted with Et_2O, dried and concentrated to yield a black slurry. The residue was purified by sublimation under a vacuum (0.1 mbar), and the obtained orange solid was recrystallized with cyclohexane to yield **25** as a white crystalline solid (32 g, 171 mmol, 46% yield): R_f 0.25 (85:15 PE/AcOEt); mp 96−98 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.0, 1.1 Hz, 1H), 6.92 (td, J = 8.0, 0.5 Hz, 1H), 6.71 (ddd, J = 8.0, 1.1, 0.5 Hz, 1H), 4.87 (s, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.5, 127.6, 126.2, 125.1, 124.6, 114.2, 15.7; IR ν_{max}/cm^{-1} (neat) 3283, 1435, 1241, 998, 762 cm^{-1}; GC−MS (EI) m/z $[M]^{+\cdot}$ calcd for $C_7H_7{}^{79}BrO$ 186, found 186.

Methyl 3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoate (15).[14] 3-Bromo-2-methylphenol (**25**) (17.8 g, 95 mmol) was dissolved in DMF (240 mL) and K_2CO_3 (39.4 g, 285 mmol, 3 equiv) was added; the mixture was then stirred during 5 min at room temperature. After this period, methyl iodide (29.6 mL, 475 mmol, 5 equiv) was added in one portion and the reaction was stirred at 50 °C during 2 h. The reaction was then diluted with water, extracted with EtOAc and concentrated to yield the corresponding anisole which was used in the next step without further purification. This anisole was mixed with *N*-bromosuccinimide (17.75 g, 100 mmol, 1.05 equiv) and benzoyl peroxide (75%) (1.23 g, 3.8 mmol, 4 mol %) in CCl_4 (190 mL) and was heated to reflux and stirred overnight. The reaction mixture was then cooled to room temperature and filtered. The filtrate was diluted with DCM and washed successively with 2 M NaOH, water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding benzyl bromide which was used in the next step without further purification. A solution of LDA (100 mmol, 1.05 equiv) in THF (190 mL) was prepared from diisopropylamine (14 mL, 100 mmol, 1.05 equiv) and 2.5 M ^{n}BuLi in hexane (40 mL, 100 mmol, 1.05 equiv), stirred at 0 °C during 15 min. To the LDA solution, methyl isobutyrate (10.9 mL, 95 mmol, 1 equiv) was added dropwise at 0 °C and the mixture was stirred at the same temperature for 45 min. The benzyl bromide, obtained previously, in THF (95 mL) was added slowly to the solution always at 0 °C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then added to the reaction at 0 °C. The mixture was extracted three times with Et_2O; the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered, concentrated under a

vacuum and purified by column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **15** as a colorless oil (21.4 g, 71 mmol, 75% over 3 steps) that solidified upon standing: R_f 0.22 (90:10 PE/AcOEt); mp 42−44 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, J = 8.1, 1.1 Hz, 1H), 7.04 (t, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.1, 1.1 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.18 (s, 2H), 1.21 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.3, 159.1, 128.4, 127.4, 127.3, 125.2, 109.3, 55.6, 51.8, 43.4, 39.3, 25.6; IR ν_{max}/cm^{-1} (neat) 2980, 1716, 1265, 1146, 1029, 771 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{17}{}^{79}BrNaO_3$ 323.0253, found 323.0251.

Methyl 3-(2-bromo-3-methoxyphenyl)-2,2-dimethylpropanoate (16). 2-Bromo-1-methoxy-3-methylbenzene (**26**) (1.16 g, 5.77 mmol) was mixed with *N*-bromosuccinimide (1.08 g, 6.06 mmol, 1.05 equiv) and benzoyl peroxide (75%) (75 mg, 0.23 mmol, 4 mol %) in CCl_4 (13 mL) and was heated to reflux and stirred overnight. The reaction mixture was then cooled to room temperature and filtered. The filtrate was diluted with DCM and washed successively with 2 M NaOH, water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding benzyl bromide which was used in the next step without further purification. A solution of LDA (6.06 mmol, 1.05 equiv) in THF (12 mL) was prepared from diisopropylamine (0.85 mL, 6.06 mmol, 1.05 equiv) and 2.5 M ^{n}BuLi in hexane (2.43 mL, 6.06 mmol, 1.05 equiv), stirred at 0 °C during 15 min. To the LDA solution, methyl isobutyrate (0.66 mL, 5.77 mmol, 1 equiv) was added dropwise at 0 °C and the mixture was stirred at the same temperature for 45 min. The benzyl bromide, obtained previously, in THF (6 mL) was added slowly to the solution always at 0 °C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then added to the reaction at 0 °C. The mixture was extracted three times with Et_2O; the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered, concentrated under a vacuum and purified by column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **16** (1.35 g, 4.48 mmol, 78%) as a colorless oil: R_f 0.24 (90:10 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, J = 7.9 Hz, 1H), 6.79−6.72 (m, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.18 (s, 3H), 1.23 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.1, 156.2, 139.8, 127.4, 123.5, 115.9, 110.0, 77.4, 77.2, 76.9, 56.5, 52.0, 44.5, 44.4, 25.2; IR ν_{max}/cm^{-1} (neat) 2974, 2948, 1728, 1468, 1431, 1029, 1264, 1127, 1068, 780 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{17}{}^{79}BrNaO_3$ 323.0253, found 323.0257.

Methyl 3-(2-bromophenyl)-2,2-dimethylpropanoate (28).[14] A solution of LDA (8.4 mmol, 1.05 equiv) in THF (17 mL) was prepared from diisopropylamine (1.18 mL, 8.4 mmol, 1.05 equiv) and 2.5 M ^{n}BuLi in hexane (3.36 mL,8.4 mmol, 1.05 equiv), stirred at 0 °C during 15 min. To the LDA solution, methyl isobutyrate (0.92 mL, 8 mmol, 1 equiv) was added dropwise at 0 °C and the mixture was stirred at the same temperature for 45 min. Then 2-bromobenzyl bromide (2 g, 8 mmol, 1 equiv) in THF (8 mL) was added slowly to the solution always at 0 °C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then added to the reaction at 0 °C. The mixture was extracted three times with Et_2O; the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered, concentrated under a vacuum and purified by column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **28** (1.97 g, 7.26 mmol, 91%) as a colorless oil: R_f 0.35 (90:10 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.0, 1.3 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.13 (dd, J = 7.8, 1.8 Hz, 1H), 7.06 (ddd, J = 7.9, 7.2, 1.8 Hz, 1H), 3.69 (s, 3H), 3.12 (s, 2H), 1.24 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.0, 137.9, 133.2, 131.5, 128.2, 127.2, 126.2, 52.0, 44.4, 44.4, 25.1; IR ν_{max}/cm^{-1} (neat) 2977, 2950, 1728, 1469, 1192, 1134, 1024, 749 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{17}{}^{79}BrNaO_3$ 323.0253, found 323.0257.

Methyl 4-methoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (14).[14] In an oven dry Schlenk tube, **15** (1.36 g, 4.5 mmol) was introduced. Then the Schlenk tube was transferred in a glovebox, and $[Pd(\pi\text{-cin})Cl]_2$ (117 mg, 0.23 mmol, 5 mol %), $\mathbf{L^2}$ (161 mg, 0.45 mmol, 10 mol %), cesium pivalate (1.05 g, 4.5 mmol, 1 equiv) and cesium carbonate (2.20 g, 6.75 mmol, 1.5 equiv) were introduced and the tube was close with a septum. Outside of the glovebox, mesitylene (45 mL) was added. The reaction was stirred at room temperature for 10 min. The tube was then introduced in a 160 °C preheated oil bath and stirred at this temperature for 18 h. After this period the reaction was cooled to room temperature and filtered over a pad of Celite (washed with DCM). The crude material was analyzed by GC−MS and then concentrated and purified by flash column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield the corresponding indane **14** (915 mg, 4.15 mmol, 92%) as a yellowish oil: R_f 0.21 (95:5 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.50 (d, J = 16.0 Hz, 1H), 3.39 (d, J = 16.4 Hz, 1H), 2.84 (d, J = 16.4 Hz, 1H), 2.82 (d, J = 16.0 Hz, 1H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.3, 156.3, 143.3, 128.9, 128.2, 117.1, 108.2, 55.3, 52.2, 49.4, 44.5, 41.0, 25.6; IR ν_{max}/cm^{-1} (neat) 2950, 1730, 1590, 1261, 1075, 766 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}NaO_3$ 243.0992, found 243.0990.

Methyl 4-(allyloxy)-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (30). **14** (911 mg, 4.14 mmol) was dissolved in glacial acetic acid (11 mL) and 48% aqueous hydrobromic acid (54 mL). The reaction mixture was refluxed for 2 h. After this period, the reaction was diluted with water and extracted with DCM. The organic layer was dried over $MgSO_4$ and concentrated under a vacuum. Two portions of toluene were added and evaporated to remove excess of AcOH. The crude product was then diluted in DMF (6 mL) and $KHCO_3$ (1.12 g, 12.42 mmol, 3 equiv) was added. The suspension was stirred 10 min at room temperature, and then methyl iodide (0.77 mL, 12.42 mmol, 3 equiv) was added. The mixture was stirred at 40 °C until total consumption of starting material (approximately 3 h). To remove the excess of iodomethane, the reaction was heated to 65 °C under a flow of argon for 15 min. After this period, the temperature was lowered to 40 °C, and then NaH (300 mg, 12.42 mmol, 3 equiv) and allyl bromide (1.07 mL, 12.42 mmol, 3 equiv) were added successively carefully. The reaction mixture was stirred for 30 min and then cooled with an ice bath, and then water was added. The reaction was extracted three times with DCM. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (Cy/AcOEt: 90/10) leading to **30** as a light yellow oil (835 mg, 3.39 mmol, 82% over 2 steps): R_f 0.33 (90:10 PE/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.06 (ddt, J = 17.3, 10.4, 5.1 Hz, 1H), 5.42 (dq, J = 17.3, 1.6 Hz, 1H), 5.27 (dq, J = 10.4, 1.6 Hz, 1H), 4.54 (dt, J = 5.1, 1.6 Hz, 2H), 3.72 (s, 3H), 3.51 (d, J = 16.0 Hz, 1H), 3.42 (d, J = 16.4 Hz, 1H), 2.89 (d, J = 16.4 Hz, 1H), 2.82 (d, J = 16.0 Hz, 1H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 178.3, 155.3, 143.4, 133.6, 129.3, 128.1, 117.3, 117.2, 109.5, 68.7, 52.2, 49.4, 44.5, 41.1, 25.6; IR ν_{max}/cm^{-1} (neat) 2950, 1730, 1590, 1480, 1262, 1112, 1061, 767 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{18}NaO_3$ 269.1148, found 269.1151.

Methyl 5-allyl-4-hydroxy-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (31). A sealed tube charged with **30** (409 mg, 1.66 mmol) and *N*,*N*-diethylaniline (3 mL) was heated under stirring at 200 °C for 24 h. After this period, the reaction was poured into 1 M HCl and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (Cy/AcOEt: 90/10) leading to **31** (368 mg, 1.49 mmol, 90%) as a yellow oil: R_f 0.20 (85:15 PE/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.01 (ddt, J = 16.5, 10.0, 6.4 Hz, 1H), 5.21−5.10 (m, 2H), 4.99 (brs, 1H), 3.72 (s, 3H), 3.47 (d, J = 16.0 Hz, 1H), 3.42−3.35 (m, 3H), 2.80 (d, J = 16.0 Hz, 1H), 2.80 (d, J = 15.9 Hz, 1H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 178.4, 150.8, 141.8, 137.0, 129.2, 127.3, 123.3, 116.9, 116.3, 52.3, 49.9, 44.2, 40.3, 35.0, 25.5; IR ν_{max}/cm^{-1} (neat) 3460, 2952, 1712, 1445, 1284, 1209, 1114, 913 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{18}NaO_3$ 269.1148, found 269.1147.

Methyl 4-hydroxy-5-(2-hydroxyethyl)-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (31a). In a round-bottom flask

containing a stirred biphasic solution of **31** (441 mg, 1.79 mmol) in EtOAc (20 mL) and water (12 mL) was added OsO_4 (23 mg, 90.5 μmol, 5 mol %). After 5 min, $NaIO_4$ (957 mg, 4.48 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in MeOH (20 mL) and cooled to 0 °C. After this, $NaBH_4$ (205 mg, 5.42 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 30 min, H_2O was added and the reaction was extracted three times with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (Cy/AcOEt: 60/40) leading to **31a** (389 mg, 1.55 mmol, 87%) as a light yellow oil. R_f 0.19 (70:30 PE/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 4.01−3.93 (m, 2H), 3.71 (s, 3H), 3.46 (d, J = 16.0 Hz, 1H), 3.40 (d, J = 16.2 Hz, 1H), 2.89−2.83 (m, 3H), 2.79 (d, J = 16.0 Hz, 1H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.5, 152.0, 142.3, 129.9, 128.7, 124.6, 116.6, 65.1, 52.3, 49.7, 44.3, 40.9, 34.5, 25.6; IR ν_{max}/cm^{-1} (neat) 3416, 3296, 2933, 1710, 1437, 1283, 1214, 1114, 1039, 809 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{18}NaO_4$ 273.1097, found 273.1098.

Methyl 5-(2-hydroxyethyl)-2-methyl-4,7-dioxo-2,3,4,7-tetrahydro-1*H*-indene-2-carboxylate (32). In a round-bottom flask, **31a** (385 mg, 1.54 mmol) and Salcomine (202 mg, 0.62 mmol, 40 mol %) were mixed in acetonitrile (20 mL). Oxygen was bubbled through the stirred suspension during 5 min. Then the reaction was stirred under oxygen atmosphere during 24 h. After this period, acetonitrile was removed under reduced pressure and the crude was purified by flash chromatography (Cy/AcOEt: 50/50) leading to **32** (280 mg, 1.06 mmol, 69%) as a yellow oil: R_f 0.23 (50:50 PE/AcOEt); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (t, J = 1.2 Hz, 1H), 3.82 (t, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.38−3.31 (m, 2H), 2.74−2.69 (m, 2H), 2.68 (tt, J = 6.0, 1.0 Hz, 2H), 1.74 (brs, 1H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 186.3, 185.9, 177.0, 146.6, 146.2, 146.0, 134.5, 61.2, 52.6, 47.3, 42.5, 42.2, 32.6, 26.1; IR ν_{max}/cm^{-1} (neat) 3492, 3447, 2955, 1729, 1650, 1268, 1211, 1039, 851 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{16}NaO_5$ 287.0890, found 287.0886.

Methyl 5-(2-hydroxyethyl)-2,6-dimethyl-4,7-dioxo-2,3,4,7-tetrahydro-1*H*-indene-2-carboxylate (33). A solution of **33** (90.6 mg, 0.343 mmol), acetic acid (63.0 mg, 60 μL, 3 equiv) in acetonitrile/H_2O 1:1 (1 mL) was heated at 70 °C. Subsequently, silver nitrate (17.5 mg, 0.103 mmol, 0.3 equiv) and ammonium persulfate (102 mg, 0.446 mmol, 1.3 equiv) were added and the reaction was stirred for 2 h. After this period, the solution was diluted with ethyl acetate (15 mL). The organic layer was washed with water (10 mL), dried over $MgSO_4$ and concentrated under a vacuum. The crude was purified by flash chromatography (Cy/AcOEt: 50/50) leading to **33** (52 mg, 0.187 mmol, 55%) as a yellow oil: R_f 0.25 (50:50 PE/AcOEt); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77−3.73 (m, 1H), 3.72 (s, 3H), 3.38−3.31 (m, 2H), 2.78 (t, J = 6.5 Hz, 2H), 2.75−2.69 (m, 2H), 2.07 (s, 3H), 1.65 (brs, 1H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 186.4, 185.9, 177.1, 146.0, 145.6, 142.9, 141.5, 61.7, 52.6, 47.2, 42.6, 42.6, 30.1, 26.1, 12.3; IR ν_{max}/cm^{-1} (neat) 3443, 2953, 1730, 1646, 1207, 1042, 714 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{18}NaO_5$ 301.1046, found 301.1042.

2,4,5-Tribromo-3,6-dimethylphenol (34a)..[14,20] Aluminum (4.01 g, 0.15 mol, 0.45 equiv) was cautiously added in small portions to bromine (100 mL, 1.94 mol, 5.8 equiv) cooled to 0 °C, and the mixture was stirred for 20 min. A solution of 2,5-dimethylphenol (**35**) (40.3 g, 330 mmol) in DCM (200 mL) was added over 2 h, and the mixture was stirred for additional 2 h at 0 °C. (***Caution!*** *A copious amount of HBr is evolved in this reaction which can be trapped by a water trap connected to an aqueous sodium carbonate scrubber.*) The reaction was then diluted at 0 °C with DCM (200 mL) and water (200 mL). Then a 5% aqueous $NaHSO_3$ solution was added until the color of bromine disappeared. The phases were separated, the aqueous layer was extracted twice with DCM, and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield **34a** (115 g, 320 mmol) as a white solid which was used in the next step without further purification: R_f 0.39 (90:10 PE/AcOEt); mp 179−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 2.66 (s, 3H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.9, 136.2, 128.2, 125.3, 118.4, 112.7, 26.5, 19.1; IR ν_{max}/cm^{-1} (neat) 3491, 1365, 1444, 1032, 654 cm^{-1}; HRMS (ESI) m/z [M − H]$^-$ calcd for $C_8H_6{}^{79}Br_3O$ 354.7974, found 354.7976.

3-Bromo-2,5-dimethylphenol (34b)..[14,20] A suspension of the **34a** (115 g, 320 mmol) in aqueous HI (57%, 250 mL) was heated at reflux under argon for 16 h and cooled. TBME (500 mL) was added, and at 0 °C under stirring, $NaHSO_3$ (40%, 900 mL) was added dropwise. The layers were separated and the aqueous layer was extracted twice with TBME (300 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield **34b** (54.7 g, 272 mmol) nearly pure as a light brown solid which was used in the next step without further purification: R_f 0.29 (85:15 PE/AcOEt); mp 85−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.54 (s, 1H), 4.73 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.1, 137.8, 125.8, 125.7, 121.3, 115.1, 20.78, 15.3; IR ν_{max}/cm^{-1} (neat) 3306, 2921, 1399, 1272, 1124, 1007, 814 cm^{-1}; HRMS (ESI) m/z [M − H]$^-$ calcd for $C_8H_8{}^{79}BrO$ 198.9764, found 198.9765.

1-Bromo-3-methoxy-2,5-dimethylbenzene (35)..[14,20] **34b** (54.4 g, 271 mmol) was dissolved in acetone (500 mL), then potassium carbonate (56.0 g, 405 mmol, 1.5 equiv) and methyl iodide (51.0 mL, 115 g, 810 mmol, 3.0 equiv) were added. The resulting dark brown mixture was stirred under reflux for 24 h; after 12 h, another equivalent of methyl iodide (16.0 mL, 270 mmol, 1.0 equiv) was added. The dark brown suspension was concentrated carefully under reduced pressure. The residue was diluted with diethyl ether (700 mL) and water (500 mL) and the layers were separated. The aqueous phase was extracted twice with diethyl ether (200 mL). The combined organic phases were washed twice with water (200 mL), then with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was obtained as a brown liquid which was distilled under reduced pressure to give **35** as a colorless liquid (53.47 g, 249 mmol, 76% over 3 steps): R_f 0.53 (95:5 PE/AcOEt); bp 54−59 °C at 0.1 mbar; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.59 (s, 1H), 3.81 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.2, 137.4, 125.6, 125.0, 123.8, 110.4, 55.9, 21.3, 15.4; IR ν_{max}/cm^{-1} (neat) 2925, 1264, 1144, 1046, 828 cm^{-1}; GC−MS (EI) m/z [M]$^{+\cdot}$ calcd for $C_9H_{11}{}^{79}BrO$ 214, found 214.

Methyl 3-(2-bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,2-dimethylpropanoate (15a). In an oven dry Schlenk tube, **15** (1.0 g, 3.32 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (22.3 mg, 83 μmol, 2.5 mol %) and Bis(pinacolato)-diboron (843 mg, 3.32 mmol, 1 equiv) were charged. Then, this Schlenk tube was transferred in a glovebox, and $[Ir(COD)OMe]_2$ (27.5 mg, 41.5 μmol, 1.25 mol %) was added. The tube was closed with a septum and transferred outside of the glovebox. The reaction was diluted with THF (10 mL) and heated at 50 °C during 48 h. Afterward, THF was removed under a vacuum, and the crude was purified by column chromatography to yield **15a** as a white solid (1.38 g, 3.23 mmol, 97% yield): R_f 0.3 (80:20 PE/AcOEt); mp 81−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.14 (s, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.20 (s, 2H), 1.34 (s, 12H), 1.20 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.2, 158.6, 131.5, 130.5, 127.2, 114.6, 84.3, 55.7, 51.9, 43.5, 39.5, 25.6, 25.0; IR ν_{max}/cm^{-1} (neat) 2977, 1720, 1350, 1141, 1046, 853, 694 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{28}B{}^{79}BrNaO_5$ 449.1109, found 449.1098.

Methyl 3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoate (36).[14] From **35**: **35** (3.50 g, 16.3 mmol) was dissolved in tetrachloromethane (20 mL) and *N*-bromosuccinimide (3.77 g, 21.2 mmol, 1.32 equiv) was added followed by AIBN (321 mg, 1.86 mmol, 12 mol %). The resulting light yellow suspension was stirred under refluxed overnight. The reaction mixture was cooled in

an ice bath, filtered and washed with a minimal amount of cold DCM. The filtrate was concentrated under reduced pressure to give an orange oil which was used without further purification. A solution of LDA (25.3 mmol, 1.55 equiv) in THF (25 mL) was prepared from freshly distilled diisopropylamine (25.3 mmol, 1.55 equiv) and 2.5 M (titrated) *n*-BuLi in hexane (10.1 mL, 25.3 mmol, 1.55 equiv), mixed for 15 min at 0 °C. To the LDA solution, methyl isobutyrate (24.5 mmol, 1.5 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 45 min. Freshly prepared crude 3-bromo-2-bromomethyl-5-methyl-methoxybenzene from the previous step was diluted in THF (16 mL) and added slowly to the LDA solution at 0 °C. The mixture was slowly warmed to room temperature and stirred for 16 h. The reaction was quenched at 0 °C with water (30 mL). The mixture was extracted three times with diethyl ether (30 mL); the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and then concentrated in vacuum to give the crude ester. The crude material was purified by flash column chromatography to yield **36** as a colorless oil, which crystallized on standing (3.85 g, 12.2 mmol, 75% yield over 2 steps). From **15a**: in an oven dry Schlenk tube, **15a** (1.28 g, 3 mmol) was introduced. Then, this Schlenk tube was transferred in a glovebox, and CuI (57 mg, 0.3 mmol, 10 mol %), LiI (80 mg, 0.6 mmol, 20 mol %) and ^{t}BuOLi (480 mg, 6 mmol, 2 equiv) were added. The tube was closed with a septum and transferred outside of the glovebox. The reaction was diluted with DMI (4.5 mL) and trimethyl phosphate (0.73 mL, 6 mmol, 2 equiv) was added. The mixture was heated at 50 °C during 16 h. The reaction was quenched by H_2O, extracted by toluene. The organic layer was condensed, and the residue was purified by flash column chromatography to yield **36** as a colorless oil, which crystallized on standing (3.85 g, 12.2 mmol, 75% yield over 2 steps): R_f 0.26 (90:10 PE/AcOEt); mp 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.57 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.13 (s, 2H), 2.29 (s, 3H), 1.20 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.4, 158.8, 138.6, 126.9, 125.6, 124.2, 110.4, 55.5, 51.8, 43.4, 39.0, 25.6, 21.3; IR ν_{max}/cm^{-1} (neat) 2968, 1719, 1266, 1148, 1042, 822 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{19}{}^{79}BrNaO_3$ 337.0410, found 337.0413.

Methyl 4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (39).[14] In an oven dry catalysis tube, **36** (506 mg, 1.15 mmol) was introduced. Then the tube was transferred in a glovebox, and [Pd(π-cin)Cl]$_2$ (29.8 mg, 57.5 μmol, 5 mol %), **L^2** (67.7 mg, 115 μmol, 10 mol %), cesium pivalate (269 mg, 1.15 mmol, 1 equiv) and cesium carbonate (562 mg, 1.72 mmol, 1.5 equiv) were introduced, and the tube was closed with a septum. Outside of the glovebox, mesitylene (6 mL) was added. The reaction was stirred at room temperature for 10 min, and then, under pressure of argon, the septum was rapidly exchanged for a screw cap. The tube was then introduced in a 160 °C preheated aluminum heating block and stirred at this temperature for 18 h. After this period the reaction was cooled to room temperature, diluted with DCM (6 mL), filtered over a pad of Celite (washed three times with 6 mL of DCM). The crude material was analyzed by GC−MS, then concentrated and purified by flash column chromatography to yield **39** as a yellowish liquid (361 mg, 1.00 mmol, 87%): R_f 0.38 (95:5 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.50 (s, 1H), 3.80 (s, 7H), 3.71 (s, 6H), 3.45 (d, J = 16.0 Hz, 3H), 3.33 (d, J = 16.1 Hz, 3H), 2.79 (d, J = 16.1 Hz, 3H), 2.76 (d, J = 16.0 Hz, 3H), 2.33 (s, 8H), 1.36 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.4, 156.0, 143.3, 138.3, 125.9, 117.7, 109.4, 77.4, 77.2, 76.9, 55.3, 52.2, 49.5, 44.4, 40.8, 25.6, 21.8; IR ν_{max}/cm^{-1} (neat) 2950, 2843, 1730, 1593, 1461, 1317, 1199, 1111, 1083, 829 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{18}NaO_3$ 257.1154, found 257.1148.

3-(2-Bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoic acid (36a).[14] **36** (3.5 g, 11.1 mmol) was dissolved in a mixture of THF (20 mL), MeOH (20 mL) and 2 M aqueous LiOH (20 mL). The reaction was then heated at 80 °C for 6 h. After cooling to room temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH < 0 and extracted three times with DCM. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield **36a** as a yellow solid, which was engaged in the next step without further purifications: R_f 0.3 (70:30 PE/AcOEt); mp 100−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.57 (s, 1H), 3.69 (s, 3H), 3.19 (s, 2H), 2.29 (s, 3H), 1.22 (s, 6H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 184.9, 158.8, 138.7, 126.9, 125.6, 123.8, 110.4, 54.9, 43.2, 39.1, 25.2, 21.3; IR ν_{max}/cm^{-1} (neat) 2974, 2939, 1691, 1271, 1159, 1045, 830 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{17}{}^{79}BrNaO_3$ 323.0253, found 323.0259.

Isopropyl (3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoyl)-L-prolinate (43).[14] **36a** from the previous step was dissolved in dry DCM (90 mL), and then oxalyl chloride (1.05 mL, 12.2 mmol, 1.1 equiv) was added, followed by a few drops of DMF to initiate the reaction. After 1 h of stirring at room temperature, the reaction was cooled to 0 °C and H-L-Pro-O^{i}Pr·HCl (6.45 g, 33.3 mmol, 3 equiv) and 1 M aqueous NaOH (110 mL, 110 mmol, 10 equiv) were added in one portion. The mixture was vigorously stirred for 16 h with the ice bath warming to room temperature. The organic layer was then separated, washed with 2 M HCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude material was then purified by flash column chromatography to yield **43** as a colorless wax, which crystallized on standing (4.25 g, 9.66 mmol, 87%): R_f 0.24 (70:30 PE/AcOEt); mp 75−79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.58 (s, 1H), 5.02 (sept, J = 6.3 Hz, 1H), 4.51−4.42 (m, 1H), 3.87−3.67 (m, 2H), 3.73 (s, 3H), 3.21 (d, J = 13.6 Hz, 1H), 3.13 (d, J = 13.6 Hz, 1H), 2.28 (s, 3H), 2.20−2.09 (m, 1H), 2.09−1.97 (m, 1H), 1.95−1.76 (m, 2H), 1.29 (s, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 1.17 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.4, 172.5, 158.9, 138.6, 126.9, 125.7, 124.2, 110.5, 68.1, 61.6, 55.5, 48.5, 44.1, 36.5, 28.0, 26.4, 26.0, 25.4, 21.9, 21.8, 21.2; IR ν_{max}/cm^{-1} (neat) 2977, 2932, 1741, 1615, 1400, 1161, 1040, 833 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{30}{}^{79}BrNNaO_4$ 462.1250, found 462.1257; $[\alpha]_D^{23}$ −39.4° (c = 1.00, $CHCl_3$).

Isopropyl ((*S*)-4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carbonyl)-L-prolinate (44).[14] In an oven dry catalysis tube, **43** (506 mg, 1.15 mmol) was introduced. Then the tube was transferred in a glovebox, and [Pd(π-cin)Cl]$_2$ (29.8 mg, 57.5 μmol, 5 mol %), **L^3** (67.7 mg, 115 μmol, 10 mol %), cesium pivalate (269 mg, 1.15 mmol, 1 equiv) and cesium carbonate (562 mg, 1.72 mmol, 1.5 equiv) were introduced, and the tube was close with a septum. Outside of the glovebox, mesitylene (6 mL) was added. The reaction was stirred at room temperature for 10 min, and then, under pressure of argon, the septum was rapidly exchange for a screw cap. The tube was then introduced in a 160 °C preheated aluminum heating block and stirred at this temperature for 18 h. After this period the reaction was cooled to room temperature, diluted with DCM (6 mL), filtered over a pad of Celite (washed three times with 6 mL of DCM). The crude material was analyzed by GC−MS, then concentrated and purified by flash column chromatography to yield **44** as a wax (361 mg, 1.00 mmol, 87%): R_f 0.29 (70:30 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.50 (s, 1H), 5.02 (sept, J = 6.2 Hz, 1H), 4.48 (dd, J = 8.6, 4.8 Hz, 1H), 3.79 (s, 3H), 3.78−3.59 (m, 2H), 3.56 (d, J = 16.3 Hz, 1H), 3.33 (d, J = 16.2 Hz, 1H), 2.89 (d, J = 16.2 Hz, 1H), 2.80 (d, J = 16.3 Hz, 1H), 2.33 (s, 3H), 2.21−2.10 (m, 1H), 2.09−2.00 (m, 1H), 1.97−1.81 (m, 2H), 1.34 (s, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.9, 172.2, 156.1, 143.1, 138.2, 125.6, 117.7, 109.2, 68.2, 60.9, 55.2, 49.7, 47.7, 44.7, 40.4, 28.3, 25.9, 25.4, 21.9, 21.8, 21.8; IR ν_{max}/cm^{-1} (neat) 2976, 1736, 1626, 1400, 1185, 1108, 1085, 830 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{29}NNaO_4$ 382.1989, found 382.1994; HPLC separation: with **L^2** Chiralpak IA; 95:5 (n-heptane/i-PrOH), 1.0 mL min^{-1}, 205 nm, t_R (major) = 12.8 min, t_R (minor) = 22.2 min, 66:34 d.r., with **L^3** Chiralpak IA; 95:5 (n-heptane/i-PrOH), 1.0 mL min^{-1}, 205 nm, t_R (major) = 12.8 min, t_R (minor) = 21.7 min, 85:15 d.r.

(*S*)-4-Hydroxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylic acid (45).[14] To **44** (931 mg, 2.59 mmol) was added glacial acetic acid (8 mL) and 48% aqueous hydrobromic acid (40 mL). The reaction mixture was refluxed for 2 h. After this period, the reaction

was diluted with water (50 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Two portions of toluene (10 mL) were added and evaporated to remove the last traces of AcOH. The crude material was purified by flash chromatography using cyclohexane/EtOAc (6:4) affording **45** (491 mg, 2.38 mmol, 92%) as a light yellow solid. Then the product was enantioenriched by recrystallization as follows: the purified product was solubilized under heating in a mixture of $CHCl_3$ and cyclohexane (3:1) (proportion 40 mg/mL). The solution was then stored at room temperature for 4 days for crystallization. After separation, nearly racemic crystals (187 mg, 0.908 mmol, 35%) and concentrated enantioenriched mother liquor (304 mg, 1.47 mmol, 57%) were engaged in the next step to measure the enantiomeric ratio by HPLC using a chiral stationary phase. Racemic material was prepared using the same procedure from racemic **39** (890 mg, 3.80 mmol), glacial acetic acid (12 mL) and 48% aqueous hydrobromic acid (58 mL) to yield racemic **45** (682 mg, 3.31 mmol, 87%): R_f 0.25 (60:40 PE/AcOEt); ^{1}H NMR (500 MHz, DMSO-d6) δ 12.24 (brs, 1H), 9.03 (brs, 1H), 6.45 (s, 1H), 6.39 (s, 1H), 3.27 (d, J = 16.3 Hz, 1H), 3.16 (d, J = 16.3 Hz, 1H), 2.60 (d, J = 16.3 Hz, 1H), 2.63 (d, J = 16.3 Hz, 1H), 2.16 (s, 3H), 1.25 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d6) δ 178.7, 153.3, 143.2, 136.9, 123.9, 116.0, 113.7, 48.8, 43.8, 40.2, 25.1, 21.0; IR ν_{max}/cm^{-1} (neat) 3282, 2924, 1696, 1306, 1121, 835 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{12}H_{14}NaO_3$ 229.0835, found 229.0838; $[\alpha]_D^{23}$ + 6.9° (c = 0.57, $CHCl_3$).

Methyl (*S*)-4-(allyloxy)-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (45a).[14] **45** (304 mg, 1.47 mmol) was dissolved in DMF (12 mL) and $KHCO_3$ (442 g, 4.41 mmol, 3 equiv) was added. The suspension was stirred for 10 min at room temperature, and then iodomethane (0.28 mL, 4.41 mmol, 3 equiv) was added. The mixture was stirred at 40 °C until total consumption of starting material (approximately 3 h). To remove the excess of iodomethane, the reaction was heated to 65 °C under a flow of argon for 15 min. After this period, the temperature was lowered to 40 °C, then NaH (106 mg, 4.41 mmol, 3 equiv) and allyl bromide (0.40 mL, 4.41 mmol, 3 equiv) were added successively carefully. The reaction mixture was stirred for 30 min and then cooled with an ice bath, and then water (30 mL) was added. The reaction was extracted three times with DCM (15 mL); the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography using cyclohexane/EtOAc (9:1) leading to **45a** as a light yellow oil (315 mg, 1.21 mmol, 82%). Racemic material was prepared using the same procedure from racemic **45** (650 mg, 3.15 mmol), $KHCO_3$ (947 mg, 9.45 mmol, 3 equiv), iodomethane (0.59 mL, 9.45 mmol, 3 equiv), NaH (227 mg, 9.45 mmol, 3 equiv) and allyl bromide (0.82 mL, 9.45 mmol, 3 equiv) to yield racemic **45a** (730 mg, 2.80 mmol, 89%): R_f 0.25 (95:5 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.50 (s, 1H), 6.06 (ddt, J = 17.2, 10.5, 5.1 Hz, 1H), 5.42 (dq, J = 17.2, 1.6 Hz, 1H), 5.27 (dq, J = 10.5, 1.6 Hz, 1H), 4.53 (dt, J = 5.1, 1.6 Hz, 2H), 3.72 (s, 3H), 3.47 (d, J = 16.1 Hz, 1H), 3.37 (d, J = 16.1 Hz, 1H), 2.84 (d, J = 16.1 Hz, 1H), 2.77 (d, J = 16.1 Hz, 1H), 2.32 (s, 3H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.3, 155.1, 143.3, 138.1, 133.7, 126.3, 117.9, 117.1, 110.6, 68.7, 52.2, 49.5, 44.4, 40.8, 25.6, 21.8; IR ν_{max}/cm^{-1} (neat) 2926, 1730, 1591, 1315, 1112, 1073, 829 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}NaO_3$ 283.1305, found 283.1307; HPLC separation: Chiralpak IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL min^{-1}, 208 nm, t_R (major) = 5.0 min, t_R (minor) = 6.1 min, 96:4 e.r.; $[\alpha]_D^{23}$ + 5.2° (c = 1.00, $CHCl_3$).

Methyl (*S*)-5-allyl-4-hydroxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (40).[14] A sealed tube charged with **45a** (204 mg, 0.784 mmol) and *N*,*N*-diethylaniline (3 mL) was heated under stirring at 200 °C for 24 h. After this period, the reaction was poured into 1 M HCl (30 mL) and extracted three times with DCM (30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using cyclohexane/EtOAc (9:1) leading to **40** (163 mg, 0.626 mmol, 80%) as a yellow oil which solidified on standing. Racemic material was prepared using the same procedure from racemic **45a** (700 mg, 2.69 mmol) to yield racemic **40** (616 mg, 2.37 mmol, 88%): R_f 0.25 (85:15 PE/AcOEt); mp 65–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.95 (ddt, J = 17.1, 10.2, 5.9 Hz, 1H), 5.07 (dq, J = 10.2, 1.8 Hz, 1H), 5.05 (dq, J = 17.1, 1.8 Hz, 1H), 4.79 (s, 1H), 3.72 (s, 3H), 3.44 (d, J = 16.0 Hz, 1H), 3.40 (dt, J = 5.9, 1.8 Hz, 2H), 3.37 (d, J = 15.6 Hz, 1H), 2.77 (d, J = 16.0 Hz, 1H), 2.76 (d, J = 15.6 Hz, 1H), 2.26 (s, 3H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.2, 150.6, 1401.0, 136.8, 136.0, 124.6, 121.6, 118.9, 115.5, 52.3, 49.8, 44.3, 40.3, 30.8, 25.6, 20.0; IR ν_{max}/cm^{-1} (neat) 3464, 2929, 1712, 1195, 1113, 909 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}NaO_3$ 283.1305, found 283.1308; HPLC separation: Chiralpak IA; 97:3 (*n*-heptane/*i*-PrOH), 1.0 mL min^{-1}, 208 nm, t_R (minor) = 14.6 min, t_R (major) = 16.8 min, 96:4 e.r.; $[\alpha]_D^{23}$ + 10.8° (c = 1.00, $CHCl_3$).

Methyl (*S*)-4-hydroxy-5-(2-hydroxyethyl)-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (46).[14] In a round-bottom flask containing a stirred biphasic solution of **40** (102 mg, 0.392 mmol) in EtOAc (10 mL) and water (5 mL) was added OsO_4 (5.0 mg, 19.6 μmol, 5 mol %). After 5 min, $NaIO_4$ (210 mg, 0.98 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous phase was extracted twice with ethyl acetate (6 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in MeOH (10 mL) and cooled to 0 °C. After this, $NaBH_4$ (44.5 mg, 1.18 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 30 min, H_2O was added and the reaction was extracted three times with ethyl acetate (6 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using cyclohexane/EtOAc (6:4) leading to **46** (78 mg, 0.295 mmol, 75%) as a light yellow oil. Racemic material was prepared using the same procedure from racemic **40** (257 mg, 0.987 mmol), OsO_4 (12.5 mg, 49.4 μmol, 5 mol %), $NaIO_4$ (528 mg, 2.47 mmol, 2.5 equiv) and $NaBH_4$ (112 mg, 2.96 mmol, 3 equiv) to yield racemic **46** (195 mg, 0.737 mmol, 75%): R_f 0.26 (70:30 PE/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 3.95–3.86 (m, 2H), 3.71 (s, 3H), 3.42 (d, J = 16.0 Hz, 1H), 3.37 (d, J = 16.0 Hz, 1H), 2.88 (dd, J = 6.4, 4.6 Hz, 2H), 2.82 (d, J = 16.0 Hz, 1H), 2.75 (d, J = 16.0 Hz, 1H), 2.24 (s, 3H), 1.36 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.6, 151.9, 141.3, 136.1, 126.2, 123.1, 118.7, 64.0, 52.2, 49.6, 44.3, 40.9, 29.4, 25.6, 20.3; IR ν_{max}/cm^{-1} (neat) 3313, 2924, 1722, 1188, 1110, 905 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_4$ 287.1254, found 287.1256; $[\alpha]_D^{23}$ + 1.5° (c = 1.00, $CHCl_3$).

(*S*)-(+)-Puraquinonic acid (4)..[2,6,7,14] Title compound was made following a procedure of Yakura.[26] In a round-bottom flask equipped with a condenser, **46** (66 mg, 0.25 mmol) and LiOH (157 mg, 3.75 mmol, 15 equiv) in 1,4-dioxane/H_2O (1:1, 6 mL) were refluxed for 1.5 h. After this period, the mixture was acidified with 1 M HCl and extracted three times with EtOAc (15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in a mixture of 2,2,2-trifluoroethanol/H_2O (1:2, 3 mL). Then Oxone (305 mg, 0.992 mmol, 4 equiv) and 4-iodophenoxyacetic acid (7.0 mg, 24.8 μmol, 10 mol %) were added at room temperature. The reaction mixture was stirred until total consumption of starting material (approximately 1 h), then EtOAc and water were added (5 mL each). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using DCM/MeOH (93:7) leading to (*S*)-(+)-puraquinonic acid (**4**) (54.0 mg, 0.204 mmol, 82% over two steps) as a yellow oil. Racemic material was prepared using the same procedure from racemic **46** (29.2 mg, 0.110 mmol), LiOH (39.7 mg, 1.66 mmol, 15 equiv), Oxone (135.8 mg, 0.442 mmol, 4 equiv) and 4-iodophenoxyacetic acid (3.1 mg, 11.0 μmol, 10 mol %) to yield racemic puraquinonic acid (**4**) (25.1 mg, 0.095 mmol, 86%): R_f 0.12 (95:5 DCM/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (t, J = 6.4 Hz, 2H), 3.41–3.34 (m, 2H), 2.79 (t, J = 6.4 Hz, 2H), 2.77–2.71 (m,

2H), 2.07 (s, 3H), 1.42 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.4, 185.9, 181.7, 145.9, 145.5, 143.0, 141.5, 61.6, 47.1, 42.5, 42.4, 30.0, 25.8, 12.4; IR ν_{max}/cm^{-1} (neat) 3394, 2925, 1706, 1221, 1172, 1103, 914 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{16}NaO_5$ 287.0890, found 287.0891; $[\alpha]_D^{23}$ + 1.4° (c = 0.50, $CHCl_3$) {lit.[2] $[\alpha]_D^{22}$ − 2.2° (c = 0.55, $CHCl_3$) (*R*)-*ent*}.

(*S*)-(+)-Deliquinone (5)..[3,14,15] In a round-bottom flask containing a stirred biphasic solution of **40** (114 mg, 0.438 mmol) in EtOAc (14 mL) and water (7 mL) was added OsO_4 (5.57 mg, 21.9 μmol, 5 mol %). After 5 min, $NaIO_4$ (234 mg, 1.10 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc (8 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in dry THF (10 mL) and cooled to 0 °C. After this, $LiAlH_4$ (49.9 mg, 1.31 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 1 h, H_2O was added and the reaction was extracted three times with ethyl acetate (8 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Then, the title compound was made following a procedure of Yakura.[25] The crude material was diluted in a mixture of 2,2,2-trifluoroethanol/H_2O (1:2, 9 mL). Then Oxone (541 mg, 1.76 mmol, 4 equiv) and 4-iodophenoxyacetic acid (12.2 mg, 44.0 μmol, 10 mol %) were added at room temperature. The reaction mixture was stirred until total consumption of the starting material (approximately 1 h), and then EtOAc and water were added (10 mL each). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using DCM/MeOH (93:7) leading to (*S*)-(+)-deliquinone (**5**) (62.7 mg, 0.276 mmol, 62% over two steps) as a yellow oil. Racemic material was prepared using the same procedure from racemic **40** (220 mg, 0.845 mmol), OsO_4 (11.1 mg, 43.7 μmol, 5 mol %), $NaIO_4$ (450 mg, 2.10 mmol, 2.5 equiv), $LiAlH_4$ (98.0 mg, 2.58 mmol, 3 equiv), Oxone (1,04 g, 3.38 mmol, 4 equiv) and 4-iodophenoxyacetic acid (22.1 mg, 84.5 μmol, 10 mol %) to yield racemic deliquinone (**5**) (153 mg, 0.647 mmol, 76%): R_f 0.28 (95:5 DCM/MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, J = 6.5 Hz, 2H), 3.49 (s, 2H), 2.87−2.80 (m, 2H), 2.78 (t, J = 6.5 Hz, 2H), 2.53−2.47 (m, 2H), 2.06 (s, 3H), 1.75 (brs, 1H), 1.69 (brs, 1H), 1.16 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 187.0, 186.4, 147.2, 146.8, 142.8, 141.4, 70.2, 61.7, 43.0, 40.8, 40.7, 30.1, 25.0, 12.3; IR ν_{max}/cm^{-1} (neat) 3395, 2925, 1644, 1249, 1033 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_4$ 273.1097, found 273.1095; $[\alpha]_D^{23}$ + 0.9° (c = 1.00, $CHCl_3$) {lit.[3] $[\alpha]_D^{22}$ − 0.5° (c = 0.6, $CHCl_3$) (*R*)-*ent*}.

Methyl (*S*)-5-allyl-2,6-dimethyl-4-(((trifluoromethyl)-sulfonyl)oxy)-2,3-dihydro-1*H*-indene-2-carboxylate (40a).[14] To a solution of **40** (58.1 mg, 0.223 mmol) in DCM (1.2 mL), pyridine (54 μL, 0.669 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (41 μL, 0.245 mmol, 1.1 equiv) were added. The reaction mixture was stirred at room temperature during 6 h. The reaction was then concentrated and purified by flash column chromatography to yield **40a** (80.9 mg, 0.206 mmol, 93%) as a colorless liquid. Racemic material was prepared using the same procedure from racemic **40** (50 mg, 0.192 mmol), pyridine (47 μL, 0.576 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (36 μL, 0.211 mmol, 1.1 equiv) to yield racemic **40a** (87.1 mg, 0.167 mmol, 87%): R_f 0.25 (95:5 PE/AcOEt); ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 5.83 (ddt, J = 17.1, 10.1, 5.8 Hz, 1H), 5.04 (dq, J = 10.1, 1.7 Hz, 1H), 4.89 (dq, J = 17.1, 1.7 Hz, 1H), 3.72 (s, 3H), 3.54 (d, J = 16.3 Hz, 1H), 3.49 (d, J = 16.1 Hz, 1H), 3.45 (dt, J = 5.8, 1.7 Hz, 2H), 2.95 (d, J = 16.3 Hz, 1H), 2.82 (d, J = 16.1 Hz, 1H), 2.30 (s, 2H), 1.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.3, 144.3, 142.9, 139.0, 134.4, 132.0, 129.2, 126.7, 118.7 (q, J = 319.8 Hz), 116.0, 52.4, 50.1, 44.1, 41.9, 31.2, 25.0, 19.9; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −73.8; IR ν_{max}/cm^{-1} (neat) 2955, 1735, 1405, 1206, 1137, 817 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{19}F_3NaO_5S$ 415.0798, found 415.0795; $[\alpha]_D^{23}$ + 4.0° (c = 1.09, $CHCl_3$).

Methyl (*S*)-5-allyl-2,4,6-trimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (42).[14] Title compound was made following a procedure of Woodward.[27] In an oven dry catalysis tube, **40a** (80 mg, 0.204 mmol) was introduced. Then the tube was transferred in a glovebox, and $[Pd_2dba_3{\cdot}CHCl_3]$ (5.3 mg, 5.1 μmol, 2.5 mol %) and XPhos (5.0 mg, 10.2 μmol, 5 mol %) were introduced, and the tube was closed with a septum. Outside of the glovebox, THF (2.5 mL) and DABAL-Me_3 (41.8 mg, 0.163 mmol, 0.8 equiv, as a solution in 0.8 mL of THF) were added. The septum was rapidly exchanged for a screw cap. The tube was then introduced in a 75 °C preheated aluminum heating block and stirred at this temperature for 4 h. After this period the reaction was cooled to room temperature, quenched with 2 M HCl (2 mL), and extracted three times with diethyl ether (3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield **42** as a colorless liquid (51.7 mg, 0.200 mmol, 98%). Racemic material was prepared using the same procedure from racemic **40a** (50.2 mg, 0.128 mmol), $[Pd_2dba_3{\cdot}CHCl_3]$ (3.3 mg, 3.2 μmol, 2.5 mol %), XPhos (3.2 mg, 6.4 μmol, 5 mol %) and DABAL-Me_3 (26.3 mg, 0.102 mmol, 0.8 equiv) to yield racemic **42** (32.4 mg, 0.167 mmol, 98%): R_f 0.33 (95:5 PE/AcOEt); ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 5.88 (ddt, J = 17.1, 10.1, 5.7 Hz, 1H), 4.99 (dq, J = 10.1, 1.8 Hz, 1H), 4.88 (dq, J = 17.1, 1.8 Hz, 1H), 3.72 (s, 3H), 3.46 (d, J = 15.9 Hz, 1H), 3.40 (d, J = 15.9 Hz, 1H), 3.38 (dt, J = 5.7, 1.8 Hz, 3H), 2.79 (d, J = 15.9 Hz, 1H), 2.78 (d, J = 15.9 Hz, 1H), 2.27 (s, 3H), 2.18 (s, 3H), 1.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 178.5, 138.8, 138.3, 135.8, 135.3, 134.3, 132.7, 124.0, 114.9, 52.2, 49.1, 44.3, 43.7, 33.7, 25.8, 20.3, 16.0; IR ν_{max}/cm^{-1} (neat) 2931, 1732, 1208, 1112, 911 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_2$ 281.1512, found 281.1508; $[\alpha]_D^{23}$ + 9.4° (c = 1.05, $CHCl_3$).

(*S*)-(+)-Russujaponol F (6)..[4,14] In a round-bottom flask containing a stirred biphasic solution of **42** (51.7 mg, 0.200 mmol) in EtOAc (4 mL) and water (2 mL) was added OsO_4 (2.5 mg, 10.0 μmol, 5 mol %). After 5 min, $NaIO_4$ (107 mg, 0.500 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc (5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in dry THF (5 mL) and cooled to 0 °C. After this, $LiAlH_4$ (22.8 mg, 0.600 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature overnight. After this period, H_2O was added and the reaction was extracted three times with ethyl acetate (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield (*S*)-(+)-russujaponol F (**6**) as a colorless oil (39.8 mg, 0.170 mmol, 85%). Racemic material was prepared using the same procedure from racemic **42** (20.5 mg, 0.079 mmol), OsO_4 (1.0 mg, 4.0 μmol, 5 mol %), $NaIO_4$ (42.5 mg, 0.199 mmol, 2.5 equiv) and $LiAlH_4$ (9.1 mg, 0.238 mmol, 3 equiv) to yield racemic russujaponol F (**6**) (16.2 mg, 0.069 mmol, 87%): R_f 0.23 (50:50 DCM/MeOH); ^1H NMR (400 MHz, C_5D_5N) δ 6.90 (s, 1H), 5.76 (brs, 2H), 3.99 (t, J = 7.6 Hz, 2H), 3.75 (s, 2H), 3.18 (d, J = 15.9 Hz, 1H), 3.15 (t, J = 7.6 Hz, 2H), 3.09 (d, J = 15.8 Hz, 1H), 2.71 (d, J = 15.8 Hz, 1H), 2.60 (d, J = 15.9 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 1.35 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, C_5D_5N) δ 140.9, 140.7, 135.3, 134.1, 133.3, 125.0, 70.3, 62.0, 45.4, 43.9, 43.1, 34.5, 25.6, 20.9, 16.5; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 3.74 (t, J = 7.5 Hz, 2H), 3.52 (s, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.88 (d, J = 16.0 Hz, 1H), 2.84 (d, J = 16.0 Hz, 1H), 2.63 (d, J = 16.0 Hz, 1H), 2.59 (d, J = 16.0 Hz, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 1.18 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 140.3, 139.8, 135.3, 133.2, 132.3, 124.4, 71.1, 62.1, 44.3, 43.1, 42.4, 32.9, 24.6, 20.5, 16.2; IR ν_{max}/cm^{-1} (neat) 3313, 2920, 2867, 1460, 1037 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{22}NaO_2$ 257.1512, found 257.1514; $[\alpha]_D^{23}$ + 1.0° (c = 1.07, $CHCl_3$); $[\alpha]_D^{23}$ + 2.1° (c = 0.53, MeOH) {lit.[4] $[\alpha]_D^{20}$ + 1.3° (c = 3.1, MeOH) (*S*)}.

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Notes

The authors declare no competing financial interest.

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