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Formal synthesis of (±)-brazilin and total synthesis of (±)-brazilane

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ABSTRACT

A convergent synthesis towards (±)-brazilin and (±)-brazilane has been reported from 3,4-dimethoxy benzaldehyde in <15 reaction steps. Palladium(II)-catalysed intramolecular Friedel–Crafts cyclisation and Lewis acid supported intermolecular Friedel–Crafts alkylation reactions have been demonstrated. A tetracyclic substituted indane common key intermediate is employed to furnish the desired two molecules in good to excellent yield. $Pd(OH)_2$ has played a crucial role in the total synthesis of (±)-brazilane.

1. Introduction

The compounds (+)-brazilin (**1**),[1] (+)-haematoxylin (**4**),[1] (+)-brazilide A (**3**) and (−)-brazilein (**6**) are homoisoflavanoids, collectively isolated from the alcoholic extraction of heartwood of *Caesalpinia sappan* L. (Legminosae).[2] Among these, brazilide A (**3**) has been proposed as the newest constituent of this natural product family.[3] The ethanolic tinctures of above compounds are famous in traditional Chinese medicine used for the treatment of emmeniopathy, convulsion, straumatic disease and menstrual disorders.[4] Recent report reveals that brazilin (**1**) possesses antitumour activity and acts as telomerase inhibitor and produces DNA nicks.[5] Haematoxylin (**4**) is proven to be a potent inhibitor of protein tyrosine kinase.[6] In addition, haematoxylin and brazilin are easily oxidised by air to brazilein (**6**) and haematein, respectively, and therefore haematoxylin is used in histology as a dye[7] finding application in the production of dyes and ink. Brazilane (**2**) and haematoxylane (**5**) are the reduced counterparts of brazilin and haematoxylin, respectively, and have been known for some time[8] (Fig. 1).

Unique structures and diverse biological activities of brazilin and its related compounds have attracted many research groups towards their synthesis.[9] Most recently Zhang et al. have reported an elegant enantioselective synthesis of (+)-brazilin, (−)-brazilein and (+)-brazilide A[10] followed by Hong-Bo Qin et al. reporting the synthesis of (±)-brazilin and formal synthesis of (±)-brazilien and (±)-brazilide A.[11] Recently we have reported the total synthesis of some structurally unique natural products.[12] In continuation of our interest, herein we wish to report a formal synthesis of (±)-brazilin and a total synthesis of (±)-brazilane using facile convergent approach.

2. Result and discussion

Retrosynthetically (Scheme 1), we envisioned that the tetracyclic skeleton of brazilin could arise from ether linkage between primary alcohol with appropriate deprotected phenolic group of intermediate (±)-**8**, while D ring could be installed by taking advantage of Lewis acid mediated feasible electrophilic substitution of benzylic alcohol of diol (±)-**10** with protected resorcinol **9**.[13] The

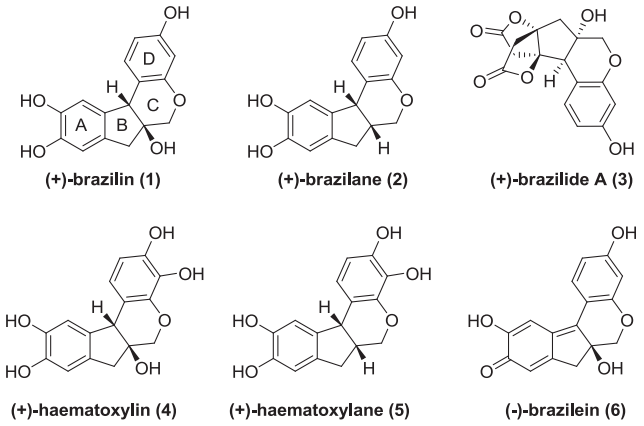

Fig. 1. Structure of selected homoisoflavonoids.

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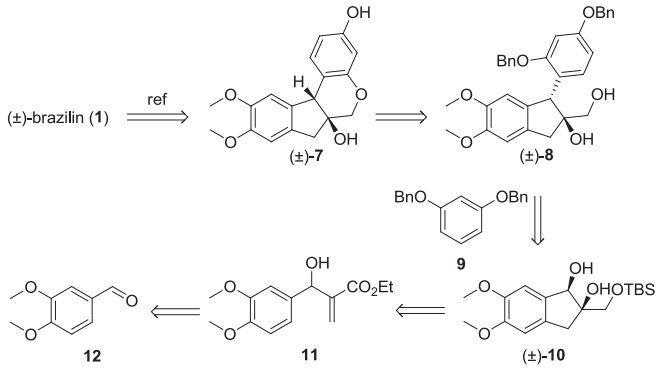
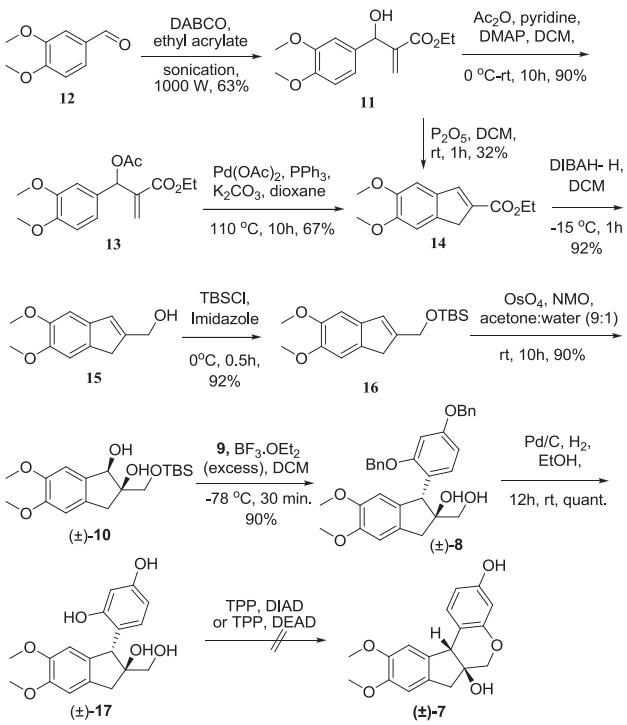
diol (±)-**10** could be accessed through intramolecular Friedel–-Crafts reaction of Baylis–Hillman adduct **11** following a simple reaction sequence.[14]



Scheme 1. Retrosynthetic analysis for (±)-brazilin.

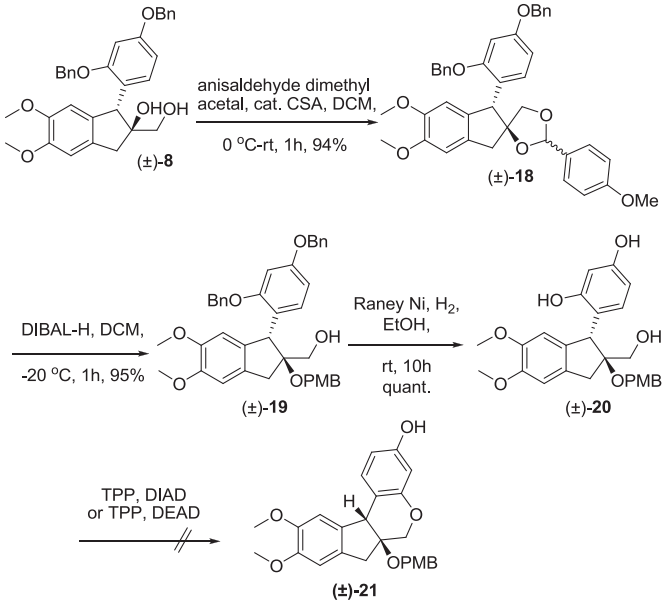
The synthesis of brazilin has begun with construction of Baylis–Hillman adduct **11** from commercially available aldehyde **12**[15] in reasonable yield. Then compound **11** was converted into its substituted indene **14** using P_2O_5 in low yield.[14] It is noteworthy to mention that the yield of compound **14** was improved by employing a protocol[16] appeared during the same time by Xiangsheng Xu et al. where palladium-catalysed synthesis of indene derivatives was achieved by intramolecular allylic arylation of Baylis–Hillman acetate to build substituted indenes. Henceforth, we have protected the free alcohol of Baylis–Hillman **11** with Ac_2O and pyridine in 90% yield followed by treatment with $Pd(OAc)_2$, K_2CO_3 and triphenylphosphine to achieve desired indene derivative **14** in 67% yield. Then, the ester moiety in **14** was reduced by using DIBAL-H to obtain alcohol **15** in 92% yield.[10] It was followed by TBS protection of alcohol **15**, which has provided the corresponding TBS-ether **16** in excellent yield. And the dihydroxylation of **16** with *N*-methylmorpholine (NMO) and OsO_4 gave the desired diol (±)-**10** (Scheme 2) in 90% yield.



Scheme 2.

After gaining access to the diol (±)-**10**, which contained A and B rings of the target molecule, the next task was to introduce remaining two rings, C and D. For introducing ring D we have treated the diol (±)-**10** with the di *O*-benzyl protected resorcinol[17] **9** in the presence of excess $BF_3{\cdot}OEt_2$ to afford the addition product (±)-**8** with in situ deprotection of TBS group in 90% yield.[12b,13] Substitution has occurred at the desired position was confirmed by H NMR of the product where one singlet at δ 4.82 ppm was found as a characteristic chemical sift for dibenzylic proton and three singlets at δ 6.80, 6.76 and 6.49 and two doublets at δ 6.91, J=8.39 Hz and 6.60, J=8.39 Hz, displaying J value corresponds to *ortho–ortho* coupling were observed in aromatic region. Having compound (±)-**8** in hand, we turned our attention towards the incorporation of ring C, for that we have deprotected the benzylether groups of compound (±)-**8** using Pd/C and H_2 to have the tetraol (±)-**17** in quantitative yield.[18] Tetraol (±)-**17** was then subjected to Mitsunobu conditions to achieve anticipated cyclised product (±)-**7**, unfortunately all our attempts have ended with loss of starting material as it has formed a complex mixture, presumably due to the presence and influence of more free hydroxyl groups.

Subsequently, we have decided to selectively protect the tertiary hydroxyl group of compound (±)-**8**. Initially protection of diol (±)-**8** was achieved (Scheme 3) with the treatment of anisaldehyde dimethyl acetal and catalytic CSA to give (±)-**18** in 94% yield.[19] Regioselective reductive ring-opening of the PMB acetal with DIBAL-H in CH_2Cl_2 at −20 °C has furnished the primary alcohol (±)-**19** in 95% yield.[17]

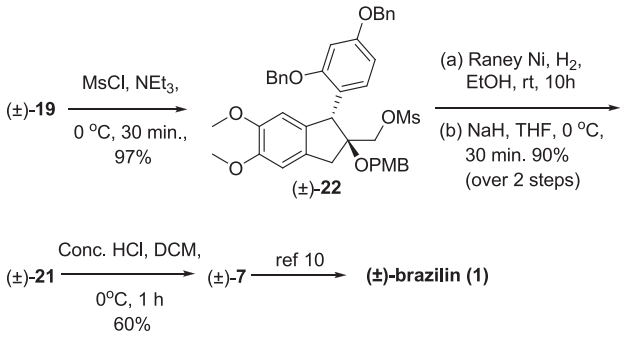


Scheme 3.

Now after selective protection of tertiary alcohol, compound (±)-**19** was selectively di-*O*-debenzylated by using Raney-Ni and hydrogen to produce triol (±)-**20** in quantitative yield.[20] By designing triol (±)-**20**, we have reached a venue from where we were ready to try Mitsunobu etherification to installed final C ring in compound (±)-**21** towards the target compound, brazilin. Unfortunately, this attempt also has met with no success, which might be attributed to the earlier reason as well.

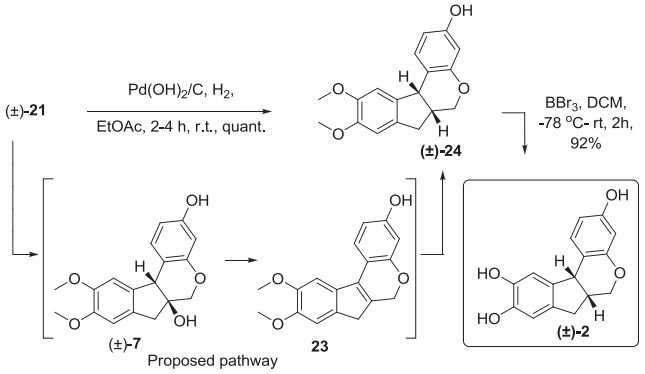
The strategy to construct C ring of the target molecule **1** was changed and decided to prepare the primary alcohol of compound (±)-**19** as a leaving group. Therefore, mesylation of compound (±)-**19** using MsCl and triethylamine in 97% yield was obtained. Then we selectively has deprotected the di *O*-benzyl groups of mesylated

compound (±)-**22** with Raney-Ni and hydrogen[20] and subsequently treated the unstable crude phenol with base (NaH) in THF at 0 °C temperature expecting the desired cyclised compound. To our delight the anticipated product (±)-**21** was achieved in 90% yield over two steps. The final steps for brazilin consisted of deprotection of PMB ether and methoxy groups, we screened the conditions including BBr_3, DDQ, CAN, hydrogenation with Pd/C and $Pd(OH)_2$/C, but could not obtain the desired deprotected compound. Eventually the deprotection of PMB ether group has accomplished using concd HCl in dichloromethane at 0 °C, to complete the formal synthesis of (±)-brazilin **1** (Scheme 4). All spectra of compound (±)-**7** were in accordance with the reported value[10].



Scheme 4.

Herein, we also report the total synthesis (±)-brazilane, which was obtained en route while deprotection of PMB group of compound (±)-**21**, as an instance of serendipity on the way for hydrogenation reaction in the synthetic strategy of (±)-brazilin (Scheme 5). In order to deprotect PMB group, cyclised product (±)-**21** was treated with Pd/C, H_2 in methanol solvent to complete the formal synthesis of (±)-brazilin, but TLC has showed number of products. The mass analysis of the crude mixture has showed a base peak with value 299, attributed as the $[M+H]^+$ of the dimethyl brazilane (±)-**24**.



Scheme 5.

With the above assumption in mind, the reaction was repeated with slight change in conditions, this time a non-protic solvent (EtOAc) and Pearlmann reagent was used for hydrogenation. To our success a solo product was formed, which was characterised as compound (±)-**24**, established by ^1H, ^{13}C NMR and DEPT. This transformation is believed to proceed through more than one transformations, which have occurred in situ, initial deprotection of PMB ether group to form (±)-**7**, followed by $Pd(OH)_2$ promoted dehydration (most probably unsaturation occurred at B/C ring junction) to obtain **23**, which was further followed by hydrogenation furnishing (±)-**24** in excellent yields. Deprotection of providentially formed compound (±)-**24** with boron tribromide at −78 °C to room temperature gave the desired (±)-brazilane **2**, which is a synthetic derivative of brazilin **1**. The spectroscopic data of (±)-**2** were found in full accordance with those reported in the literature in all respects.[8]

3. Conclusion

In conclusion, a formal synthesis of (±)-brazilin **1** has been accomplished in 13 steps with 12% overall yield. During the synthesis of (±)-brazilin **1**, we could unveil $Pd(OH)_2$ assisted reaction, which has compiled in situ three steps (PMB deprotection, dehydration and hydrogenation) in it and has led to the synthesis of (±)-brazilane **2** in 14 steps with 19% overall yield. All the compounds obtained in these protocols have looked promising and has been submitted for their biological screening.

4. Experimental section

4.1. General

All the reagents and solvents were reagent grade and used without purification unless specified otherwise. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. When used as a reaction solvent, THF was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. FTIR spectra were recorded as KBr discs or neat. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6 and MeOH-d_4 on 300, 500, 150 or 75 MHz spectrometers at ambient temperature. HRMS were recorded at 5 ppm concentration in Agilent qtof instrument at 'National Center for Mass Spectroscopy, CSIR-Indian Institute of Chemical Technology.'

4.2. Ethyl 2-((3,4-dimethoxyphenyl)(hydroxyl)methyl)acrylate (11)

A mixture of the aromatic aldehyde **12** (1 g, 6.02 mmol) an excess of ethyl acrylate (20 equiv, used as solvent and reagent), and 1,4-diazabicyclo[2.2.2.]octane, DABCO (439 mg, 3.92 mmol) was sonicated (1000 W, 25 kHz) for a certain period of time. The ultrasound bath temperature was constantly monitored and kept at 30–40 °C during the reaction, through ice addition or by using a refrigerated circulator. After a period for reaction completion (10 h), the mixture was evaporated under reduced pressure to remove the excess of acrylate. The residue was diluted with ethyl acetate (30 mL). The organic solution was washed with 10% aqueous HCl (2×10 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration and solvent removal, the residue was filtered through a pad of gel of silica to afford BH adduct **11** (1 g, 63% yield) as a colourless liquid; R_f 0.3 (*n*-hexane/ethyl acetate, 4:1); IR (KBr) ν_{max} 3300, 2851, 1622, 1599, 1200, 1050; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, d, J=1.98 Hz, ArH), 6.87 (1H, dd, J=8.24, 1.98 Hz, ArH), 6.81 (1H, d, J=8.24 Hz, ArH), 6.31 (1H, t, J=0.91 Hz, CH_2=C), 5.80 (1H, dist. t, J=1.22, 1.37 Hz, CH_2=C), 5.50 (1H, s, OHCH), 4.16 (2H, dq, J=7.17, 1.22 Hz, $CO_2CH_2CH_3$), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 1.24 (3H, t, J=7.17 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 148.9, 148.5, 142.3, 133.9, 125.5, 118.9, 110.8, 109.7, 72.9, 60.9, 55.8, 55.76, 14.01; MS (ESI): m/z=249 $[M+H-H_2O]^+$, 289 $[M+Na]^+$; HRMS (ESI): calcd for $C_{14}H_{17}O_4$ $[M+H-H_2O]^+$: 249.1126; found: 249.1123.

4.3. Ethyl 2-(acetoxy(3,4-dimethoxyphenyl)methyl)acrylate (13)

To the stirred solution of **11** (250 mg, 0.94 mmol) in DCM were sequentially added pyridine (0.09 mL, 1.13 mmol), acetic anhydride (0.1065 mL, 1.13 mmol) and catalytic amount of DMAP at 0 °C. Reaction mixture was allowed to stir for 10 h at room temperature. Reaction mass quenched with water saturated solution of copper sulfate, extracted with DCM, organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude product was purified by column chromatography to afford acetate **13** (260.24 mg, 90%) as a colourless oil; R_f 0.51 (*n*-hexane/ethyl acetate, 7:3); IR (KBr) ν_{max} 2926, 2851, 1744, 1722, 1516, 1463, 1370, 1230, 1141, 1027; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (1H, dd, J=8.31, 1.88 Hz, ArH), 6.89 (1H, d, J=1.88 Hz, ArH), 6.83 (1H, d, J=8.31 Hz, ArH), 6.64 (1H, s, CH_2=C), 6.39 (1H, s, CH_2=C), 5.84 (1H, s, CHOAc), 4.16 (2H, q, J=6.98 Hz, $CO_2CH_2CH_3$), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.11 (3H, s, $COCH_3$), 1.23 (3H, t, J=6.98 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 165.0, 149.1, 148.8, 139.9, 130.2, 125.0, 120.4, 111.0, 110.9, 73.1, 60.9, 55.85, 55.83, 21.1, 14.0; LCMS: m/z=331 $[M+Na]^+$.

4.4. Ethyl 5,6-dimethoxy-1*H*-indene-2-carboxylate (14)

To a stirred solution of **11** (2 g, 7.5 mmol) in CH_2Cl_2 was added P_2O_5 (0.20 g) at room temperature. After 1 h, the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (2×40 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and the solvent was evaporated in reduced pressure. The crude product obtained was purified by column chromatography (silica gel, 8% EtOAc in hexanes) to afford indene **14** (0.58 g, 32%), as a colourless crystalline solid.

4.5. Compound 14 from Baylis–Hillman acetate 13

Baylis–Hillman acetate **13** (250 mg, 0.81 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), K_2CO_3 (112 mg, 0.81 mmol), and Ph_3P (8.5 mg, 0.16 mmol) were placed in an RB under nitrogen atmosphere. 1,4-Dioxane (2.0 mL) was added via cannula. After the reaction mixture was stirred at 110 °C for 10 h, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (EtOAc/PE=1:20) to give indenes **14** (135 mg, 67%) as a crystalline solid; R_f 0.5 (*n*-hexane/ethyl acetate, 7:3); mp 101 °C; IR (KBr) ν_{max} 2976, 2840, 1702, 1606, 1557, 1337, 1221, 1098; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, s, ArH), 7.06 (1H, s, ArH), 7.02 (1H, s, CH=C), 4.28 (2H, q, J=7.17 Hz, $CO_2CH_2CH_3$), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.62 (2H, d, J=1.32 Hz, $ArCH_2$), 1.35 (3H, t, J=7.17 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 149.7, 148.7, 141.1, 138.3, 135.8, 135.3, 107.6, 105.9, 60.2, 56.1, 38.3, 14.4; MS (ESI): m/z=249 $[M+H]^+$, 271 $[M+Na]^+$; HRMS (ESI): calcd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.11214; found: 249.11212.

4.6. (5,6-Dimethoxy-1*H*-inden-2-yl)methanol (15)

To a solution of ethyl ester **14** (0.8 g, 3.22 mmol) in dry CH_2Cl_2 (15 mL) at −15 °C was added DIBAL 2.5 M in hexane (5.72 mL, 8.0 mmol). Reaction mixture was stirred at same temperature for 1.0 h. Then reaction mixture was quenched with saturated aqueous solution of sodium potassium tartarate, kept for vigorous stirring until the two layers separated. Reaction mixture was extracted with DCM (2×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product obtained was purified by column chromatography (silica gel, 27% EtOAc in hexanes) to afford compound **15** (0.611 g, 92%), R_f 0.1 (*n*-hexane/ethyl acetate, 7:3); as a white solid; mp 99–100 °C; IR (KBr) ν_{max} 3403, 2924, 2853, 1462, 1216, 1099, 1026; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (1H, s, ArH), 6.91 (1H, s, ArH), 6.66 (1H, s, CH=C), 4.56 (2H, s, CH_2OH), 3.90 (6H, s, OCH_3), 3.38 (2H, s, $ArCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 147.3, 147.1, 137.2, 135.8, 127.6, 108.2, 104.7, 61.8, 56.3, 56.1, 38.9. MS (ESI): m/z=229 $[M+H]^+$, 189 $[M+H-H_2O]^+$; HRMS (ESI): calcd for $C_{12}H_{13}O_2$ $[M+H-H_2O]^+$: 189.09101; found: 189.09146.

4.7. *tert*-Butyl((5,6-dimethoxy-1*H*-inden-2-yl)methoxy)dimethylsilane (16)

To a solution of **15** (1.0 g, 4.8 mmol) in DCM (20 mL) at 0 °C was added imidazole (0.5 g, 7.2 mmol) followed by TBSCl (0.88 g, 5.8 mmol). Reaction mixture was stirred at same temperature until complete consumption of starting material as indicated by TLC (0.5 h). The reaction mixture was quenched with ice and extracted with DCM (25 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (5% EtOAc/hexanes) to give **16** (1.43 g, 92%) as a white solid; R_f 0.45 (*n*-hexane/ethyl acetate, 9:1); mp 44–45 °C; IR (KBr) ν_{max} 2929, 2855, 1464, 1254, 1215, 1103, 840; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (1H, s, ArH), 6.82 (1H, s, ArH), 6.52 (1H, s, CH=C), 4.54 (2H, s, CH_2OTBS), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.26 (2H, s, $ArCH_2$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 147.9, 146.7, 137.6, 135.6, 126.4, 108.2, 104.5, 62.2, 56.2, 56.1, 38.8, 25.9, 18.4, −5.3; MS (ESI): m/z=343 $[M+Na]^+$, 189 $[M-OTBS]^+$; HRMS (ESI): calcd for $C_{12}H_{13}O_2$ $[M+OTBS]^+$: 189.09101; found: 189.09160.

4.8. 2-((*tert*-Butyldimethylsilyloxy)methyl)-5,6-di,ethoxy-2,3-dihydro-1*H*-indene-1,2-diol [(±)-10]

The TBS-ether **16** (1.0 g, 3.1 mmol) was dissolved in acetone/H_2O (9:1, 10 mL) and cooled to 0 °C. 4-Methylmorpholine-*N*-oxide (0.73 g, 6.23 mmol) was added followed by osmium tetroxide (4% in *t*-BuOH, 0.6 mL, 0.09 mmol) and the solution was warmed to room temperature and was stirred for 10 h. Saturated aqueous solution of $Na_2S_2O_3$ (5 mL) was added and the mixture was stirred for 1 h. Saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAc (3×100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. Crude product purified with flash column chromatography on silica gel to afford (±)-**10** (0.65 g, 90%) as brown solid; R_f 0.24 (*n*-hexane/ethyl acetate, 7:3); mp 70–71 °C; IR (KBr) ν_{max} 3439, 2930, 2855, 1504, 1466, 1305, 1253, 1099, 1064, 988, 846; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (1H, s, ArH), 6.72 (1H, s, ArH), 4.90 (1H, d, J=4.88 Hz, ArCH), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.76 (1H, d, J=9.91 Hz, CH_2OTBS), 3.71 (1H, d, J=9.91 Hz, CH_2OTBS), 3.07 (1H, br s, OH), 2.93 (1H, d, J=16.17 Hz, $ArCH_2$), 2.86 (1H, d, J=16.02 Hz, $ArCH_2$), 2.79 (1H, br s d, J=5.95 Hz, OH), 0.91 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 148.7, 133.9, 131.4, 107.9, 107.7, 81.7, 77.4, 67.9, 55.9, 40.43, 25.8, 18.2, −5.43, −5.46; MS (ESI): m/z=377 $[M+Na]^+$; HRMS (ESI): calcd for $C_{18}H_{30}NaO_5Si$ $[M+Na]^+$: 377.1778; found: 377.1778.

4.9. 1-(2,4-Bis(benzyloxy)phenyl)-2-(hydroxymethyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-2-ol [(±)-8]

To a solution of diol (±)-**10** (0.50 g, 1.41 mmol) and dibenzylether protected resorcinol **9** (0.60 g, 2.1 mmol) in dry dichloromethane (12 mL) at −78 °C was added $BF_3\cdot Et_2O$ (1.04 mL, 8.4 mmol) in two portions in the gap of 20 min. The reaction mixture was stirred at −78 °C for 30 min, then it was stirred at 0 °C for another 30 min. A solution of saturated aqueous $NaHCO_3$

(10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic phases were washed subsequently with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was chromatographed on silica gel to afford (±)-**8** (0.65 g, 90%) as a white solid; R_f 0.51 (*n*-hexane/ethyl acetate, 1:1); mp 129–130 °C; IR (KBr) ν_{max} 3503, 3431, 2915, 1608, 1503, 1458, 1267, 1215, 1172, 1096, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.33 (10H, m, ArHOBn), 6.92 (1H, d, *J*=8.39 Hz, ArH), 6.81 (1H, s, ArH), 6.77 (1H, s, ArH), 6.61 (1H, d, *J*=8.39 Hz, ArH), 6.50 (1H, s, ArH), 5.15–5.02 (4H, m, $(-OCH_2Ph)_2$), 4.83 (1H, s, Ar*CH*Ar), 3.88 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.65–3.47 (2H, m, CH_2OH), 3.10 (1H, d, *J*=16.17 Hz, ArCH), 2.92 (1H, d, *J*=16.02 Hz, ArCH), 2.31 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.7, 148.5, 148.3, 136.7, 135.8, 135.1, 133.1, 131.3, 128.8, 128.6, 128.1, 127.9, 127.6, 118.9, 108.5, 107.9, 106.1, 100.7, 84.1, 70.89, 70.2, 68.4, 56.0, 55.9, 49.3, 41.8: MS (ESI): *m*/*z*=513 $[M+H]^+$, 535 $[M+Na]^+$; HRMS (ESI): calcd for $C_{32}H_{36}NO_6$ $[M+NH_4]^+$: 530.25371; found: 530.25507.

4.10. 4-(2-Hydroxy-2-(hydroxymethyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)benzene-1,3-diol [(±)-17]

Mixture of (±)-**8** (100 mg, 0.19 mmol) and Pd/C (10% Pd, 35 mg) in EtOH was stirred for 12 h at room temperature under hydrogen atmosphere. Reaction mixture was filtered over Celite, the filtrate was concentrated under reduced pressure and purification by silica gel column chromatography afforded (±)-**17** (64 mg, quant.) as a viscous liquid; R_f 0.54 (ethyl acetate); IR (KBr) ν_{max} 3381, 2925, 2854, 1724, 1612, 1508, 1462, 1247, 1217, 1091, 1032, 757; ^{1}H NMR (300 MHz, CD_3OD) δ 6.84 (1H, s, ArH), 6.71 (1H, d, *J*=8.31 Hz, ArH), 6.45 (1H, s, ArH), 6.32 (1H, d, *J*=2.27 Hz, ArH), 6.25 (1H, dd, *J*=8.31, 2.45 Hz, ArH), 4.53 (1H, s, Ar*CH*Ar), 3.78 (3H, s, OMe), 3.64 (3H, s, OMe), 3.57 (2H, s, CH_2OH), 3.12 (1H, d, *J*=16.05 Hz, $ArCH_2$), 2.83 (1H, d, *J*=16.05 Hz, $PhCH_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 158.6, 158.1, 149.9, 149.8, 137.7, 134.5, 133.3, 117.3, 110.2, 110.0, 107.9, 104.0, 86.6, 68.2, 56.8, 56.7, 43.2, 30.8; MS (ESI): *m*/*z*=355 $[M+Na]^+$; HRMS (ESI): calcd for $C_{18}H_{19}O_6$ $[M-H]^+$: 331.11890; found: 331.11906.

4.11. 1′-(2,4-Bis(benzyloxy)phenyl)-5′,6′-dimethoxy-2-(4-methoxybenzyl)-1′,3′-dihydrospiro[[1,3]dioxolane-4,2′-indene] [(±)-18]

Anisaldehyde dimethyl acetal (0.2 mL, 1.17 mmol) and a catalytic amount of azeotropically dried CSA were added to a stirred solution of diol (±)-**8** (0.50 g, 0.97 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. It was then quenched with aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3×20 mL), dried with anhydrous Na_2SO_4, evaporated and purified on silica gel using 15% EtOAc/hexane as eluent to furnish the protected diol (±)-**18** (0.60 g, 94%) as a viscous liquid. R_f 0.51 (*n*-hexane/ethyl acetate, 7:3); IR (KBr) ν_{max} 1610, 1503, 1455, 1249, 1169, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.31 (17H, m, ArH), 7.21–7.16 (1H, m, ArH), 6.99 (1H, d, *J*=8.49 Hz, ArH), 6.84–6.50 (12H, m, ArH), 5.73 (1H, s, OCHO), 5.14–5.03 (8H, m, OCH_2Ph), 4.94 (1H, d, *J*=6.23 Hz, ArCHAr), 4.43 (1H, d, *J*=8.30 Hz, CH_2PhOCH_3), 4.26–4.14 (1H, m, CH_2PhOCH_3), 3.97 (1H, d, *J*=8.12 Hz, CH_2PhOCH_3), 3.87 (5H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.75 (5H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.35–3.05 (4H, m, $ArCH_2$, $-OCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.7, 148.5, 148.3, 136.6, 135.8, 135.1, 133.1, 132.7, 132.5, 131.9, 131.3, 130.6, 129.9, 128.8, 128.6, 128.3, 128.1, 127.9, 127.6, 118.8, 114.2, 108.4, 107.9, 106.1, 100.7, 84.1, 70.9, 70.2, 68.4, 56.1, 56.0, 55.5, 49.3, 41.7; MS (ESI): *m*/*z*=631 $[M+H]^+$, 653 $[M+Na]^+$; HRMS (ESI): calcd for $C_{40}H_{39}O_7$ $[M+H]^+$: 631.26903; found: 631.27020.

4.12. (1-(2,4-Bis(benzyloxy)phenyl)-5,6-dimethoxy-2-(4-methoxybenzyloxy)-2,3-dihydro-1*H*-inden-2-yl)methanol [(±)-19]

DIBAL-H (0.60 mL, 1.03 mmol, 25% of DIBAL-H in toluene) was added slowly to a solution of compound (±)-**18** (0.05 g, 0.79 mmol) in CH_2Cl_2 at −20 °C and the reaction mixture was stirred at the same temperature while monitoring the progress of reaction by TLC (1 h). After consumption of all the starting materials, the reaction mixture was quenched with a saturated aqueous potassium sodium tartrate solution and it was stirred vigorously at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3×20 mL), concentrated under reduced pressure and purified by silica gel column chromatography to afford alcohol (±)-**19** (600 mg, 95%) as a yellow viscous liquid. R_f 0.25 (*n*-hexane/ethyl acetate, 7:3); IR (KBr) ν_{max} 3511, 2933, 1609, 1505, 1459, 1248, 1218, 1170, 1101, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.31 (10H, m, ArH), 6.84 (2H, d, *J*=8.5 Hz, ArH), 6.77–6.66 (5H, m, ArH), 6.57 (1H, s, ArH), 6.51 (1H, dd, *J*=8.54, 2.44 Hz, ArH), 5.07–5.03 (3H, m, OCH_2Ph), 4.96 (1H, d, *J*=10.98 Hz, OCH_2Ph), 4.90 (1H, s, ArCHAr), 4.31 (1H, d, *J*=11.44 Hz, OCH_2PhOMe), 4.22 (1H, d, *J*=11.29 Hz, OCH_2PhOMe), 3.87 (3H, s, OMe), 3.77 (3H, s, OMe), 3.76 (3H, s, OMe), 3.71–3.64 (2H, m, CH_2OH), 3.18 (1H, d, *J*=16.02 Hz, $ArCH_2$), 2.96 (1H, d, *J*=15.86 Hz, $ArCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 157.8, 148.4, 136.9, 136.4, 135.9, 132.2, 131.3, 130.95, 128.7, 128.6, 128.2, 127.9, 127.8, 127.5, 121.3, 113.4, 108.4, 107.6, 105.5, 100.1, 89.0, 70.6, 70.2, 65.1, 55.9, 55.2, 48.4, 37.9, 29.7; MS (ESI): *m*/*z*=655 $[M+Na]^+$; HRMS (ESI): calcd for $C_{40}H_{41}O_7$ $[M+H]^+$: 633.28468; found: 633.28638.

4.13. 4-(2-(Hydroxymethyl)-5,6-dimethoxy-2-(4-methoxybenzyloxy)-2,3-dihydro-1*H*-inden-1-yl)benzene-1,3-diol [(±)-20]

A suspension of compound (±)-**19** (100 mg, 0.158 mmol) and Raney-Ni (50 mg) in ethanol (7 mL) was stirred under hydrogen (balloon) at room temperature for 18 h. The reaction mixture was filtered through Celite pad, washed with methanol thoroughly (5×20 mL) and concentrated to give the crude triol, which is purified by the column chromatography to afford (±)-**20** (71 mg, quant. yield) as a colourless viscous liquid. R_f 0.83 (ethyl acetate); IR (KBr) ν_{max} 3280, 2921, 2852, 1729, 1601, 1527, 1461, 1212, 1169, 1097, 763; ^{1}H NMR (300 MHz, CD_3OD) δ 6.83 (1H, s, ArH), 6.77 (2H, d, *J*=8.68 Hz, ArH), 6.66 (2H, d, *J*=8.68 Hz, ArH), 6.62–6.53 (2H, m, ArH), 6.31 (1H, d, *J*=2.45 Hz, ArH), 6.20 (1H, dd, *J*=8.30, 2.45 Hz, ArH), 4.62 (1H, s, ArCHAr), 4.36 (2H, s, $-OCH_2PhOMe$), 3.89 (1H, d, *J*=11.89 Hz, CH_2OH), 3.80 (3H, s, OMe), 3.69 (3H, s, OMe), 3.68 (3H, s, OMe), 3.71–3.65 (1H, m, CH_2OH), 3.13 (2H, d, *J*=3.58 Hz, $ArCH_2$); MS (ESI): *m*/*z*=475 $[M+Na]^+$.

4.14. (1-(2,4-Bis(benzyloxy)phenyl)-5,6-dimethoxy-2-(4-methoxybenzyloxy)-2,3-dihydro-1*H*-inden-2-yl)methyl-methanesulfonate [(±)-22]

To a cooled solution (0 °C) of alcohol (±)-**19** (400 mg, 0.632 mmol) and triethylamine (0.34 mL, 2.52 mmol) in dichloromethane (10 mL) was added dropwise mesylchloride (0.103 mL, 1.26 mmol). After stirring at the same temperature for 30 min, water (10 mL) was added, aqueous solution was extracted with DCM (3×30 mL), dried (anhydrous $MgSO_4$) and concentrated to give the crude mesylate, which is purified by the column chromatography to afford (±)-**22** (448 mg, 97%) as a colourless viscous liquid. R_f 0.24 (*n*-hexane/ethyl acetate, 7:3); IR (KBr) ν_{max} 3449, 2923, 2854, 1608, 1504, 1353, 1288, 1248, 1172, 1098; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.29 (11H, m, ArH), 6.88–6.47 (8H, m, ArH), 5.12–4.96 (4H, m, OCH_2Ph), 4.83 (1H, s, ArCHAr), 4.48–4.26 (4H, m, OCH_2PhOMe and CH_2OMs), 3.88 (3H, s, OMe), 3.76 (3H, s, OMe), 3.74 (3H, s, OMe), 3.32

(1H, d, J=15.86 Hz, $ArCH_2$), 3.11 (1H, d, J=15.10 Hz, $ArCH_2$), 2.68 (3H, s, CH_3SO_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 158.6, 157.7, 148.6, 136.9, 136.7, 135.6, 131.5, 130.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.7, 127.5, 120.2, 118.1, 113.3, 108.2, 107.5, 105.7, 100.2, 87.2, 73.0, 70.53, 70.16, 66.2, 56.0, 55.2, 48.9, 38.2, 37.1, 31.5, 29.7; MS (ESI): m/z=728 $[M+H]^+$, 733 $[M+Na]^+$; HRMS (ESI): calcd for $C_{41}H_{46}NO_9S$ $[M+NH_4]^+$: 728.2888; found: 728.2901.

4.15. 9,10-Dimethoxy-6a-(4-methoxybenzyloxy)-6,6a,7,11b-tetrahydroindeno[2,1-*c*]chromen-3-ol [(±)-21]

A suspension of mesylate (±)-**22** (400 mg, 0.60 mmol) and Raney-Ni (100 mg) in ethanol (7 mL) was stirred under hydrogen (balloon) at room temperature for 18 h. The reaction mixture was filtered through Celite pad, washed with methanol thoroughly (5×20 mL) and concentrated. Due to unstable nature of hydrogenated product it was used in next step without any further purification. To cooled (0 °C) solution of hydrogenated diol (283 mg, 0.534 mmol) was added NaH (25 mg, 1.07 mmol). After stirring at the same temperature for 30 min, reaction was quenched with ice, solution was extracted with EtOAc (3×30 mL), dried (anhydrous $MgSO_4$) and concentrated to give the crude product, which is purified by the column chromatography to afford (±)-**21** (220 mg, 90.25% for two steps) as a yellow solid; mp 148 °C (decomposition); R_f 0.6 (*n*-hexane/ethyl acetate, 1:1); IR (KBr) ν_{max} 3393, 1614, 1506, 1462, 1337, 1298, 1250, 1216, 1164, 1126, 1078, 1027; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.51 (1H, m, ArH), 7.29 (1H, s, ArH), 6.87 (1H, s, ArH), 6.72–6.63 (4H, m, ArH), 6.48–6.45 (2H, m, ArH), 4.61 (1H, dd, J=10.68, 1.52 Hz, CH_2O–), 4.42 (1H, d, J=10.83 Hz, CH_2O–), 4.33 (1H, s, ArCHAr), 4.12 (2H, q, J=11.29 Hz, OCH_2PhOMe), 3.97 (3H, s, OMe), 3.89 (3H, s, OMe), 3.70 (3H, s, OMe), 3.23 (1H, d, J=15.71 Hz, $ArCH_2$), 2.88 (1H, d, J=15.71 Hz, $ArCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 155.6, 155.1, 148.2, 148.1, 133.2, 130.1, 128.3, 125.0, 116.7, 113.4, 108.9, 108.3, 106.9, 103.5, 83.1, 73.2, 65.5, 56.4, 56.2, 55.2, 49.9, 37.3; MS (ESI): m/z=435 $[M+H]^+$; HRMS (ESI): calcd for $C_{26}H_{26}NaO_6$ $[M+Na]^+$: 457.1622; found: 457.1650.

4.16. 9,10-Dimethoxy-6,6a,7,11b-tetrahydroindeno[2,1-*c*]chromene-3,6a-diol [(±)-7]

To the stirred solution of compound (±)-**21** (25 mg, 0.057 mmol) in dichloromethane was added concd HCl (0.1 mL). Reaction mixture was allowed to stir for 1 h. After consumption of all the starting material (monitored by TCL), the reaction mixture was quenched with solid sodium bicarbonate. The reaction mixture was extracted with CH_2Cl_2 (3×20 mL), washed with sodium bicarbonate solution, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography to afford the dimethylbrazilin (±)-**7** (10 mg, 60%) as a yellow solid; R_f 0.48 (*n*-hexane/ethyl acetate, 1:1); mp 184–185 °C; IR (KBr) ν_{max} 3422, 2924, 2853, 1715, 1619, 1501, 1463, 1259, 1220, 1084; ^1H NMR (300 MHz, methanol-d_4) δ 7.28 (1H, d, J=8.31 Hz, ArH), 6.89 (1H, s, ArH), 6.83 (1H, s, ArH), 6.50 (1H, dd, J=8.31, 2.27 Hz, ArH), 6.31 (1H, d, J=2.27 Hz, ArH), 4.06 (1H, s, ArCHAr), 3.96 (1H, d, J=10.76 Hz, CH_2O–), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 3.73 (1H, d, J=11.33 Hz, CH_2O–), 3.10 (1H, d, J=15.86 Hz, $ArCH_2$), 2.91 (1H, d, J=15.86 Hz, $ArCH_2$); ^{13}C NMR (125 MHz, methanol-d_4) δ 156.6, 154.4, 148.8, 148.4, 137.1, 131.4, 130.7, 113.9, 108.78, 108.76, 102.9, 76.8, 69.4, 55.3, 55.2, 50.1, 41.7; MS (ESI): m/z=315 $[M+H]^+$; HRMS (ESI): calcd for $C_{18}H_{18}NaO_5$ $[M+Na]^+$: 337.1046; found: 337.1065.

4.17. 9,10-Dimethoxy-6,6a,7,11b-tetrahydroindeno[2,1-*c*]chromen-3-ol [(±)-24]

To a solution of (±)-**21** (50 mg, 0.115 mmol) in EtOAc (3 mL) was added Pearlman's catalyst $Pd(OH)_2/C$ (10%, 30 mg). The mixture was stirred under hydrogen (balloon) for 2 h. The reaction mixture was filtered through Celite pad, washed with EtOAc thoroughly (5×20 mL) and concentrated, crude product purified with column chromatography to afford dimethyl brazilane (±)-**24** in quantitative yield as a solid; R_f 0.34 (*n*-hexane/ethyl acetate, 7:3); mp 169 °C (decomposition); IR (KBr) ν_{max} 3380, 2925, 2853, 1741, 1621, 1595, 1501, 1465, 1304, 1277, 1153; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, s, ArH), 6.86 (1H, s, ArH), 6.77 (1H, s, ArH), 6.52 (1H, dd, J=8.39, 2.59 Hz, ArH), 6.37 (1H, d, J=2.44 Hz, ArH), 4.21 (1H, d, J=6.56, Hz, ArCHAr), 4.11 (1H, dd, J=10.98, 4.42 Hz, CH_2O–), 3.84 (6H, s, OMe), 3.61 (1H, dist. t, J=10.52, 10.68 Hz, CH_2O–), 3.17 (1H, dd, J=15.71, 7.17 Hz, $ArCH_2$), 2.95–2.87 (1H, m, CH_2CHCH_2), 2.59 (1H, dd, J=15.71, 1.98 Hz, $ArCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 155.1, 148.4, 148.2, 137.2, 132.6, 130.9, 116.0, 108.6, 108.4, 107.9, 103.7, 66.8, 56.1, 56.0, 43.2, 36.8, 33.9; MS (ESI): m/z=299 $[M+H]^+$, 321 $[M+Na]^+$

4.18. 6,6a,7,11b-Tetrahydroindeno[2,1-*c*]chromene-3,9,10-triol (2) [(±)-brazilane]

To a solution of compound (±)-**24** (20 mg, 0.067 mmol) in dry dichloromethane (3 mL) at −78 °C was added dropwise a solution of boron tribromide (0.019 mL, 0.20 mmol). The reaction mixture was then stirred at −78 °C for 1 h and further was stirred at room temperature for 1 h. The reaction was quenched by the addition of methanol (0.6 mL), then diluted with water (5 mL). The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography on silica gel afforded the (±)-brazilane **2** (17 mg, 92%) as a white solid; R_f 0.48 (*n*-hexane/ethyl acetate, 1:1); mp 155–156 °C; IR (KBr) ν_{max} 3421, 2925, 2854, 1728, 1658, 1505, 1461, 1280, 1157, 1118, 1074; ^1H NMR (500 MHz, acetone-d_6) δ 8.22 (1H, s, ArOH), 7.67 (1H, s, ArOH), 7.59 (1H, s, ArOH), 7.21 (1H, d, J=8.24 Hz, ArH), 6.81 (1H, s, ArH), 6.68 (1H, s, ArH), 6.47 (1H, dd, J=8.24, 2.44 Hz, ArH), 6.26 (1H, d, J=2.44 Hz, ArH), 4.09 (1H, d, J=6.56, Hz, ArCHAr), 4.04 (1H, dd, J=10.98, 4.57 Hz, CH_2O–), 3.49 (1H, t, J=10.37 Hz, CH_2O–), 3.04 (1H, dd, J=15.56, 7.17 Hz, $ArCH_2$), 2.83–2.76 (1H, m, CH_2CHCH_2), 2.50 (1H, dd, J=15.6, 2.28 Hz, $ArCH_2$); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.5, 156.4, 144.9, 144.6, 137.8, 132.7, 131.8, 116.1, 112.6, 112.3, 109.3, 104.0, 67.2, 43.5, 37.8, 34.2; MS (ESI): m/z=271 $[M+H]^+$, 293 $[M+Na]^+$; HRMS (ESI): calcd for $C_{16}H_{13}O_4$ $[M-H]^+$: 269.08138; found: 269.08224.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.08.001.

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