An Improved Synthetic Route to Angularly Functionalized Hydrofluorene Derivatives through Pd(0)-Catalyzed Heck Reaction

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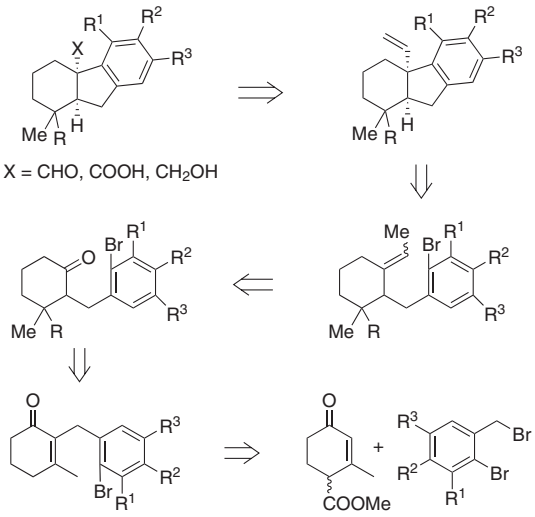
Abstract: 4a-Substituted 1,1-dimethyl or 1-carbomethoxy-1-methyl hydrofluorenes carrying various substituents in the aromatic ring could be conveniently synthesized by Pd(0)-catalyzed Heck reaction. The required bromobenzyl-substituted ethylidene cyclohexane substrates were derived from Hagemann's ester (methyl analogue) via condensation with appropriate benzyl bromide, hydrolytic decarboxylation of the ester, 1,4-addition of methyl or cyano group followed by necessary functional group manipulation, and Wittig olefination. Simple organic transformations converted the vinyl group to carboxy, formyl or hydroxymethyl. The ring juncture stereochemistry of the products could be ascertained by correlation approach.

Key words: 4a-substituted hydrofluorenes, Heck reaction, Wittig reaction, Hagemann's ester

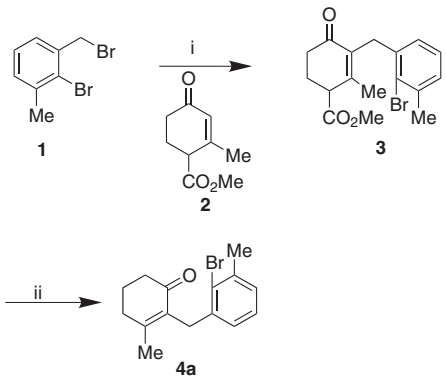
Hydrofluorenes constitute the basic skeleton of a large number of highly functionalized diterpenoids of the gibberellin and rearranged abietane groups, but synthetic methodologies for these important and apparently simple molecules have been scant. Though there are few reports on the syntheses of 4a-substituted hydrofluorenes,[1,2] only a single methodology established by Ghatak and coworkers[2] is available, to our knowledge, for the synthesis of 4a-(carboxyl)-substituted hydrofluorenes carrying substituents at C-1 position; the corresponding position in gibberellins usually carry a methyl and a carboxyl group. As these products are expected to serve as putative intermediates to C-10 functionalized gibberellins, we became interested to develop an improved synthetic methodology for 1,1-disubstituted hydrofluorenes with diverse functional groups at the 4a-position.

Inserting a vinyl group at the angular position of hydrofluorenes appeared to us as particularly promising, as it can be easily transformed to other functional groups. Trost et al. first reported[3] the synthesis of hydrofluorenes with a 4a-vinyl substituent by palladium-catalyzed reductive cyclization. Although the yields achieved were moderate to good, the methodology involves a complex reagent system and only C-1 unsubstituted hydrofluorenes were synthesized. We have recently reported the results of our fruitful venture in harnessing the Pd(0)-catalyzed Heck reaction for the synthesis of several complex diterpenoids.[4] In continuation of that exercise we now describe a simple, generalized and high-yielding method using Pd(0)-catalyzed intramolecular cyclization to produce a series of functionalized hydrofluorenes with substituents at C-1, C-4a and the aromatic ring. Easy transformations of the vinyl group to many other functionalities are also demonstrated.

The retrosynthetic plan is described in Scheme 1. The required 2-(2-bromobenzyl)-1-ethylidenecyclohexane intermediates were obtainable from the respective cyclohexanones. The latter could in turn be prepared through alkylation of suitably substituted benzyl bromides with the methyl analogue of Hagemann's ester, easy decarboxylation to the cyclohexenones, and subsequent introduction of a methyl or carbomethoxy group at the β-position of the conjugated carbonyl system.



Scheme 1 Retrosynthetic plan



Scheme 2 *Reagents and conditions*: i) *t*-BuOK, NaI, *t*-BuOH, reflux, 6 h, 65%; ii) KOH, EtOH, reflux, 12 h, 66%.

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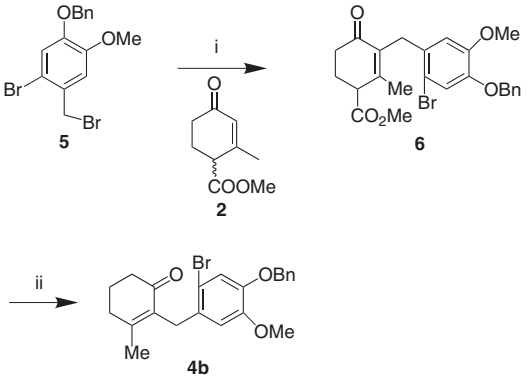
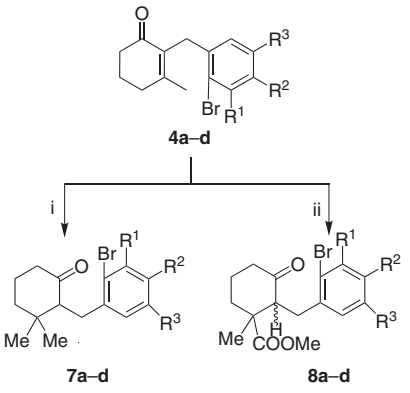
Thus, the freshly prepared 2-bromobenzyl bromide **1**[5] was reacted[6] (Scheme 2) with the methyl analogue (**2**) of Hagemann's ester in the presence of potassium *tert*-butoxide and sodium iodide to afford **3**. The ester **3** was hydrolyzed and decarboxylated in one pot by refluxing with potassium hydroxide in aqueous ethanol to furnish the cyclohexenone **4a**. The other bromide **5**[7] (easily derived from vanillin) afforded the ester **6** after alkylation with **2** using the above procedure. For decarboxylation of **6**, a two-step procedure[4a] was adopted from our earlier experience, as similar catechol derivatives produce a complex mixture of products when refluxed with strong alkali presumably due to oxidative degradation. Thus, hydrolysis of **6** with lithium hydroxide in methanol–water and subsequent decarboxylation by heating a silica gel slurry of the resulting acid afforded the cyclohexenone **4b** (Scheme 3). Syntheses of the other cyclohexenones **4c**[6] and **4d**[4a] (Scheme 4) were reported earlier.



Scheme 3 *Reagents and conditions*: i) *t*-BuOK, NaI, *t*-BuOH, reflux, 3 h, 85%; ii) a) LiOH, MeOH–H_2O (9:1), r.t., 12 h; b) SiO_2, 90 °C, 4 h, 71%.

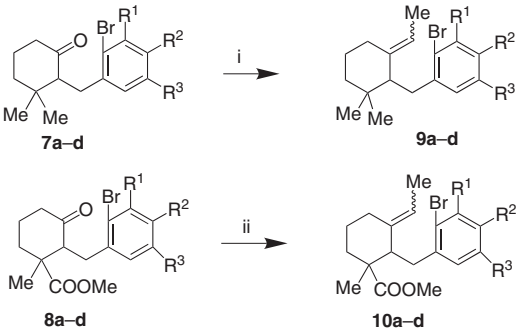


a: R^1 = Me; R^2, R^3 = H **b**: R^1 = H; R^2 = OBn; R^3 = OMe
c: R^1, R^2, R^3 = H **d**: R^1 = OMe; R^2 = OBn; R^3 = H

Scheme 4 *Reagents and conditions*: i) Me_2CuLi, $BF_3{\cdot}Et_2O$, Et_2O, –30 °C to 0 °C, 1 h, 85–90%; ii) a) KCN, EtOH, H_2O, reflux, 14 h; b) KOH, H_2O, reflux, 96 h; c) LiOH, Me_2SO_4, THF, reflux, 4 h, 60–80%.

For the preparation of **7a** and **7b**, the substrates **4a** and **4b** required to be subjected (Scheme 4) to 1,4-addition of a methyl group.[4a,8] This was conveniently carried out by treatment with an excess of Gilman's reagent (Me_2CuLi) in the presence of a large excess of $BF_3{\cdot}Et_2O$. Conversion of **4c** to the known substrate **7c** was performed by the published[6] procedure, while the synthesis of **7d** has been described in our earlier communication.[4a] For preparing substrates carrying a carbomethoxy group, addition of a cyano group[9] to the cyclohexenone substrates was followed by hydrolysis with potassium hydroxide and esterification with dimethyl sulfate in presence of lithium hydroxide.[10] By this method, **4a**, **4b** and **4d** afforded diastereomeric mixtures of the 2-(2-bromobenzyl)cyclohexanones **8a**, **8b** and **8d** (Scheme 4), respectively. Synthesis of **8c** was carried out following the known procedure.[6]

The ketones **7a–d** or **8a–d** were smoothly transformed (Scheme 5) to the corresponding olefins **9a–d** or **10a–d** in excellent yields (85–95%) by Wittig reaction with an excess of ethylenetriphenylphosphorane.[11] The reactions with **8a–d** appeared to produce stereoisomeric mixtures of olefins when carried out at room temperature. However, adding the substrates to the ylide at 80–90 °C and then refluxing for three hours afforded a single diastereomer of each ethylidene derivative (**10a–d**).

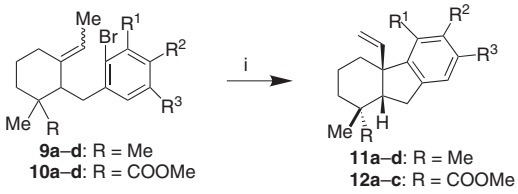


a: R^1 = Me; R^2, R^3 = H **b**: R^1 = H; R^2 = OBn; R^3 = OMe
c: R^1, R^2, R^3 = H **d**: R^1 = OMe; R^2 = OBn; R^3 = H

Scheme 5 *Reagents and conditions*: i) $EtPPh_3I$, *t*-BuOK, r.t., 12 h, 85–95%; ii) $EtPPh_3I$, *t*-BuOK, reflux, 3 h, 85–90%.

The olefins **9a–d** and **10a–d** were then subjected to Pd(0)-catalyzed Heck cyclization[12] (Scheme 6). Experiments were carried out by varying the reaction parameters to get the best yields of the 4a-vinyl hydrofluorenes as shown in Table 1. The results reveal that the olefinic substrates without any substituent at the position *ortho* to the bromo group (other than the one occupied by the cyclohexylmethyl group) produced the corresponding 4a-vinyl substituted hydrofluorenes (the *cis*-stereochemistry was established as discussed later) in excellent yields, while an *ortho*-substituent reduced the yield of the cyclized product a considerable extent. Only the olefin **10d** (entry 8) failed to produce any cyclized product even after a long time; an intractable product resulted instead. These results, taken together with previous reports from other lab-

oratories,[3] serve in addition to underline the relevance of Heck reaction in synthesizing angularly substituted polycyclic systems.



9a–d: R = Me
10a–d: R = COOMe

11a–d: R = Me
12a–c: R = COOMe

a: R^1 = Me; R^2, R^3 = H **b**: R^1 = H; R^2 = OBn; R^3 = OMe
c: R^1, R^2, R^3 = H **d**: R^1 = OMe; R^2 = OBn; R^3 = H

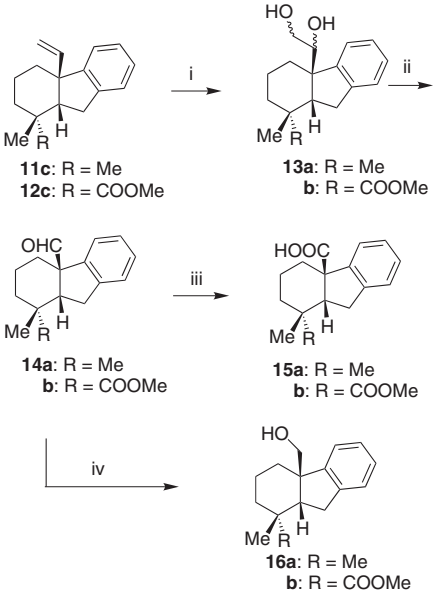
Scheme 6 *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), K_2CO_3 (4 equiv), DMF, Δ.

Table 1 Heck Cyclization of **9a–d** and **10a–d**

Entry	Olefin	Temp (°C)	Time (h)	Cyclized product and yield (%)
1	**9a**	130	40	**11a** (82)
2	**9b**	100	24	**11b** (96)
3	**9c**	100	24	**11c** (95)
4	**9d**	140	48	**11d** (62)
5	**10a**	140	48	**12a** (61)
6	**10b**	130	36	**12b** (86)
7	**10c**	100	24	**12c** (87)
8	**10d**	160	30	–

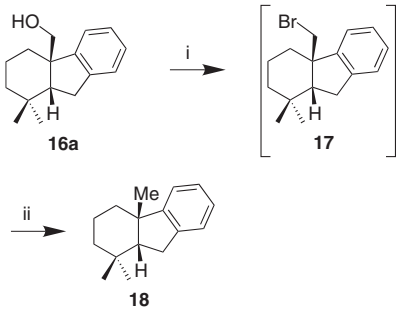
Taking one example from each series (**11c** and **12c**) the angular vinyl group was converted to other functionalities, e.g. CH_2OH, CHO or COOH by simple organic transformations (Scheme 7). Thus, dihydroxylation[13] by treatment with *N*-methyl morpholine oxide and a catalytic amount of osmium tetraoxide in acetone–*tert*-butanol (1:1) afforded the 1,2-dihydroxy hydrofluorenes **13a**,**b** as diastereomeric mixtures in excellent yields. Cleavage of the diols by stirring with sodium periodate[13] in aqueous methanol to afford **14a** and **14b** also proved equally successful. Oxidation of **14a**,**b** to the corresponding acids (**15a**,**b**) was effected by treatment with an aqueous solution of sodium chlorite[14] in dimethyl sulfoxide in the presence of sodium dihydrogen phosphate buffer, while reduction to the corresponding alcohols **16a** and **16b** was carried out with sodium borohydride in methanol; the yields achieved in all cases were >95%.

The *cis* stereochemistry at the ring junctures of the compounds **11a–d** was established by converting **16a** to the known[15] 4a-methyl analogue through bromination (with CBr_4 and PPh_3[16]) to **17** followed by reduction using TBTH[17] to furnish **18** (Scheme 8). Similarly, to establish the ring juncture stereochemistry along with the relative disposition of C-1 carbomethoxy and C-4a vinyl groups for **12a–c**, the acid **15b** was converted to the diester by re-

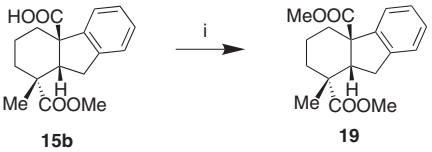


Scheme 7 *Reagents and conditions*: i) OsO_4 (2 mol%), NMO (5 equiv, 50% in H_2O), acetone–*t*-BuOH (1:1), r.t., 8–10 h, 85–95%; ii) $NaIO_4$ (1.2 equiv), MeOH–H_2O, 0 °C, 2 h, > 95%; iii) $NaClO_2$, NaH_2PO_4, DMSO–H_2O, r.t., 3 h, > 95%; iv) $NaBH_4$, MeOH, 0 °C, 1 h, 95–98%.

fluxing with lithium hydroxide and dimethyl sulfate (Scheme 9). The melting point of the synthetic compound and its spectral data are in accordance with the literature[2] values for **19**. This clearly disclosed the *cis* stereochemistry of the ring juncture for hydrofluorenes **12a–c** and also established the relative orientation of the 4a-vinyl and the 1-carbomethoxy substituents.



Scheme 8 *Reagents and conditions*: i) CBr_4, PPh_3, CH_2Cl_2, –10 °C, 30 min; ii) TBTH, AIBN, benzene, reflux, 4 h. Overall yield: 26%.



Scheme 9 *Reagents and conditions*: i) LiOH, Me_2SO_4, THF, reflux, 4 h, 90%.

In conclusion, an efficient and high-yielding methodology based on Pd(0)-mediated Heck cyclization has been developed for the synthesis of 4a-vinyl-1-substituted hy-

drofluorenes, which are models used towards gibberellins. Easy transformation of the vinyl moiety to other functional groups could be realized. The stereochemistry of the products was established through correlation approach. The utility of Pd(0)-catalyzed Heck reaction for the construction of angularly vinyl-substituted structures has also been demonstrated.

Melting points recorded for the compounds were measured on a REMCO melting-point apparatus (India) and are uncorrected. ^{1}H and ^{13}C NMR spectra of the compounds were recorded in $CDCl_3$ solutions with a Bruker DPX-300 spectrometer at 300 MHz and 75 MHz, respectively. In all cases, chemical shifts are in δ relative to TMS as internal standard. Protonation levels of the carbons indicated in ^{13}C NMR (75 MHz) data were derived from DEPT spectra. Mass spectra were recorded using a JEOL AX-500 or Q-Tof Micro™ (Waters) mass spectrometer. IR spectra were recorded using a JASCO FT/IR-410 spectrometer. Microanalyses were performed on a Perkin-Elmer 2400 Series II CHN Analyzer.

All reagents were of commercial grade and were used from freshly opened containers without purification. Organic solvents were dried by standard methods and were distilled before use. All the reactions were performed under nitrogen atmosphere. Reaction progress was monitored by TLC on precoated aluminum-backed plates (Merck Kieselgel $60F_{254}$) and the spots were visualized by UV light. Anhydrous Na_2SO_4 was used as drying agent for extracts. Silica gel was usually employed for column chromatography. Petroleum ether used was of boiling range 60–80 °C.

3-(2-Bromo-3-methylbenzyl)-2-methyl-4-oxocyclohex-2-enecarboxylic Acid Methyl Ester (3)

To a stirred solution of *t*-BuOK (3.57 g, 31.8 mmol) in anhyd *t*-BuOH (30 mL) was added a solution of the methyl analogue of Hagemann's ester **2** (5.6 g, 33 mmol, in 20 mL of anhyd *t*-BuOH) slowly over 30 min and the mixture was allowed to stir for another hour. The freshly prepared benzyl bromide **1** (7 g, 27 mmol) and NaI (1.6 g, 10.6 mmol) were then added followed by *t*-BuOH (30 mL), and the reaction mixture was refluxed for 6 h. After cooling, it was decomposed by addition of sat. NH_4Cl solution. The organic part was separated out and the aqueous part was extracted with EtOAc (2 × 30 mL). The combined organic part was washed with brine, dried and concentrated. The residue was purified by column chromatography to afford **3** (6.2 g, 65%) as a colorless liquid.

IR (neat): 2951, 1733, 1668, 1201, 1162 cm^{-1}.

^{1}H NMR: δ = 1.88 (s, 3 H), 2.42 (s, 3 H), 2.27–2.52 (overlap. m, 3 H), 2.59–2.70 (m, 1 H), 3.41 (t, *J* = 4.5 Hz, 1 H), 3.78 (s, 3 H), 3.69–3.89 (overlap. m, 2 H), 6.74–6.77 (m, 1 H), 7.06–7.10 (m, 2 H).

MS (ESI): *m*/*z* (%) = 375, 373 (100) [M$^+$ + Na, Br isotopes], 353, 351 (47) [M$^+$ + 1, Br isotopes].

2-(2-Bromo-3-methylbenzyl)-3-methylcyclohex-2-enone (4a)

To a stirred solution of **3** (5.3 g, 0.015 mol) in rectified spirit (50 mL) was added a solution of KOH (5 g, 0.09 mol) in H_2O (7 mL). The reaction mixture was refluxed for 12 h, and was then cooled down. EtOH was removed under reduced pressure, the mixture was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The organic extract was washed with H_2O (until neutral) and brine, and dried. It was then concentrated and the residue was purified by column chromatography to give enone **4a** (2.9 g, 66%) as a colorless liquid.

IR (neat): 2951, 1652, 1027, 727 cm^{-1}.

^{1}H NMR: δ = 1.85 (s, 3 H), 2.03 (quint, *J* = 6.3 Hz, 2 H), 2.42 (s, 3 H), 2.42–2.50 (overlap. m, 4 H), 3.76 (s, 2 H), 6.66 (app t, *J* = 4.9, 4.3 Hz, 1 H), 7.04 (app d, *J* = 5.2 Hz, 2 H).

^{13}C NMR: δ = 21.6 (CH_3), 22.1 (CH_2), 23.8 (CH_3), 31.5 (CH_2), 32.7 (CH_2), 37.4 (CH_2), 125.3 (CH), 126.6 (CH), 127.2 (C), 128.0 (CH), 133.3 (C), 138.0 (C), 139.1 (C), 158.6 (C), 198.0 (C).

MS (EI): *m*/*z* (%) = 295, 293 (87) [M$^+$ + 1, Br isotopes], 213 (100), 123.

Anal. Calcd for $C_{15}H_{17}BrO$: C, 61.45; H, 5.84. Found: C, 61.38; H, 5.72.

3-(4-Benzyloxy-2-bromo-5-methoxybenzyl)-2-methyl-4-oxocyclohex-2-enecarboxylic Acid Methyl Ester (6)

The same procedure as that described for **3** was followed to synthesize **6** (85%) from **5** and **2** as a colorless viscous liquid.

IR (neat): 2951, 1730, 1668, 1502, 1201, 1163 cm^{-1}.

^{1}H NMR: δ = 1.89 (s, 3 H), 2.27–2.35 (m, 2 H), 2.43–2.51 (m, 1 H), 2.58–2.67 (m, 1 H), 3.40 (t, *J* = 4.2 Hz, 1 H), 3.52 (d, *J* = 16.2 Hz, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.87 (d, *J* = 16.2 Hz, 1 H), 5.07 (s, 2 H), 6.59 (s, 1 H), 7.06 (s, 1 H), 7.30–7.43 (m, 5 H).

MS (EI): *m*/*z* (%) = 474, 472 (53) [M$^+$, Br isotopes], 394 (100), 393 (100), 307, 305, 243, 91.

2-(4-Benzyloxy-2-bromo-5-methoxybenzyl)-3-methylcyclohex-2-enone (4b)

To a stirred solution of **6** (22.3 g, 0.047 mol) in MeOH (180 mL) was added a solution of $LiOH·H_2O$ (5.94 g, 0.141 mol) in H_2O (20 mL) and the mixture was stirred for 16 h. The solvent was removed, the solid was dissolved in a minimum volume of H_2O and the solution was acidified with dilute HCl. The aqueous part was extracted with EtOAc (3 × 50 mL); the organic layer was washed with brine and dried over anhyd Na_2SO_4. EtOAc was removed; the residue was added as a CH_2Cl_2 solution to silica gel to form a slurry which was heated at 90 °C for 4 h. The slurry was then purified by column chromatography to obtain **4b** (13.8 g, 71%) as a white solid; mp 88–90 °C.

IR (KBr): 2936, 1668, 1501, 1256 cm^{-1}.

^{1}H NMR: δ = 1.89 (s, 3 H), 1.96–2.05 (m, 2 H), 2.41–2.50 (m, 4 H), 3.68 (s, 2 H), 3.75 (s, 3 H), 5.07 (s, 2 H), 6.50 (s, 1 H), 7.04 (s, 1 H), 7.30–7.43 (m, 5 H).

^{13}C NMR: δ = 21.7 (CH_3), 22.0 (CH_2), 30.0 (CH_2), 32.8 (CH_2), 37.4 (CH_2), 55.9 (CH_3), 71.0 (CH_2), 112.5 (CH), 113.9 (C), 117.7 (CH), 127.1 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 131.9 (C), 133.6 (C), 136.4 (C), 146.7 (C), 148.8 (C), 158.6 (C), 198.2 (C).

MS (EI): *m*/*z* (%) = 416, 414 (22) [M$^+$, Br isotopes], 335, 128, 115 (100).

Anal. Calcd for $C_{22}H_{23}BrO_3$: C, 63.62; H, 5.58. Found: C, 63.46; H, 5.70.

2-(2-Bromo-3-methylbenzyl)-3,3-dimethylcyclohexanone (7a)

To a stirred suspension of CuI (2.6 g, 13.8 mmol) in anhyd Et_2O (20 mL) under nitrogen atmosphere was added MeLi (13.8 mL, 1.2 M) slowly at –25 °C over 30 min and the mixture was allowed to stir for another 30 min. Then the temperature was lowered to –50 °C, $BF_3·Et_2O$ (1.75 mL, 13.8) was added dropwise, and the solution was stirred for 5 min. The temperature was raised to –30 °C, an ethereal solution of **4a** (810 mg, 2.76 mmol in 5 mL of Et_2O) was added slowly over 15 min, and the mixture was stirred for another 30 min. Another lot of $BF_3·Et_2O$ (1.75 mL) was added slowly and the stirring was continued for 1 h. The temperature was brought up to 0 °C and the reaction mixture was decomposed by adding sat. NH_4Cl solution. The Et_2O layer was separated out and the aqueous part was extracted with Et_2O (2 × 50 mL). The combined organic part was washed with 5% $Na_2S_2O_3$ and brine, dried and concentrated. Column chromatography of the residue gave **7b** (750 mg, 88%) as a colorless liquid.

IR (neat): 2964, 1708, 1458, 769 cm^{-1}.

^1H NMR: δ = 0.88 (s, 3 H), 1.27 (s, 3 H), 1.58–1.66 (m, 1 H), 1.70–1.95 (m, 3 H), 2.17–2.35 (m, 2 H), 2.39 (s, 3 H), 2.75 (dd, *J* = 1.5, 10.5 Hz, 1 H), 2.86 (dd, *J* = 2.1, 13.6 Hz, 1 H), 3.09 (dd, *J* = 10.6, 13.6 Hz, 1 H), 7.03–7.10 (m, 2 H), 7.26–2.28 (m, 1 H).

^{13}C NMR: δ = 21.1 (CH_3), 23.4 (CH_2), 23.9 (CH_3), 29.7 (CH_3), 30.8 (CH_2), 39.9 (CH_2), 40.9 (C), 41.8 (CH_2), 60.0 (CH), 126.3 (CH), 126.9 (C), 128.3 (CH), 129.9 (CH), 137.9 (C), 140.5 (C), 211.8 (C).

MS (FAB): *m*/*z* (%) = 311, 309 (61) [M^+, Br isotopes], 229 (100), 185, 183.

Anal. Calcd for $C_{16}H_{21}BrO$: C, 62.14; H, 6.84. Found: C, 62.39; H, 6.73.

2-(4-Benzyloxy-2-bromo-5-methoxybenzyl)-3,3-dimethylcyclohexanone (7b)

The same procedure as that described for **7a** was followed to synthesize **7b** (81%) from **4b** as a white solid; mp 83–84 °C.

IR (KBr): 2954, 1700, 1506, 1256, 1165 cm^{-1}.

^1H NMR: δ = 0.84 (s, 3 H), 1.28 (s, 3 H), 1.58–1.60 (m, 1 H), 1.64–1.91 (m, 3 H), 2.18–2.28 (m, 2 H), 2.66 (d, *J* = 10.3 Hz, 1 H), 2.73 (d, *J* = 13.5 Hz, 1 H), 2.97 (dd, *J* = 11.0, 13.2 Hz, 1 H), 3.87 (s, 3 H), 5.06 (s, 2 H), 6.97 (s, 1 H), 7.08 (s, 1 H), 7.30–7.43 (m, 5 H).

^{13}C NMR: δ = 20.8 (CH_3), 23.4 (CH_2), 29.6 (CH_2), 29.7 (CH_3), 40.1 (CH_2), 40.9 (C), 42.0 (CH_2), 55.8 (CH_3), 60.5 (CH), 71.0 (CH_2), 113.5 (C), 116.0 (CH), 117.5 (CH), 127.1 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 132.9 (C), 136.5 (C), 146.8 (C), 148.3 (C), 211.9 (C).

MS (EI): *m*/*z* (%) = 432, 430 (58) [M^+, Br isotopes], 341, 339, 217, 215, 91 (100).

Anal. Calcd for $C_{23}H_{27}BrO_3$: C, 64.04; H, 6.31. Found: C, 64.41; H, 6.23.

Synthesis of 8a,8b,8d; General Procedure

To a stirred solution of **4a**,**b**, or **4d** (10 mmol) in 95% EtOH (60 mL) was added a solution of KCN (37 mmol) in H_2O (5.6 mL). The mixture was gently refluxed for 14 h. After cooling, an aq KOH solution (2.5 N, 28 mL) was added and the refluxing was continued for 96 h. The alcohol was removed under reduced pressure and the reaction mixture was acidified with 6 N HCl in cold. The solid acid was taken up in EtOAc and the aqueous part was extracted with EtOAc (2 × 30 mL). The combined organic extract was washed with brine and dried. Removal of the solvent afforded the crude keto-acid as a brownish solid, which was dissolved in anhyd THF (30 mL) and treated with $LiOH·H_2O$ (13.3 mmol). After stirring at r.t. for 30 min, dimethyl sulfate (25 mmol) was added and the mixture was refluxed for 6 h. THF was removed and the residue was partitioned between H_2O (80 mL) and EtOAc (40 mL). The organic part was separated and the aqueous part was extracted with EtOAc (2 × 20 mL). The pooled organic extract was washed with brine and dried. The solvent was evaporated to dryness and the oily residue was purified by column chromatography to afford the two diastereomeric esters in pure form.

2-(2-Bromo-3-methylbenzyl)-1-methyl-3-oxo-cyclohexanecarboxylic Acid Methyl Ester (8a)
Less Polar, Major Diastereomer

White solid; yield: 50%; mp 70–71 °C.

IR (KBr): 2973, 1715, 1228, 762 cm^{-1}.

^1H NMR: δ = 1.18 (s, 3 H), 1.71–1.76 (m, 1 H), 1.87–1.91 (m, 1 H), 2.01–2.04 (m, 1 H), 2.39 (s, 3 H), 2.28–2.57 (m, 4 H), 3.27 (dd, *J* = 8.2, 14.4 Hz, 1 H), 3.51 (s, 3 H), 3.45–3.50 (overlap. m, 1 H), 7.04–7.12 (m, 3 H).

^{13}C NMR: δ = 16.2 (CH_3), 23.1 (CH_2), 24.0 (CH_3), 32.2 (CH_2), 36.1 (CH_2), 41.8 (CH_2), 50.7 (C), 51.9 (CH_3), 54.9 (CH), 126.3 (CH), 127.3 (C), 128.6 (CH), 129.3 (CH), 138.2 (C), 139.3 (C), 175.2 (C), 209.8 (C).

MS (EI): *m*/*z* (%) = 354, 352 (12) [M^+, Br isotopes], 295, 293, 273, 213 (100), 185, 183, 123.

Anal. Calcd for $C_{17}H_{21}BrO_3$: C, 57.80; H, 5.99. Found: C, 58.08; H, 6.16.

More Polar, Minor Diastereomer

Colorless crystals; yield: 28%; mp 65–66 °C.

IR (KBr): 2952, 1735, 1205, 1142, 764 cm^{-1}.

^1H NMR: δ = 1.47 (s, 3 H), 1.82–1.93 (m, 3 H), 2.14–2.26 (m, 2 H), 2.38 (s, 3 H), 2.38–2.52 (overlap. m, 1 H), 2.74 (dd, *J* = 2.3, 9.3 Hz, 1 H), 2.84 (dd, *J* = 2.9, 14.0 Hz, 1 H), 3.34 (dd, *J* = 9.5, 14.0 Hz, 1 H), 3.71 (s, 3 H), 7.04–7.11 (m, 2 H), 7.25 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR: δ = 22.4 (CH_2), 24.0 (CH_3), 24.6 (CH_3), 32.7 (CH_2), 35.4 (CH_2), 40.2 (CH_2), 51.5 (C), 51.8 (CH_3), 57.8 (CH), 126.4 (CH), 126.8 (C), 128.6 (CH), 129.7 (CH), 138.1 (C), 139.9 (C), 175.2 (C), 208.5 (C).

MS (EI): *m*/*z* (%) = 354, 352 (16) [M^+, Br isotopes], 295, 293, 273, 213 (100), 185, 183, 121, 81.

Anal. Calcd for $C_{17}H_{21}BrO_3$: C, 57.80; H, 5.99. Found: C, 57.97; H, 6.09.

2-(4-Benzyloxy-2-bromo-5-methoxybenzyl)-1-methyl-3-oxo-cyclohexanecarboxylic Acid Methyl Ester (8b)
Less Polar, Major Diastereomer

White solid; yield: 38%; mp 98–100 °C.

IR (KBr): 2950, 1719, 1503, 1234, 1167, 1001 cm^{-1}.

^1H NMR: δ = 1.15 (s, 3 H), 1.69–1.75 (m, 1 H), 1.81–1.94 (m, 1 H), 2.00–2.07 (m, 1 H), 2.28–2.44 (m, 4 H), 3.14 (dd, *J* = 8.6, 14.1 Hz, 1 H), 3.32 (dd, *J* = 4.2, 8.6 Hz, 1 H), 3.55 (s, 3 H), 3.86 (s, 3 H), 5.07 (s, 2 H), 6.93 (s, 1 H), 6.98 (s, 1 H), 7.28–7.42 (m, 5 H).

^{13}C NMR: δ = 16.0 (CH_3), 23.1 (CH_2), 31.0 (CH_2), 35.9 (CH_2), 41.8 (CH_2), 50.8 (C), 51.9 (CH_3), 55.5 (CH), 55.9 (CH_3), 70.9 (CH_2), 113.8 (C), 115.5 (CH), 117.7 (CH), 127.2 (2 × CH), 127.8 (CH), 128.3 (2 × CH), 131.5 (C), 136.4 (C), 146.8 (C), 148.3 (C), 175.1 (C), 209.8 (C).

MS (FAB): *m*/*z* (%) = 476, 474 (44) [M^+, Br isotopes], 395, 335, 325, 323, 243, 91 (100).

Anal. Calcd for $C_{24}H_{27}BrO_5$: C, 60.64; H, 5.72. Found: C, 60.38; H, 5.85.

More Polar, Minor Diastereomer

Colorless liquid; yield: 20%.

IR (neat): 2945, 1721, 1505, 1256, 1208 cm^{-1}.

^1H NMR: δ = 1.52 (s, 3 H), 1.82–1.91 (m, 3 H), 2.13–2.25 (m, 2 H), 2.43–2.49 (m, 1 H), 2.61 (dd, *J* = 1.8, 9.5 Hz, 1 H), 2.72 (dd, *J* = 2.6, 13.9 Hz, 1 H), 3.20 (dd, *J* = 9.7, 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.87 (s, 3 H), 5.07 (s, 2 H), 6.96 (s, 1 H), 7.12 (s, 1 H), 7.28–7.43 (m, 5 H).

^{13}C NMR: δ = 22.5 (CH_2), 24.9 (CH_3), 31.4 (CH_2), 36.1 (CH_2), 40.5 (CH_2), 51.7 (C), 51.8 (CH_3), 56.0 (CH_3), 58.2 (CH), 71.1 (CH_2), 113.5 (C), 116.1 (CH), 117.6 (CH), 127.3 (2 × CH), 127.9 (CH), 128.5 (2 × CH), 132.4 (C), 136.5 (C), 147.1 (C), 148.5 (C), 175.2 (C), 208.7 (C).

MS (EI): *m*/*z* (%) = 476, 474 (27) [M^+, Br isotopes], 395 (100), 385, 383, 325, 323, 215.

Anal. Calcd for $C_{24}H_{27}BrO_5$: C, 60.64; H, 5.72. Found: C, 60.52; H, 5.81.

2-(4-Benzyloxy-2-bromo-3-methoxybenzyl)-1-methyl-3-oxocyclohexanecarboxylic Acid Methyl Ester (8d)
Less Polar, Major Diastereomer
Colorless liquid; yield: 38%.

IR (neat): 2948, 1727, 1483, 1269, 1034 cm^{-1}.

^1H NMR: δ = 1.16 (s, 3 H), 1.63–1.75 (m, 1 H), 1.81–1.92 (m, 1 H), 1.99–2.06 (m, 1 H), 2.27–2.49 (m, 4 H), 3.18 (dd, *J* = 8.4, 14.3 Hz, 1 H), 3.38–3.43 (m, 1 H), 3.51 (s, 3 H), 3.86 (s, 3 H), 5.08 (s, 2 H), 6.79 (d, *J* = 8.6 Hz, 1 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 7.28–7.43 (m, 5 H).

^{13}C NMR: δ = 16.1 (CH_3), 23.1 (CH_2), 31.1 (CH_2), 36.0 (CH_2), 41.8 (CH_2), 50.7 (C), 51.9 (CH_3), 55.0 (CH), 60.2 (CH_3), 70.8 (CH_2), 112.8 (CH), 120.4 (C), 126.5 (CH), 127.1 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 132.3 (C), 136.7 (C), 146.6 (C), 150.7 (C), 175.2 (C), 209.9 (C).

MS (FAB): *m*/*z* (%) = 477, 475 (26) [M^+ + 1, Br isotopes], 476, 474 (41) [M^+, Br isotopes], 395, 335, 307, 305 (100), 215, 183.

Anal. Calcd for $C_{24}H_{27}BrO_5$: C, 60.64; H, 5.72. Found: C, 60.56; H, 5.78.

More Polar, Minor Diastereomer
Colorless liquid; yield: 21%.

IR (neat): 2943, 1727, 1484, 1270, 1034 cm^{-1}.

^1H NMR: δ = 1.49 (s, 3 H), 1.82–1.92 (m, 3 H), 2.12–2.28 (m, 2 H), 2.43–2.49 (m, 1 H,), 2.65–2.79 (m, 2 H), 3.26 (dd, *J* = 9.6, 14.1 Hz, 1 H), 3.70 (s, 3 H), 3.86 (s, 3 H), 5.08 (s, 2 H), 6.82 (d, *J* = 8.5 Hz, 1 H), 7.15 (d, *J* = 8.5 Hz, 1 H), 7.31–7.43 (m, 5 H).

^{13}C NMR: δ = 22.4 (CH_2), 24.7 (CH_3), 31.6 (CH_2), 35.6 (CH_2), 40.3 (CH_2), 51.5 (C), 51.7 (CH_3), 57.8 (CH), 60.3 (CH_3), 70.8 (CH_2), 112.9 (CH), 120.0 (C), 127.1 (3 × CH), 127.8 (CH), 128.4 (2 × CH), 132.9 (C), 136.7 (C), 146.4 (C), 150.7 (C), 175.1 (C), 208.7 (C).

MS (FAB): *m*/*z* (%) = 477, 475 (31) [M^+ + 1, Br isotopes], 476, 474 (38) [M^+, Br isotopes], 395 (100), 385, 383, 307, 305, 215, 136.

Anal. Calcd for $C_{24}H_{27}BrO_5$: C, 60.64; H, 5.72. Found: C, 60.72; H, 5.83.

Wittig Olefination of 7; General Procedure
To a stirred suspension of ethyl triphenyl phosphonium iodide (17.5 mmol) in anhyd toluene (30 mL) was added solid *t*-BuOK (15.0 mmol) and the mixture was stirred at r.t. for 2 h. Then, a solution of the ketone (5 mmol) in anhyd toluene (10 mL) was added slowly and the stirring was continued for another 12 h. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O (2 × 50 mL). The organic extract was washed with brine and dried. The solvent was removed and the residue was purified by column chromatography to give the product.

2-Bromo-1-(6-ethylidene-2,2-dimethylcyclohexylmethyl)-3-methylbenzene (9a)
Colorless liquid; yield: 84%.

IR (neat): 2950, 1451, 1024, 772 cm^{-1}.

^1H NMR: δ = 0.93 (s, 3 H), 1.06 (s, 3 H), 1.26–1.35 (m, 1 H), 1.37 (dd, *J* = 1.0, 6.6 Hz, 3 H), 1.44–1.66 (m, 3 H), 1.94–2.10 (m, 2 H), 2.30–2.37 (dt, *J* = 3.3, 13.9 Hz, 1 H), 2.40 (s, 3 H), 2.73 (dd, *J* = 12.0, 13.5 Hz, 1 H), 3.09 (dd, *J* = 3.3, 13.5 Hz, 1 H), 4.57 (q, *J* = 6.6 Hz, 1 H), 6.77–6.80 (m, 1 H), 7.01 (d, *J* = 4.9 Hz, 2 H).

^{13}C NMR: δ = 12.5 (CH_3), 22.6 (CH_2), 24.1 (CH_2), 24.2 (CH_3), 27.9 (CH_3), 28.2 (CH_3), 34.5 (CH_2), 34.8 (C), 35.7 (CH_2), 55.0 (CH), 119.2 (CH), 125.7 (CH), 127.2 (C), 127.9 (CH), 128.7 (CH), 137.0 (C), 137.8 (C), 141.5 (C).

MS (EI): *m*/*z* (%) = 322, 320 (72) [M^+, Br isotopes], 241, 197, 185 (98), 183 (100), 81, 69.

Anal. Calcd for $C_{18}H_{25}Br$: C, 67.29; H, 7.84. Found: C, 67.37; H, 7.73.

1-Benzyloxy-5-bromo-4-(6-ethylidene-2,2-dimethylcyclohexylmethyl)-2-methoxybenzene (9b)
White solid; yield: 94%; mp 88–90 °C.

IR (KBr): 2940, 1506, 1254, 1211, 1003 cm^{-1}.

^1H NMR: δ = 0.92 (s, 3 H), 1.05 (s, 3 H), 1.25–1.30 (m, 2 H), 1.41 (d, *J* = 6.5 Hz, 3 H), 1.47–1.63 (m, 2 H), 1.95–1.98 (m, 2 H), 2.37 (bd, *J* = 13.9 Hz, 1 H), 2.63 (m, 1 H), 2.95 (dd, *J* = 3.2, 13.5 Hz, 1 H), 3.78 (s, 3 H), 4.64 (q, *J* = 6.5 Hz, 1 H), 5.06 (s, 2 H), 6.50 (s, 1 H), 7.01 (s, 1 H), 7.28–7.44 (m, 5 H).

^{13}C NMR: δ = 12.6 (CH_3), 22.6 (CH_2), 24.0 (CH_2), 28.1 (CH_3), 28.2 (CH_3), 33.4 (CH_2), 34.8 (C), 35.4 (CH_2), 55.7 (CH), 56.1 (CH_3), 71.3 (CH_2), 114.2 (C), 114.8 (CH), 118.0 (C), 119.4 (CH), 127.5 (2 × CH), 127.9 (CH), 128.5 (2 × CH), 134.1 (C), 136.7 (C), 137.2 (C), 146.6 (C), 148.3 (C).

MS (EI): *m*/*z* (%) = 444, 442 (68) [M^+, Br isotopes], 364, 362, 307 (100), 305, 227.

Anal. Calcd for $C_{25}H_{31}BrO_2$: C, 67.72; H, 7.05. Found: C, 67.88; H, 7.03.

1-Bromo-2-(6-ethylidene-2,2-dimethylcyclohexylmethyl)-benzene (9c)
Colorless liquid; yield: 82%.

IR (neat): 2950, 1468, 1441, 1025, 750 cm^{-1}.

^1H NMR: δ = 0.93 (s, 3 H), 1.05 (s, 3 H), 1.36 (d, *J* = 6.7 Hz, 3 H), 1.26–1.31 (m, 1 H), 1.43–1.66 (m, 3 H), 1.93–2.08 (m, 2 H), 2.32–2.37 (m, 1 H), 2.71 (dd, *J* = 12.0, 13.4 Hz, 1 H), 3.04 (dd, *J* = 3.3, 13.4 Hz, 1 H), 4.58 (q, *J* = 6.3 Hz, 1 H), 6.95–7.00 (m, 2 H), 7.12 (app t, *J* = 7.3 Hz, 1 H), 7.47 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR: δ = 12.5 (CH_3), 22.6 (CH_2), 24.1 (CH_2), 28.0 (CH_3), 28.1 (CH_3), 33.9 (CH_2), 34.8 (C), 35.6 (CH_2), 55.3 (CH), 119.3 (CH), 124.5 (CH), 126.4 (C), 127.0 (CH), 131.3 (CH), 132.4 (C), 137.0 (C), 141.4 (C).

MS (EI): *m*/*z* (%) = 308, 306 (10) [M^+, Br isotopes], 293, 291, 227 (100), 138, 137, 89, 79.

Anal. Calcd for $C_{17}H_{23}Br$: C, 66.45; H, 7.54. Found: C, 66.58; H, 7.69.

1-Benzyloxy-3-bromo-4-(6-ethylidene-2,2-dimethylcyclohexylmethyl)-2-methoxybenzene (9d)
Colorless liquid; yield: 91%.

IR (neat): 2932, 1483, 1290, 1038 cm^{-1}.

^1H NMR: δ = 0.92 (s, 3 H), 1.04 (s, 3 H), 1.35 (d, *J* = 6.6 Hz, 3 H), 1.25–1.63 (m, 4 H), 1.90–2.05 (m, 2 H), 2.28–2.33 (m, 1 H), 2.62–2.71 (app t, *J* = 12.7 Hz, 1 H), 3.00 (dd, *J* = 3.2, 13.6 Hz, 1 H), 3.87 (s, 3 H), 4.58 (q, *J* = 6.6 Hz, 1 H), 5.08 (s, 2 H), 6.63 (d, *J* = 8.5 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 7.31–7.43 (m, 5 H).

^{13}C NMR: δ = 12.5 (CH_3), 22.6 (CH_2), 24.1 (CH_2), 27.9 (CH_3), 28.1 (CH_3), 33.4 (CH_2), 34.7 (C), 35.6 (CH_2), 55.2 (CH), 60.4 (CH_3), 71.1 (CH_2), 112.9 (CH), 119.1 (CH), 120.2 (C), 125.7 (CH), 127.2 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 135.0 (C), 136.9 (C), 137.0 (C), 146.7 (C), 150.1 (C).

MS (EI): *m*/*z* (%) = 444, 442 (23) [M^+, Br isotopes], 363, 307, 305, 137, 91 (100).

Anal. Calcd for $C_{25}H_{31}BrO_2$: C, 67.72; H, 7.05; found C, 67.61; H, 7.19.

Wittig Olefination of 8; General Procedure
To a suspension of ethyl triphenyl phosphonium iodide (12 mmol) in anhyd toluene (20 mL) was added *t*-BuOK (10.62 mmol) and the

mixture was stirred at r.t. for 1 h. The suspension was heated to 80 °C and a solution of the ketone (3.54 mmol) in toluene (5 mL) was added slowly over 15 min. The reaction mixture was heated under reflux for 3 h. After cooling to r.t., it was quenched with sat. NH_4Cl solution and the organic part was separated. The aqueous part was extracted with Et_2O (2 × 20 mL); the combined organic extract was washed with brine and dried. After removal of the solvent, the residue was purified by column chromatography to give the product.

2-(2-Bromo-3-methylbenzyl)-3-ethylidene-1-methylcyclohexanecarboxylic Acid Methyl Ester (10a)
White solid; yield: 81%; mp 55–56 °C.

IR (KBr): 2938, 1718, 1253, 1108 cm^{-1}.

^1H NMR: δ = 1.26 (s, 3 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 1.55–1.58 (m, 3 H), 1.98–2.07 (m, 1 H), 2.13–2.27 (m, 2 H), 2.41 (s, 3 H), 2.85 (d, *J* = 7.3 Hz, 2 H), 3.06 (t, *J* = 7.3 Hz, 1 H), 3.58 (s, 3 H), 4.81 (q, *J* = 6.6 Hz, 1 H), 6.87–6.90 (m, 1 H), 7.03–7.04 (m, 2 H).

^{13}C NMR: δ = 12.7 (CH_3), 21.5 (CH_3), 23.5 (CH_2), 24.1 (CH_3), 24.9 (CH_2), 33.4 (CH_2), 33.9 (CH_2), 48.8 (C), 49.0 (CH), 51.5 (CH_3), 119.5 (CH), 126.0 (CH), 127.4 (C), 128.1 (CH), 128.2 (CH), 136.2 (C), 138.0 (C), 140.1 (C), 177.5 (C).

MS (EI): *m*/*z* (%) = 366, 364 (9) [M^+, Br isotopes], 307, 305, 285, 181 (100), 121.

Anal. Calcd for $C_{19}H_{25}BrO_2$: C, 62.47; H, 6.90. Found: C, 62.22; H, 6.83.

2-(4-Benzyloxy-2-bromo-5-methoxybenzyl)-3-ethylidene-1-methylcyclohexanecarboxylic Acid Methyl Ester (10b)
Colorless liquid; yield: 86%.

IR (neat): 2944, 1727, 1503, 1253, 1166 cm^{-1}.

^1H NMR: δ = 1.24 (s, 3 H), 1.44 (d, *J* = 6.7 Hz, 3 H), 1.54–1.64 (m, 3 H), 1.98–2.07 (m, 1 H), 2.16–2.18 (m, 2 H), 2.68–2.79 (m, 2 H), 2.95 (dd, *J* = 4.8, 9.8 Hz, 1 H), 3.58 (s, 3 H), 3.80 (s, 3 H), 4.88 (q, *J* = 6.7 Hz, 1 H), 5.07 (s, 2 H), 6.60 (s, 1 H), 7.02 (s, 1 H), 7.28–7.44 (m, 5 H).

^{13}C NMR: δ = 12.7 (CH_3), 21.9 (CH_3), 23.5 (CH_2), 24.6 (CH_2), 32.6 (CH_2), 33.0 (CH_2), 48.6 (C), 49.7 (CH), 51.5 (CH_3), 56.0 (CH_3), 71.1 (CH_2), 114.3 (CH), 117.7 (CH), 119.7 (CH), 127.3 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 132.5 (C), 136.2 (C), 136.6 (C), 146.7 (C), 148.3 (C), 177.4 (C); one carbon peak remained undistinguished due to overlap.

MS (EI): *m*/*z* (%) = 488, 486 (19) [M^+, Br isotopes], 407, 307, 305, 121, 91 (100).

Anal. Calcd for $C_{26}H_{31}BrO_4$: C, 64.07; H, 6.41. Found: C, 64.41; H, 6.54.

2-(2-Bromobenzyl)-3-ethylidene-1-methylcyclohexanecarboxylic Acid Methyl Ester (10c)
Colorless liquid; yield: 86%.

IR (neat): 2946, 1730, 1442, 1234, 752 cm^{-1}.

^1H NMR: δ = 1.25 (s, 3 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 1.53–1.68 (m, 3 H), 2.01–2.09 (m, 1 H), 2.18–2.19 (m, 2 H), 2.82 (d, *J* = 7.4 Hz, 2 H), 3.05 (t, *J* = 7.4 Hz, 1 H), 3.59 (s, 3 H), 4.83 (q, *J* = 6.6 Hz, 1 H), 6.97–7.18 (m, 3 H), 7.49 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR: δ = 12.5 (CH_3), 21.5 (CH_3), 23.4 (CH_2), 24.8 (CH_2), 33.1 (2 × CH_2), 48.6 (C), 49.2 (CH), 51.4 (CH_3), 119.5 (CH), 124.6 (C), 126.5 (CH), 127.1 (CH), 130.8 (CH), 132.3 (CH), 136.0 (C), 139.8 (C), 177.2 (C).

MS (EI): *m*/*z* (%) = 352, 350 (28) [M^+, Br isotopes], 293, 291, 271, 211, 181 (100), 171, 169, 121, 93.

Anal. Calcd for $C_{18}H_{23}BrO_2$: C, 61.54; H, 6.60. Found: C, 61.69; H, 6.79.

2-(4-Benzyloxy-2-bromo-3-methoxybenzyl)-3-ethylidene-1-methylcyclohexanecarboxylic Acid Methyl Ester (10d)
Colorless liquid; yield: 88%.

IR (neat): 2941, 2865, 1727, 1483, 1269, 1036 cm^{-1}.

^1H NMR: δ = 1.23 (s, 3 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 1.44–1.62 (m, 3 H), 2.02–2.14 (m, 3 H), 2.78 (, d, *J* = 7.2 Hz, 2 H), 3.00 (t, *J* = 7.2 Hz, 1 H), 3.57 (s, 3 H), 3.88 (s, 3 H), 4.83 (q, *J* = 6.6 Hz, 1 H), 5.09 (s, 2 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 7.29–7.43 (m, 5 H).

^{13}C NMR: δ = 12.6 (CH_3), 21.4 (CH_3), 23.4 (CH_2), 24.9 (CH_2), 32.8 (CH_2), 33.3 (CH_2), 48.6 (C), 49.1 (CH), 51.4 (CH_3), 60.2 (CH_3), 70.9 (CH_2), 112.8 (CH), 119.4 (CH), 120.4 (C), 125.3 (CH), 127.1 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 133.4 (C), 136.2 (C), 136.7 (C), 146.6 (C), 150.3 (C), 177.4 (C).

MS (EI): *m*/*z* (%) = 489, 487 (11) [M^+ + 1, Br isotopes], 488, 486 (8) [M^+, Br isotopes], 407, 307, 305, 215, 121 (100).

Anal. Calcd for $C_{26}H_{31}BrO_4$: C, 64.07; H, 6.41. Found: C, 64.33; H, 6.34.

Heck Cyclization of 9 and 10; General Procedure
A stirred suspension of olefin (3.58 mmol), $Pd(OAc)_2$ (0.19 mmol), triphenyl phosphine (0.76 mmol) and anhyd K_2CO_3 (14.4 mmol) in anhyd DMF (20 mL) was refluxed for several hours (details in Table 1). After cooling, H_2O (50 mL) was added to the reaction mixture and the solution was extracted with EtOAc (3 × 25 mL). The organic extract was washed with brine, dried and concentrated. Column chromatography of the crude product afforded the 4a-vinyl substituted hydrofluorenes.

1,1,5-Trimethyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (11a)
Colorless liquid; yield: 82%.

IR (neat): 2933, 1458, 910, 766 cm^{-1}.

^1H NMR: δ = 0.94 (s, 3 H), 1.03 (s, 3 H), 1.13–1.26 (m, 2 H), 1.36–1.47 (m, 2 H), 1.56–1.79 (m, 2 H), 2.04–2.10 (m, 1 H), 2.23 (s, 3 H), 2.70–2.87 (m, 2 H), 5.15–5.24 (m, 2 H), 6.10 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.85–6.87 (m, 1 H), 7.00–7.03 (m, 2 H).

^{13}C NMR: δ = 18.5 (CH_2), 19.7 (CH_3), 29.0 (CH_3), 29.7 (CH_2), 31.2 (CH_3), 32.6 (C), 33.8 (CH_2), 34.3 (CH_2), 52.3 (C), 57.5 (CH), 113.8 (CH_2), 122.1 (CH), 126.3 (CH), 129.1 (CH), 134.1 (C), 141.8 (C), 146.7 (CH), 149.4 (C).

MS (EI): *m*/*z* (%) = 241 [M^+ + 1], 240 (100) [M^+], 213, 156, 143, 69.

Anal. Calcd for $C_{18}H_{24}$: C, 89.94; H, 10.06. Found: C, 89.79; H, 10.08.

6-Benzyloxy-7-methoxy-1,1-dimethyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (11b)
White solid; yield: 96%; mp 76–78 °C.

IR (KBr): 2942, 2864, 1496, 1292, 1221 cm^{-1}.

^1H NMR: δ = 0.94 (s, 3 H), 1.00 (s, 3 H), 1.07–1.26 (m, 2 H), 1.36–1.45 (m, 2 H), 1.54–1.62 (m, 1 H), 1.89 (br d, *J* = 13.8 Hz, 1 H), 2.20 (t, *J* = 9.8 Hz, 1 H), 2.75 (d, *J* = 9.8 Hz, 2 H), 3.84 (s, 3 H), 5.05 (s, 2 H), 5.10–5.17 (m, 2 H), 5.82 (dd, *J* = 10.5, 17.8 Hz, 1 H), 6.52 (s, 1 H), 6.78 (s, 1 H), 7.27–7.44 (m, 5 H).

^{13}C NMR: δ = 18.9 (CH_2), 28.5 (CH_3), 30.7 (CH_3), 31.2 (CH_2), 32.4 (C), 33.3 (CH_2), 34.8 (CH_2), 51.5 (C), 56.2 (CH_3), 58.5 (CH), 71.4 (CH_2), 108.8 (CH), 109.9 (CH), 111.7 (CH_2), 127.6 (2 × CH), 127.6 (CH), 128.3 (2 × CH), 133.7 (C), 137.5 (C), 143.9 (C), 145.7 (CH), 146.9 (C), 148.7 (C).

MS (EI): *m*/*z* (%) = 362 (63) [M^+], 271, 86 (100).

Anal. Calcd for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34. Found: C, 82.72; H, 8.41.

1,1-Dimethyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (11c)
Colorless liquid; yield: 95%.

IR (neat): 2938, 1469, 909, 756 cm^{-1}.

^1H NMR: δ = 0.96 (s, 3 H), 1.03 (s, 3 H), 1.09–1.19 (m, 1 H), 1.22–1.29 (m, 1 H), 1.35–1.49 (m, 2 H), 1.58–1.70 (m, 1 H), 1.96 (br d, *J* = 13.9 Hz, 1 H), 2.06 (t, *J* = 9.8 Hz, 1 H), 2.83 (d, *J* = 9.7 Hz, 2 H), 5.19–5.25 (m, 2 H), 5.88 (dd, *J* = 10.8, 17.8 Hz, 1 H), 6.92–6.95 (m, 1 H), 7.10–7.13 (m, 2 H), 7.19–7.22 (m, 1 H).

^{13}C NMR: δ = 18.9 (CH_2), 28.6 (CH_3), 30.8 (CH_3), 31.1 (CH_2), 32.4 (C), 33.4 (CH_2), 34.7 (CH_2), 51.6 (C), 58.0 (CH), 111.9 (CH_2), 122.9 (CH), 124.6 (CH), 126.0 (CH), 126.3 (CH), 141.4 (C), 145.5 (CH), 152.0 (C).

MS (EI): *m*/*z* (%) = 227 [M^+ + 1], 226 (100) [M^+], 183, 155, 142, 129.

Anal. Calcd for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 90.01; H, 9.89.

6-Benzyloxy-5-methoxy-1,1-dimethyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (11d)
Colorless liquid; yield: 62%.

IR (neat): 2935, 1480, 1266, 1066 cm^{-1}.

^1H NMR: δ = 0.90 (s, 3 H), 1.02 (s, 3 H), 1.11–1.47 (m, 4 H), 1.60–1.71 (m, 1 H), 2.10–2.25 (m, 2 H), 2.25–2.82 (m, 2 H), 3.76 (s, 3 H), 5.04 (s, 2 H), 5.15–5.21 (m, 2 H), 6.16 (dd, *J* = 10.6, 17.8 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 7.29–7.45 (m, 5 H).

^{13}C NMR: δ = 18.7 (CH_2), 29.3 (CH_3), 30.7 (CH_3), 31.3 (CH_2), 32.6 (C), 33.3 (CH_2), 34.8 (CH_2), 51.7 (C), 56.9 (CH), 60.6 (CH_3), 71.1 (CH_2), 112.3 (CH), 113.2 (CH), 119.2 (CH), 127.2 (2 × CH), 127.7 (CH), 128.4 (2 × CH), 135.8 (C), 137.5 (C), 145.2 (C), 146.1 (C), 146.5 (CH), 150.9 (C).

MS (EI): *m*/*z* (%) = 363 [M^+ + 1], 362 (65) [M^+], 271, 201, 91 (100).

Anal. Calcd for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34. Found: C, 82.88; H, 8.43.

1,5-Dimethyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-1-carboxylic Acid Methyl Ester (12a)
Colorless liquid; yield: 61%.

IR (neat): 2936, 1731, 1458, 1234, 1128, 769 cm^{-1}.

^1H NMR: δ = 1.20 (s, 3 H), 1.20–1.35 (overlap. m, 3 H), 1.46–1.56 (m, 1 H), 1.82–1.97 (m, 1 H), 2.06 (br d, *J* = 13.5 Hz, 1 H), 2.22 (s, 3 H), 2.71–2.82 (m, 1 H), 2.88–2.99 (m, 2 H), 3.59 (s, 3 H), 5.13 (d, *J* = 17.8 Hz, 1 H), 5.20 (d, *J* = 10.9 Hz, 1 H), 5.86 (dd, *J* = 10.9, 17.6 Hz, 1 H), 6.87 (d, *J* = 6.5 Hz, 1 H), 7.02–7.08 (m, 2 H).

^{13}C NMR: δ = 19.3 (CH_3), 19.5 (CH_2), 26.9 (CH_3), 28.5 (CH_2), 29.5 (CH_2), 32.3 (CH_2), 43.0 (C), 51.1 (CH_3), 51.6 (CH), 52.1 (C), 114.2 (CH_2), 122.1 (CH), 126.3 (CH), 129.1 (CH), 134.0 (C), 140.6 (C), 143.7 (CH), 148.7 (C), 177.5 (C).

MS (EI): *m*/*z* (%) = 285 [M^+ + 1], 284 (70) [M^+], 225 (100), 224, 209, 197, 169, 155.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.38; H, 8.56.

7-Benzyloxy-6-methoxy-1-methyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-1-carboxylic Acid Methyl Ester (12b)
Colorless liquid; yield: 86%.

IR (neat): 2939, 1728, 1496, 1225 cm^{-1}.

^1H NMR: δ = 1.20 (s, 3 H), 1.08–1.33 (overlap. m, 2 H), 1.42–1.46 (m, 1 H), 1.58–1.75 (m, 1 H), 1.85 (br d, *J* = 14.1 Hz, 1 H), 2.07 (br d, *J* = 13.2 Hz, 1 H), 2.72–2.88 (m, 2 H), 2.98 (dd, *J* = 7.6, 11.6 Hz, 1 H), 3.61 (s, 3 H), 3.85 (s, 3 H), 5.05 (s, 2 H), 5.10 (d, *J* = 17.6 Hz, 1 H), 5.14 (d, *J* = 10.8 Hz, 1 H), 5.67 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.52 (s, 1 H), 6.81 (s, 1 H), 7.27–7.43 (m, 5 H).

^{13}C NMR: δ = 20.0 (CH_2), 26.7 (CH_3), 30.2 (CH_2), 30.8 (CH_2), 32.2 (CH_2), 43.8 (C), 51.4 (CH_3), 51.8 (C), 52.7 (CH), 56.3 (CH_3), 71.5 (CH_2), 109.0 (CH), 109.8 (CH), 113.3 (CH_2), 127.6 (2 × CH), 127.7 (CH), 128.0 (2 × CH), 132.7 (C), 138.0 (C), 142.9 (C), 143.8 (C), 147.2 (CH), 148.9 (C), 177.6 (C).

MS (EI): *m*/*z* (%) = 407 [M^+ + 1], 406 (71) [M^+], 315, 255, 91 (100).

Anal. Calcd for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.71; H, 7.38.

1-Methyl-4a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-1-carboxylic Acid Methyl Ester (12c)
Colorless liquid; yield: 87%.

IR (neat): 2942, 1731, 1459, 1227, 1132, 758 cm^{-1}.

^1H NMR: δ = 1.22 (s, 3 H), 1.13–1.36 (m, 2 H), 1.45–1.50 (m, 1 H), 1.66–1.81 (m, 1 H), 1.92 (br d, *J* = 14.1 Hz, 1 H), 2.09 (br d, *J* = 13.5 Hz, 1 H), 2.84–3.05 (m, 3 H), 3.62 (s, 3 H), 5.12–5.22 (m, 2 H), 5.73 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.92–6.95 (m, 1 H), 7.12–7.15 (m, 2 H), 7.23–7.25 (m, 1 H).

^{13}C NMR: δ = 19.9 (CH_2), 26.7 (CH_3), 30.0 (CH_2), 30.5 (CH_2), 32.2 (CH_2), 43.6 (C), 51.3 (CH_3), 51.8 (C), 52.2 (CH), 113.5 (CH_2), 122.8 (CH), 124.7 (CH), 126.3 (CH), 126.4 (CH), 140.3 (C), 142.6 (CH), 151.7 (C), 177.5 (C).

MS (EI): *m*/*z* (%) = 271 [M^+ + 1], 270 (68) [M^+], 211, 210, 183, 155, 141 (100).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.13; H, 8.32.

1-(1,1-Dimethyl-1,2,3,4,9,9a-hexahydrofluoren-4a-yl)ethane-1,2-diol (13a)
To a stirred a solution of **11c** (705 mg, 3.12 mmol) in acetone–*t*-BuOH (1:1, 3 mL) was added NMO (1.6 mL, 15.4 mmol, 50% solution in H_2O) in cold, followed by OsO_4 (7.9 mg, 1 mmol%). The reaction mixture was stirred at r.t. for 8 h. The solvent was evaporated and the residue was dissolved in EtOAc (10 mL). The solution was washed with 5 M HCl (6.5 mL) and then stirred with 45% sodium metabisulfate solution (10 mL) for 20 min. The organic part was separated, washed with brine and dried. Complete removal of the solvent followed by column chromatography of the residue gave the diastereomeric mixture of diols **13a** (680 mg, 84%) as a sticky liquid.

IR (neat): 3384, 2941, 1459, 1036 cm^{-1}.

^1H NMR [major peaks]: δ = 0.50 (s, 3 H), 0.99 (s, 3 H), 1.19–1.35 (m, 3 H), 1.49–1.64 (m, 2 H), 1.99–2.11 (m, 2 H), 2.19 (exchangeable br s, 2 H), 2.70 (dd, *J* = 4.8, 16.1 Hz, 1 H), 2.97 (dd, *J* = 7.3, 16.1 Hz, 1 H), 3.44–3.82 (m, 3 H), 7.10–7.20 (m, 3 H), 7.26–7.28 (m, 1 H).

^{13}C NMR [major peaks]: δ = 18.0 (CH_2), 25.4 (CH_3), 26.1 (CH_2), 31.5 (CH_3), 32.3 (C), 32.6 (CH_2), 37.8 (CH_2), 50.7 (CH), 52.8 (C), 62.8 (CH_2), 74.8 (CH), 123.6 (CH), 124.5 (CH), 125.7 (CH), 126.5 (CH), 143.9 (C), 147.3 (C).

MS (EI): *m*/*z* (%) = 260 (22) [M^+], 215, 200 (100), 199 (100), 143, 129.

The minor peaks attributed to minor isomers were ignored.

4a-(1,2-Dihydroxyethyl)-1-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-1-carboxylic Acid Methyl Ester (13b)
The same procedure as described for **13a** was followed to synthesize **13b** (84%) from **12c**. A second column chromatography of the product over 100–200 mesh silica gel could separate a portion of the major diastereomer in pure form (41%).

Major Diastereomer

White solid; mp 72–73 °C.

IR (KBr): 3342, 2945, 1718, 1231, 740 cm^{-1}.

^1H NMR: δ = 1.16 (s, 3 H), 1.21–1.36 (m, 2 H), 1.43–1.49 (m, 1 H), 1.55–1.68 (m, 1 H), 2.11–2.25 (m, 4 H, including exchangeable 2 H), 2.74–2.98 (m, 3 H), 3.47 (dd, *J* = 9.7, 11.2 Hz, 1 H), 3.74 (s, 3 H), 3.77–3.83 (m, 2 H), 7.09–7.20 (m, 3 H), 7.50–7.53 (m, 1 H).

^{13}C NMR: δ = 18.6 (CH_2), 26.0 (CH_3), 29.4 (CH_2), 30.3 (CH_2), 32.5 (CH_2), 44.1 (C), 45.9 (CH), 51.8 (C), 52.1 (CH_3), 63.7 (CH_2), 73.1 (CH), 124.4 (CH), 124.6 (CH), 126.2 (CH), 126.4 (CH), 140.6 (C), 148.7 (C), 179.0 (C).

MS (EI): *m*/*z* (%) = 304 (59) [M^+], 244 (100), 243 (100), 184, 183, 155, 129, 105.

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95; found C, 71.32; H, 7.81.

1,1-Dimethyl-1,2,3,4,9,9a-hexahydrofluorene-4a-carbaldehyde (14a)

To a solution of **13a** (520 mg, 2 mmol) in MeOH (20 mL) was added a solution of sodium periodate (525 mg, 2.5 mmol) in H_2O (4 mL) dropwise at 0 °C. The mixture was stirred for 2 h and filtered. The residue was washed with MeOH. The combined filtrate was concentrated. The residue was dissolved using H_2O (20 mL) and Et_2O (20 mL). The organic part was separated and the aqueous part was extracted with Et_2O (2 × 10 mL). The combined organic extract was washed with brine, dried and concentrated. Column chromatography of the residue furnished **14a** (450 mg, 99%) as a colorless liquid.

IR (neat): 2945, 1721, 1471, 1458, 754 cm^{-1}.

^1H NMR: δ = 0.90 (s, 3 H), 1.03 (s, 3 H), 1.24–1.29 (m, 2 H), 1.35–1.57 (m, 3 H), 2.35 (br d, *J* = 14.0 Hz, 1 H), 2.52 (app t, *J* = 9.7 Hz, 1 H), 2.87–3.02 (m, 2 H), 6.85 (d, *J* = 7.2 Hz, 1 H), 7.11–7.30 (m, 3 H), 9.52 (s, 1 H).

^{13}C NMR: δ = 18.9 (CH_2), 27.7 (CH_3), 28.3 (CH_2), 29.9 (CH_3), 31.9 (C), 33.5 (CH_2), 33.8 (CH_2), 52.6 (CH), 61.2 (C), 122.9 (CH), 125.2 (CH), 126.5 (CH), 127.7 (CH), 142.8 (C), 145.0 (C), 202.8 (CH).

MS: *m*/*z* (%) = 228 (31) [M^+], 200, 199 (100), 129.

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.43; H, 8.74.

4a-Formyl-1-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-1-carboxylic Acid Methyl Ester (14b)

The same procedure as described for **14a** was followed to synthesize **14b** (95%) from **13b** as a colorless liquid.

IR (neat): 2929, 1721, 1457, 1167 cm^{-1}.

^1H NMR: δ = 1.00–1.06 (m, 1 H), 1.30 (s, 3 H), 1.17–1.43 (m, 2 H), 1.50–1.56 (m, 1 H), 2.05 (br d, *J*= 12.9 Hz, 1 H), 2.38 (d, *J* = 13.5 Hz, 1 H), 2.87–3.07 (m, 2 H), 3.34 (dd, *J* = 8.1, 12.0 Hz, 1 H), 3.66 (s, 3 H), 6.86 (d, *J* = 7.2 Hz, 1 H), 7.14–7.24 (m, 2 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 9.49 (s, 1 H).

^{13}C NMR: δ = 20.4 (CH_2), 25.0 (CH_3), 27.9 (CH_2), 30.8 (CH_2), 32.8 (CH_2), 44.4 (C), 46.1 (CH), 51.7 (CH_3), 60.7 (C), 122.8 (CH), 124.9 (CH), 126.6 (CH), 127.6 (CH), 141.4 (C), 144.8 (C), 177.4 (C), 200.4 (CH).

MS (EI): *m*/*z* (%) = 272 (32) [M^+], 243, 242, 212, 183 (100), 156, 141, 130, 115.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.16; H, 7.51.

1,1-Dimethyl-1,2,3,4,9,9a-hexahydrofluorene-4a-carboxylic Acid (15a)

To a stirred solution of **14a** (80 mg, 0.35 mmol) in DMSO (2 mL) was added a solution of sodium dihydrogen phosphate dihydrate (164 mg, 1.05 mmol) in H_2O (0.6 mL) and the mixture was cooled to 0 °C. A solution of sodium chlorite (154 mg, 1.22 mmol) in H_2O (0.4 mL) was added and stirred at r.t. for 3 h. The reaction mixture was diluted with H_2O and extracted with EtOAc (2 × 10 mL). The extract was washed with brine and dried. Concentration of the extract gave a residue, which was purified by column chromatography to furnish **15a** (82 mg, 96%) as white crystals; mp 158–160 °C.

IR (KBr): 2950, 1694, 1276, 745 cm^{-1}.

^1H NMR: δ = 1.00 (s, 3 H), 1.02 (s, 3 H), 1.00–1.13 (overlap. m, 1 H), 1.27–1.49 (m, 3 H), 1.64–1.74 (m, 1 H), 2.37 (br d, *J* = 13.7 Hz, 1 H), 2.82–2.94 (m, 3 H), 7.06–7.26 (m, 4 H).

^{13}C NMR: δ = 19.5 (CH_2), 27.9 (CH_3), 30.2 (CH_3), 31.5 (CH_2), 32.2 (C), 33.2 (CH_2), 34.1 (CH_2), 53.7 (CH), 56.0 (C), 121.5 (CH), 125.0 (CH), 126.6 (CH), 127.2 (CH), 141.4 (C), 149.1 (C), 182.4 (C).

MS (EI): *m*/*z* (%) = 244 (39) [M^+], 200, 199 (100), 143, 129.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.32; H, 8.17.

1-Methyl-1,2,3,4,9,9a-hexahydrofluorene-1,4a-dicarboxylic Acid 1-Methyl Ester (15b)

The same procedure as described for **15a** was followed to synthesize **15b** (99%) from **14b** as a white solid; mp 144–145 °C.

IR (KBr): 3269, 2947, 1725, 1698, 1231, 1183, 764 cm^{-1}.

^1H NMR: δ = 1.08–1.19 (m, 1 H), 1.27 (s, 3 H), 1.27–1.39 (overlap. m, 1 H), 1.49–1.56 (m, 1 H), 1.68–1.77 (m, 1 H), 2.09 (br d, *J* = 13.5 Hz, 1 H), 2.31 (br d, *J* = 13.9 Hz, 1 H), 2.86 (dd, *J* = 12.1, 15.2 Hz, 1 H), 3.02 (dd, *J* = 8.0, 15.2 Hz, 1 H), 3.56 (dd, *J* = 8.3, 11.7 Hz, 1 H), 3.65 (s, 3 H), 7.15–7.24 (m, 4 H).

^{13}C NMR: δ = 20.4 (CH_2), 25.9 (CH_3), 30.6 (CH_2), 31.6 (CH_2), 32.7 (CH_2), 43.8 (C), 48.1 (CH), 51.6 (CH_3), 56.3 (C), 122.3 (CH), 124.7 (CH), 126.8 (CH), 127.2 (CH), 140.0 (C), 148.3 (C), 177.4 (C), 181.9 (C).

MS (EI): *m*/*z* (%) = 288 (21) [M^+], 270, 244, 242, 229, 184 (100), 183 (100), 130.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.56; H, 7.08.

(1,1-Dimethyl-1,2,3,4,9,9a-hexahydrofluoren-4a-yl)methanol (16a)

To a stirred solution of **14a** (140 mg, 0.62 mmol) in MeOH (4 mL) $NaBH_4$ (24 mg, 0.62 mmol) was added portionwise at 0 °C and the mixture was stirred for 1 h. MeOH was removed and the residue was dissolved in minimum volume of H_2O. Aq AcOH was added until effervescence ceased and the mixture was extracted with EtOAc (2 × 10 mL). The extract was washed with brine, dried and concentrated. Column chromatography of the crude alcohol over neutral alumina afforded **16a** (138 mg, 98%) as a colorless liquid.

IR (neat): 3381, 2932, 1460, 1031, 755 cm^{-1}.

^1H NMR: δ = 0.88 (s, 3 H), 1.10 (s, 3 H), 1.26–1.58 (m, 6 H), 2.30 (t, *J* = 8.8 Hz, 1 H), 2.74–2.90 (m, 2 H), 3.91 (s, 2 H), 7.09–7.24 (m, 4 H).

^{13}C NMR: δ = 18.9 (CH_2), 29.4 (CH_3), 29.7 (CH_3), 31.9 (CH_2, C), 33.4 (CH_2), 35.6 (CH_2), 48.8 (CH), 50.9 (C), 66.8 (CH_2), 121.1 (CH), 124.8 (CH), 126.2 (CH), 126.6 (CH), 143.0 (C), 149.1 (C).

MS (EI): *m*/*z* (%) = 230 (12) [M^+], 200, 199 (100), 143, 129.

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.62; H, 9.57.

4a-Hydroxymethyl-1-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-1-carboxylic Acid Methyl Ester (16b)

The same procedure as described for **16a** was followed to synthesize **16b** (92%) from **14b** as a colorless liquid.

IR (neat): 3537, 2939, 1722, 1460, 1227, 758 cm^{-1}.

^1H NMR: δ = 1.26 (s, 3 H), 1.20–1.51 (overlap. m, 5 H), 1.90 (exchangeable br s, 1 H), 2.15–2.19 (m, 1 H), 2.77–2.96 (m, 2 H), 3.14 (dd, *J* = 8.0, 11.6 Hz, 1 H), 3.60 (d, *J* = 12.5 Hz, 1 H), 3.76 (s, 3 H), 3.85 (d, *J* = 12.5 Hz, 1 H), 7.12–7.23 (m, 4 H).

^{13}C NMR: δ = 20.2 (CH_2), 26.5 (CH_3), 30.1 (CH_2), 31.9 (CH_2), 32.0 (CH_2), 43.6 (CH), 44.1 (C), 50.3 (C), 52.3 (CH_3), 63.0 (CH_2), 121.2 (CH), 124.7 (CH), 126.4 (CH), 126.5 (CH), 140.7 (C), 149.7 (C), 179.7 (C).

MS (EI): *m*/*z* (%) = 274 (14) [M^+], 256, 244, 243, 184, 183 (100), 141, 128.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.59; H, 8.13.

1,1,4a-Trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (18)

To a stirred solution of **16a** (175 mg, 0.22 mmol) in anhyd CH_2Cl_2 (1 mL) at –10 °C was added CBr_4 (87.5 mg, 0.26 mmol) and the mixture was stirred for 10 min. PPh_3 (63.5 mg, 0.24 mmol) was added portionwise and the reaction mixture was stirred at the same temperature for 30 min. The organic layer was washed with H_2O and brine, and then dried. The solvent was evaporated to afford the crude bromide **17**, which readily decomposes at r.t.

The crude bromide was immediately dissolved in anhyd benzene (20 mL) and a solution of TBTH (0.07 mL, 0.26 mmol) and AIBN (8 mg) in anhyd benzene (10 mL) was added slowly at refluxing condition over 1 h. Refluxing was continued for another 4 h before cooling. The solvent was removed and the residue was purified by column chromatography to give **18** (12 mg, 26%) as a colorless liquid.

IR (neat): 2929, 1474, 754 cm^{-1}.

^1H NMR: δ = 0.93 (s, 3 H), 1.12 (s, 3 H), 1.17–1.35 (m, 3 H), 1.44 (s, 3 H), 1.39–1.65 (m, 3 H), 1.86 (t, *J* = 9.5 Hz, 1 H), 2.78 (d, *J* = 9.5 Hz, 2 H), 7.07–7.20 (m, 4 H); [Lit.[3,9] δ = 0.93, 1.12, 1.44 (s, 3 × 3 H)].

^{13}C NMR: δ = 18.9 (CH_2), 25.6 (CH_3), 29.5 (CH_3), 30.9 (CH_3), 32.1 (C) 33.8 (CH_2), 35.1 (CH_2), 36.1 (CH_2), 45.1 (C), 57.3 (C) 121.3 (CH), 124.4 (CH), 125.9 (CH), 126.0 (CH), 141.3 (C), 154.3 (C).

MS (EI): *m*/*z* (%) = 214 (81) [M^+], 200, 199 (100), 143, 129.

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.38; H, 10.27.

1-Methyl-1,2,3,4,9,9a-hexahydrofluorene-1,4a-dicarboxylic Acid Dimethyl Ester (19)

To a stirred solution of **15b** (72 mg, 0.25 mmol) in anhyd THF (2 mL) was added $LiOH·H_2O$ (12.6 mg, 0.3 mmol) and the reaction mixture was stirred at r.t. for 30 min. Dimethyl sulfate (48 μL, 0.5 mmol) was added to it and the mixture was heated to reflux for 4 h. It was cooled and THF was removed. The residue was taken up in EtOAc (5 mL), washed with H_2O and brine, and dried. Removal of the solvent followed by column chromatography of the residue afforded **19** (69 mg, 92%) as a white solid; mp 85–88 °C (Lit.[2] mp 89 °C).

IR (KBr): 2951, 1725, 1258, 1190, 756 cm^{-1}.

^1H NMR: δ = 1.04–1.14 (m, 1 H), 1.25 (s, 3 H), 1.25–1.38 (m, 1 H), 1.54–1.74 (m, 2 H), 2.08 (br d, *J* = 13.6 Hz, 1 H), 2.31 (br d, *J* = 13.8 Hz, 1 H), 2.81–2.89 (m, 1 H), 3.00 (dd, *J* = 8.1, 15.2 Hz, 1 H), 3.54 (dd, *J* = 8.4, 11.6 Hz, 1 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 7.15–7.24 (m, 3 H) [Lit.[10] δ = 1.23, 3.63, 3.67 (s, 3 × 3 H)].

^{13}C NMR: δ = 20.4 (CH_2), 25.9 (CH_3), 30.4 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 44.1 (C), 48.2 (CH), 51.7 (CH_3), 51.8 (CH_3), 56.1 (C), 122.0 (CH), 124.6 (CH), 126.6 (CH), 126.9 (CH), 139.8 (C), 148.9 (C), 175.6 (C), 177.2 (C).

MS (EI): *m*/*z* (%) = 302 (38) [M^+], 243, 242, 184, 183 (100), 141.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.77; H, 7.21.

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