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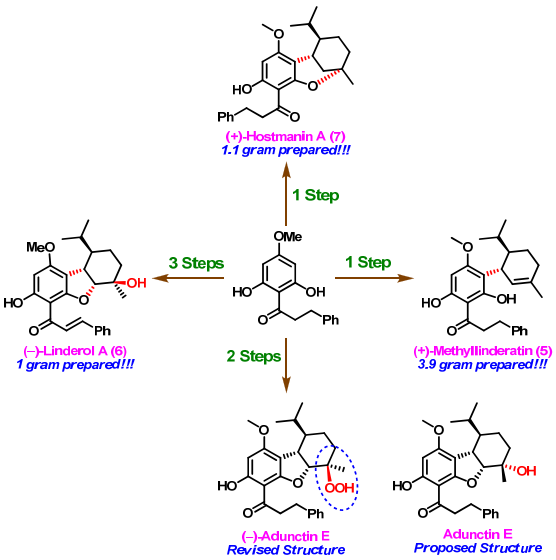
Dattatraya H. Dethe,* and Balu D. Dherange

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur-208016, India.

Fax: (+91)-512-2596537; Phone: (+91)-512-2597436; email: ddethe@iitk.ac.in



ABSTRACT: A one step protocol has been developed for the enantioselective synthesis of hexahydrodibenzofuran derivatives using a modified Friedel-Crafts reaction. The developed method was applied to the synthesis of a series of natural products including (+)-hostmanin A, (+)-methyllinderatin, and (–)-linderol A. The synthetic and spectroscopic data investigations led to the structural reassignment of natural product adunctin-E, which was further confirmed by single crystal X-ray analysis.

INTRODUCTION

The leaves of *Piper adunctum* (Piperaceae), distributed throughout tropical America, have been employed as a folk medicine for the treatment of wounds, dysentery, diarrhea and as a haemostatic agent. Investigation of extract of leaves of *P. adunctum* by Orjala et al.[1] led to

the isolation of five natural products adunctin A-E.[1] The structures of adunctin A-E[1] were confirmed by 1-D and 2-D NMR spectroscopy. The structure of adunctin B (**1**) was further established by single crystal X-ray analysis. As shown in figure 1, adunctin C (**2**) and D (**3**) were found to contain spirocyclic ring system while adunctin B (**1**) and E (**4**) were novel cinnamoyl-hexaydrodibenzofuran derivatives. Another set of natural products namely methyllinderatin (**5**) and linderol A (**6**), which has structures similar to that of adunctins were isolated from the fresh bark of *Lindera umbellata* by K. Ichino[2] and Mimaki et al.[3] respectively. In 2007, Portet et al.[4] isolated hostmanin A (**7**) and B (**8**) along with known methylinderatin (**5**), adunctin E (**4**) and related natural products from the leaves of *Piper hostmannianum*. The structures of hostmanin A (**7**) and B (**8**) were confirmed by single crystal X-ray analysis. Adunctin B (**1**), C (**2**), D (**3**) and methyllinderatin (**5**) showed antibacterial effects towards *M. luteus* at concentrations of 3.5, 2.4 and 2.5 µg respectively.

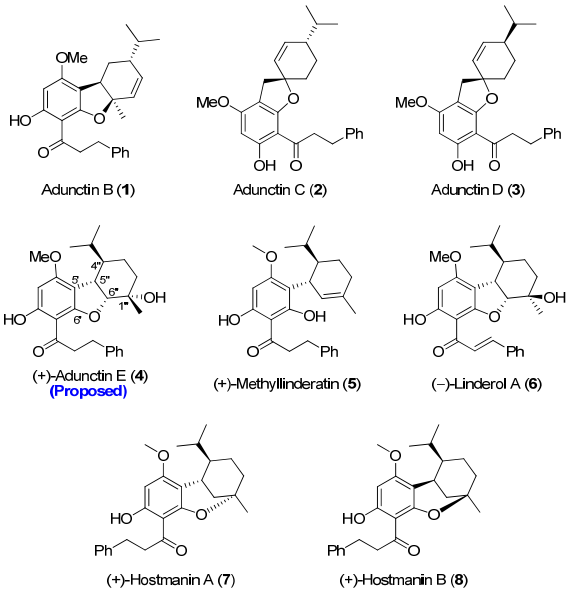


Figure 1. Adunctins and related natural products.

(–)-Methyllinderatin (**5**) also showed potent antiplasmodial activity with IC_{50} value of 5.64 µM against chloroquine sensitive and resistant strains of *Plasmodium falciparum* (F32, FcB1). The activity of (–)-methyllinderatin (**5**) was confirmed in vivo against *Plasmodium*

vinckeipetteri in mice (80% of reduction of parasitemia) at a dose of 20 mg/kg/day.[4] (–)-Linderol A (**6**) exhibited potent inhibitory activity on melanin biosynthesis of cultured B-16 melanoma cells without causing any cytotoxicity in the cultured cells or skin irritation in guinea pigs.[3] Adunctin B (**1**), E (**4**) and linderol A (**6**) have four contiguous stereocentres at 1", 4", 5" and 6" positions. Interesting structural features coupled with potent biological activities of adunctins and linderols have proven to be a fertile ground for total synthesis.[5]

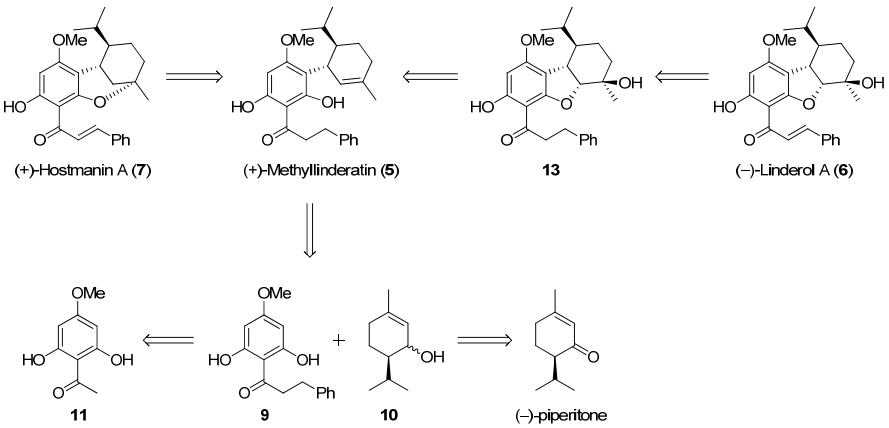
In 2001 Ohta and co-workers[5a] reported the first total synthesis of (±) linderol A (**6**) using coumarin rearrangement strategy in 20 steps longest linear sequence, followed by an asymmetric version by chiral auxiliary approach.[5f] Later in 2011 Yamashita and co-workers[5j,k] reported the first total synthesis of (±)-adunctin B (**1**) in 15 steps longest linear sequence. In 2007 Ohta and co-workers[5g] reported the total synthesis of proposed structure of adunctin E (**4**), however the spectral data of this compound, including ^{1}H and ^{13}C NMR spectra were inconsistent with the literature data for adunctin E (**4**),[1] thus proving that the proposed structure of adunctin E (**4**) was incorrect.

Most of the previously reported synthesis[5] of adunctin B (**1**) and linderol A (**6**) are racemic, tedious (15–20 steps longest linear sequence) and are not stereoselevtive. Herein we report protecting group free,[6] concise and gram scale enantioselective total syntheses of (+)-methyllinderatin (**5**), (+)-hostmanin A (**7**), (–)-linderol A (**6**) and structural reassignment of adunctin E (**4**).

RESULT AND DISCUSSION

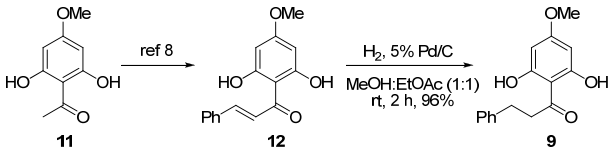
In our quest to synthesize these natural products we decided to employ the highly diastereoselective modified Friedel-Crafts reaction[7] that involved two required components, dihydrochalcone derivative **9** and alcohol **10** as shown retrosynthetically in scheme 1. This

Scheme 1. Retrosynthetic analysis.



route had the advantage of optimum convergency and it was presumed that stereochemical outcome of the Friedel-Crafts coupling reaction would be governed by bulky isopropyl group at C-4" position. The required chalcone derivative **9** was synthesized from commercially available acetophenone derivative **11** in 4 steps. Thus **11** was converted to α, β unsaturated ketone derivative **12** in 3 steps by known protocol,[8] followed by reduction of double bond of **12** by 5% Pd/C, under hydrogen atmosphere to afford required dihydrochalcone **9** in 96%

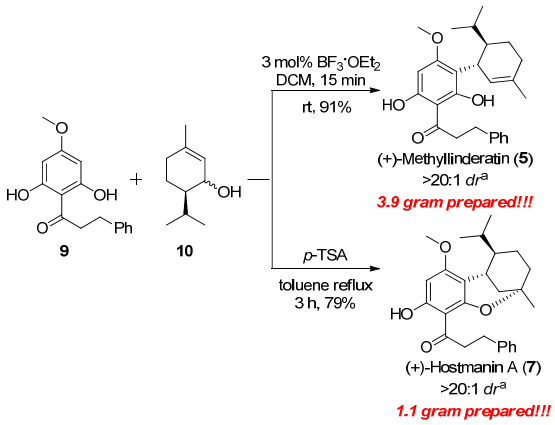
Scheme 2. Preparation of starting material.



yield (Scheme 2). The piperetol (**10**) was obtained by reduction of keto group of (–)-piperitone using Luche reduction.[9] With required fragments in hand, the stage was set to investigate the key Friedel-Crafts coupling reaction. Treatment of a mixture of **9** and **10** in presence of 3 mol% $BF_3{\cdot}OEt_2$ led to rapid formation of highly regio- and diastereoselective coupling product methyllinderatin (**5**) in 91% yield with >20:1 diastereomeric ratio (only major diastereomer is shown in Scheme 3). The spectral data (^1H, ^{13}C, IR and HRMS) and optical rotation $[\alpha]_D$ +41.2 (*c* 0.4, $CHCl_3$) was in complete agreement with natural (+)-methyllinderatin (**5**)[2] {lit[2] $[\alpha]_D$ +41.0(*c* 0.4, $CHCl_3$)}. One step synthesis of (+)-Hostmanin A

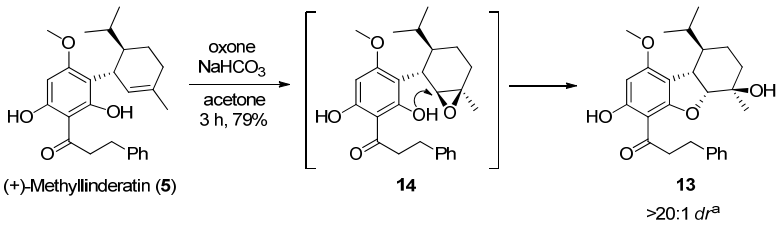
(**7**) was also achieved. Thus the reaction of dihydrochalcone derivative **9** with alcohol **10** in presence of 30 mol% *p*-TSA in refluxing toluene furnished (+)-hostmanin A (**7**) as a single diastereomer with 79% yield, whose spectral data (^{1}H, ^{13}C, IR and HRMS) and optical rotation $[\alpha]_D$ +59.4 (*c* 0.15, MeOH) was identical to those reported for the natural product[4] (scheme 3).

Scheme 3. Total synthesis of (+)-methyllinderatin (5) and (+)-hostmanin A (7).



[a]*dr* = *anti/syn* determined *via* ^{1}H NMR spectroscopy.

Scheme 4. Towards the total synthesis of (–)-linderol A (6).

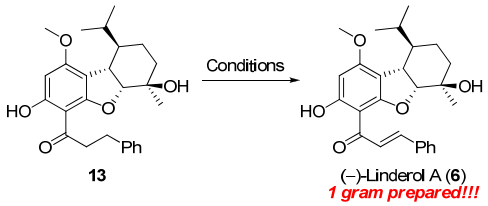


[a]*dr* = *syn/anti* determined *via* ^{1}H NMR spectroscopy.

Next we turned our attention towards total synthesis of (–)-linderol A (**6**). Treatment of DMDO with (+)-methyllindratin (**5**) directly generated the advanced tricyclic intermediate **13** in 79% yield and >20:1 diastereomeric ratio (determined by crude ^{1}H NMR) by epoxidation of double bond followed by opening of epoxide **14** by adjacent phenolic-OH

group as shown in scheme 4. Conversion of tricyclic intermediate **13** to linderol A (**6**) required the formation of double bond at benzylic position. After trying various conditions

Table 1. Screening of conditions for α, β unsaturation of 13.



Entry	Conditions	Yield[a]
1	IBX, DMSO, 70 °C	nil[b]
2	$PdCl_2(PPh)_3$, AcOH	nil[c]
3	$Ni(COD)_2$, K_3PO_4, PPh_3, dioxane	6%
4	TMS triflate, TEA, DCM $Pd(OAc)_2$, ACN TBAF, THF, rt	77%

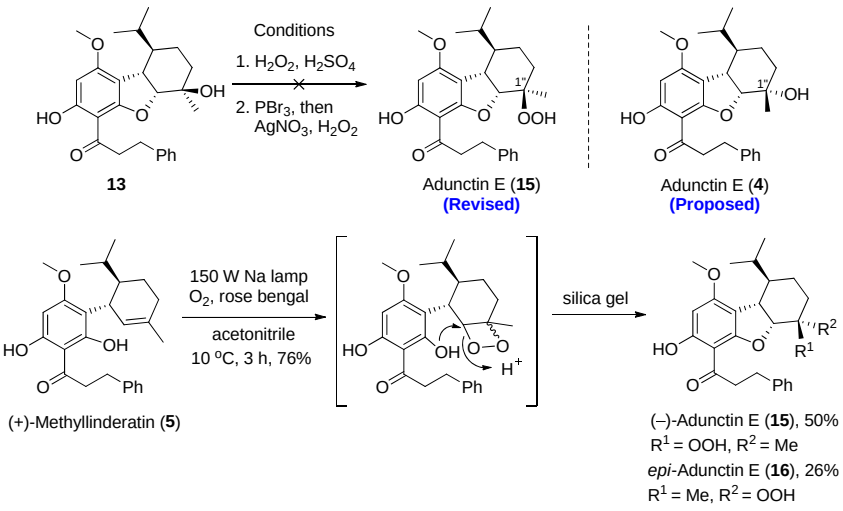
[a]Isolated yields, [b]decomposition of starting material, [c]recovered starting material

as shown in table 1, we were finally successful in achieving the enantioselective total synthesis of linderol A (**6**). Thus compound **13** under Saegusa–Ito oxidation condition[10] gave (–)-linderol A (**6**) in 77% yield. The spectral data (^1H, ^{13}C, IR and HRMS) and optical rotation {$[\alpha]_D$ –23.4 (*c* 0.42, $CHCl_3$)} of synthetic linderol A (**6**) was in complete agreement with natural linderol A (**6**).[3] {lit[3] $[\alpha]_D$ –22.7 ($CHCl_3$)}.

After completing the enantioselective total syntheses of (+)-methyllindratin (**5**), (+)-hostmanin A (**7**) and (–)-linderol A (**6**), we next turned out attention towards the structural revision of adunctin E (**4**) and the total synthesis of the revised structure. As discussed earlier, Ohta and co-workers[5g] reported that the proposed structure of adunctin E (**4**) by isolation group[1] was incorrect. After careful comparison of ^1H and ^{13}C NMR spectral data we found

that the major difference is that adunctin E (**4**) has doublet at δ 4.5 in ^{1}H and tertiary C-1" at 80.9 ppm. The values for dihydrolinderol **13** (prepared by our group) and proposed structure of adunctin E (**4**) (prepared by Ohta and co-workers)[5g] are at δ 4.13 and 4.26 in ^{1}H and 69.5 and 70.4 ppm respectively in ^{13}C NMR. This made us to think that most probably structural revision needs to be done at C-1" and or C-6", as the deshielding of C-6" proton by ~0.3 ppm in ^{1}H and C-1" by ~11 ppm in ^{13}C was observed. After going through various literature

Scheme 5. Total synthesis of revised structure of adunctin E (15).



reports and ^{1}H and ^{13}C NMR data of related compounds (e.g. artemisinin, plakortolides etc.),[11] it was observed that a tertiary carbon containing peroxide linkage also comes in the range of 78 - 84 in ^{13}C NMR. Based on above observation, we proposed the revised structure of the adunctin E as hydroperoxide **15** as shown in scheme 5. To confirm this, we attempted the synthesis of revised structure of adunctin E (**15**). Our initial attempt to convert hydroxyl group of compound **13** to hydroperoxide by using H_2O_2 under acidic condition as well as by using PBr_3 followed by H_2O_2 in presence of $AgNO_3$ were unsuccessful. Next we relied on [2+2] cycloaddition of (+)-methyllinderatin (**5**) with singlet oxygen followed by ring opening protocol. Thus [2+2] cycloaddition reaction of (+)-methyllinderatin (**5**) with singlet oxygen using sodium lamp in presence of rose bengal directly afforded diastereomeric mixture of

hydroperoxides **15** and **16** in 2:1 ratio with 76% yield, which was carefully separated by silica gel column chromatography. The spectral data (^{1}H, ^{13}C, IR and HRMS) of major isomer **15** was in complete agreement with the reported data[1] but the sign of optical rotation $[\alpha]_D$ –17.1 (*c* 0.65, MeOH) {lit[1] $[\alpha]_D$ +16.3 (*c* 0.65, MeOH)} was exactly opposite, confirming that synthetic **15** is an antipode of the natural (+)-adunctin E,[1] The stereochemistry of (–)-adunctin E (**15**) was unambiguously established by single crystal X-ray analysis (figure 2),[12] which established the absolute configuration of natural (+)-adunctin E (**15**) as (4"*S*, 5"*R*, 6"*S*,

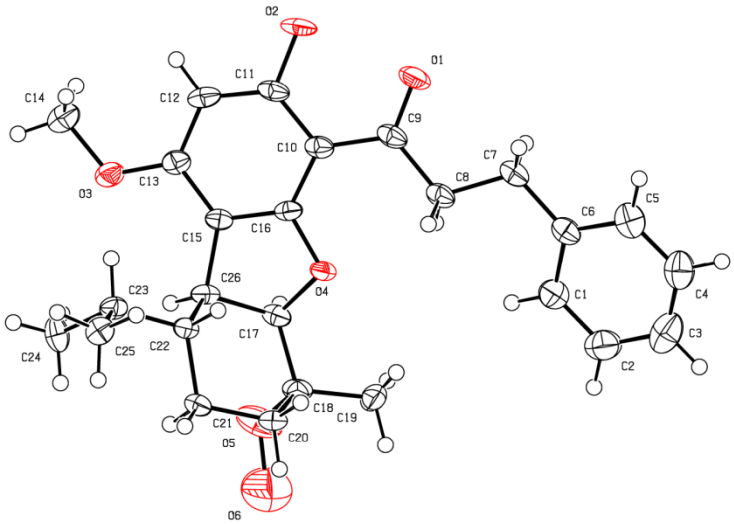


Figure 2. ORTEP diagram of (–)-adunctin E (15). Thermal ellipsoids are drawn at the 50% probability level.

1"*S*). It is worth mentioning that, the stereochemistry of tertiary carbon, containing peroxide (C-1") was found to be exactly opposite to that of proposed structure of adunctin E (**4**) (see scheme 5). Using same strategy, natural (+)-adunctin E (**15**) could be synthesized from dihydrochalcone derivative **9** and *ent*- **10**. Thus total synthesis of proposed structure of adunctin E (**4**) by Ohta and co-workers,[5g] followed by synthesis of **13**, **15** and **16** by our

group led to an unambiguous reassignment of the structural composition and established the relative and absolute stereochemical configuration of the natural product adunctin E.

In conclusion we achieved concise, protecting group free, gram scale, highly atom economic and enantioselective syntheses of four natural products namely (+)-methyllinderatin, (+)-hostmanin A, (–)-linderol A and (–)-adunctin E using modified Friedel-Crafts reaction, and photochemical [2+2] cycloaddition of olefin with singlet oxygen as key steps. The synthetic approach allows ready access to analogues that can be used for further biological studies.

EXPERIMENTAL SECTION

General Information

All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise mentioned. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically pure compounds, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) using UV light as a visualizing agent and an *p*-anisaldehyde or ninhydrine stain, and heat as developing agents. Silica gel (particle size 100-200 and 230-400 mesh) was used for flash column chromatography. Neat coumpounds were used for record IR spectra. NMR spectra were recorded on either a 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz). Mass spectrometric data were obtained using Q-Tof-Premier-HAB213 and Q-Tof-Premier-ESI-MS instruments. Melting points measurements were made using a hot stage apparatus. Optical rotations were measured using a polarimeter at 20 °C.

The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, td = triplet of a doublet, m = multiplet, br = broad.

Experimental Procedures

1-(2,6-dihydroxy-4-methoxyphenyl)-3-phenylpropan-1-one (9)

To a magnetically stirred solution of **12** (6 g, 22.2 mmol) in methanol (30 mL) and ethyl acetate (30 mL) was added 5% Pd/C (400 mg) at room temperature. The resulting mixture was stirred at rt for 2 h under H_2 bladder pressure. After completion of reaction, indicated by TLC, the reaction mixture passed through celite. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:6) as eluent furnished **9** (5.85 g, 97%) as a pale yellow solid; *Rf* = 0.30 (EtOAc-hexane 1:4); M.p.: 173-176 ^{o}C; IR (neat): ν_{max}/cm^{-1} 3253 (br.), 2922, 1593, 1526, 1440, 1229, 1081, 810; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.29 (s, 2H), 7.25 - 7.20 (m, 4H), 7.16 - 7.12 (m, 1H), 5.92 (s, 2H), 3.70 (s, 3H), 3.28 (t, *J* = 8.2 Hz, 2H), 2.87 (t, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 209.8, 170.8, 169.3, 146.9, 133.6, 131.1, 109.8, 98.5, 60.7, 50.5, 35.3; HRMS: m/z calcd for $C_{16}H_{17}O_4$ $[M+H]^+$: 273.1127; found: 273.1122. spectral data were consistent with those previously reported.[13a]

(*R*)-6-isopropyl-3-methylcyclohex-2-enol (10)

To a magnetically stirred solution of (−)-piperitone (2 g, 13.14 mmol) in MeOH was added $CeCl_3 \cdot 7H_2O$ (4.89 g, 13.14 mmol), cooled to 0 ^{o}C. After 10 min, $NaBH_4$ (497 mg, 13.14 mmol) was added portionwise for 5 min and reaction allowed to stir at same temperature. After completion of reaction indicated by TLC, the reaction was quenched by water, reaction mixture concentrated under reduced pressure and then extracted with diethyl ether (2 × 15 mL). Evaporation of the solvent and purification of the residue on silica gel column using

EtOAc-hexane (1:49) as eluent furnished **10** (1.78 g, 88%) as a colourless liquid; *Rf* = 0.42 (EtOAc-hexane 1:19); spectral data were consistent with those previously reported.[13b]

(+)-methyllinderatin (5):

To a magnetically stirred solution of compound **9** (2.9 g, 10.6 mmol) and **10** (2.14 g, 13.84 mmol) in anhydrous DCM (30 mL) was added $BF_3{\cdot}OEt_2$ (40 µL, 0.32 mmol) at room temperature. The resulting reaction mixture was then stirred at rt for 15 min After completion of reaction indicated by TLC, the reaction was quenched by saturated Na_2CO_3 solution (5 mL) and then extracted with DCM (2 × 25 mL). Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished methyllinderatin (**5**) (3.955 g, 91%) as a pale yellow oil; *Rf* = 0.60 (EtOAc-hexane 1:4); $[\alpha]_D^{20}$ +41.2 (*c* 0.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3354 (br.), 2955, 2932, 1624, 1584, 1248, 1212, 816, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 - 7.19 (m, 5H), 7.06 (s, 1H), 6.05 (s, 1H), 5.46 (br. s, 1H), 3.87 (br. d, *J* = 10.6 Hz, 1H), 3.78 (s, 3H), 3.39 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.17 - 2.05 (m, 2H), 1.79 (s, 3H), 1.78 - 1.74 (m, 1H), 1.56 - 1.50 (m, 1H), 1.47 - 1.42 (m, 1H), 1.40 - 1.34 (m, 1H), 0.84 (d, *J* = 8.0 Hz, 3H), 0.81 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 165.4, 164.0, 158.9, 142.4, 141.9, 129.0, 128.7, 126.2, 124.7, 109.2, 106.2, 92.3, 55.9, 46.4, 43.8, 35.0, 31.0, 30.9, 28.2, 24.1, 22.4, 22.0, 16.5; HRMS: m/z calcd for $C_{26}H_{33}O_4$ $[M+H]^+$: 409.2379; found: 409.2370.

(+)-hostmanin A (7)

To a magnetically stirred solution of compound **9** (1 g, 3.67 mmol) and **10** (736.42 mg, 4.77 mmol) in anhydrous toluene (10 mL) was added *p*-TSA·H_2O (209 mg, 1.1 mmol) at rt. The resulting reaction mixture was then refluxed at 110 ^oC for 3 hr. After completion of reaction indicated by TLC, the reaction was quenched by saturated solution of Na_2CO_3 (5 mL) and

then extracted with ethyl acetate (2 × 20 mL). Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:199) as eluent furnished (+)-hostmanin A (**7**) (1.19 g, 79%) as a pale yellow oil; *Rf* = 0.82 (EtOAc-hexane 1:4); $[\alpha]_D^{25}$ +59.4 (*c* 0.15, MeOH); IR (neat): ν_{max}/cm^{-1} 2928, 1617, 1586, 1216, 1146, 1108; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 - 7.21 (m, 5H), 6.02 (s, 1H), 3.83 (s, 3H), 3.52 - 3.44 (m, 2H), 3.42 - 3.36 (m, 1H), 3.06 (t, *J* = 7.8 Hz, 2H), 1.90 (dd, *J* = 13.3, 2.1 Hz, 1H), 1.81 - 1.71 (m, 2H), 1.63 (dd, *J* = 13.7, 4.6 Hz, 1H), 1.56 - 1.48 (m, 3H), 1.36 (s, 3H), 1.24 - 1.19 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 165.3, 162.2, 159.0, 141.8, 128.4, 128.3, 125.9, 106.8, 104.7, 91.2, 76.8, 55.7, 45.4, 44.0, 35.3, 30.7, 30.1, 29.2, 27.2, 26.3, 22.1, 21.0, 20.5; HRMS: m/z calcd for $C_{26}H_{33}O_4$ $[M+H]^+$: 409.2379; found: 409.2379.

1-((5a*R*,6*R*,9*R*,9a*S*)-3,6-dihydroxy-9-isopropyl-1-methoxy-6-methyl-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-4-yl)-3-phenylpropan-1-one (13)

To a magnetically stirred solution of (+)-methylinderatin (**5**) (2 g, 4.9 mmol) in acetone (20 mL) was added Na_2CO_3 (1.234 g, 14.68 mmol). The reaction mixture then cooled to 0 ^oC and stirred for 10 min. Then added dropwise solution of oxone (6.02 g, 9.8 mmol) (prepared by dissolving oxone in 25 mL water). The reaction continued at same temperature for additional 30 min and then slowly allowed to come to room temperature. After completion of reaction, indicated by TLC, reaction mixture concentrated under reduced pressure and then extracted with ethyl acetate (2 × 30 mL). Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:11) as eluent furnished **13** (1.64 g, 79%) as yellow solid; *Rf* = 0.55 (EtOAc-hexane 1:4); M.p.: 143-145 ^oC; $[\alpha]_D^{25}$ –34.9 (*c* 0.55, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3484 (br.), 2959, 1633, 1602, 1443, 1374, 1215, 1207, 1083, 977, 812, 718; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 - 7.16 (m, 5H), 6.03 (s, 1H), 4.13 (d, *J* = 5.2 Hz, 1H),

3.80 (s, 3H), 3.40 - 3.30 (m, 2H), 3.09 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.38 (br. s, 1H), 1.83 (dq, *J* = 6.7, 2.6 Hz, 1H), 1.77 - 1.72 (m, 1H), 1.66 - 1.60 (m, 1H), 1.43 - 1.35 (m, 2H), 1.37 (s, 3H), 1.09 - 1.03 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 203.6, 165.6, 162.1, 141.6, 128.7 (2C), 128.6, 126.3, 113.5, 103.0, 93.1, 92.7, 69.7, 55.8, 46.9, 44.0, 39.9, 35.6, 30.5, 28.4, 27.5, 22.1, 17.5, 15.7; HRMS: m/z calcd for $C_{26}H_{33}O_5$ $[M+H]^+$: 425.2328; found: 425.2324.

(–)-linderol A (6)

To a magnetically stirred solution of **13** (1.3 g, 3.06 mmol) and TEA (853 µL, 6.12 mmol) in DCM (2 mL) was added TMSOTf (736 µL, 3.98 mmol) drop wise. The resulting solution was stirred at 0 ^oC for 10 min and then at room temperature for additional 1 hr. The reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, concentrated at reduced pressure. The residue was dissolved in THF (10 mL) and $Pd(OAc)_2$ (687 mg, 6.12 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 2 h then filtered through a celite pad and washed with EtOAc. The filtrate was concentrated and dissolved in THF (10 mL) and TBAF (3.06 mL, 1 M in THF) was added to this mixture. The mixture was stirred at room temperature for 1 h, then quenched with water, extracted with EtOAc, washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:11) as eluent furnished the compound (–)-linderol A (**6**) (1 g, 77%) as a yellow solid; *Rf* = 0.50 (EtOAc-hexane 1:4); M.p.: 180-182 ^oC; $[\alpha]_D^{20}$ –23.4 (*c* 0.42, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3446 (br.), 2925, 1639, 1589, 1346, 1031, 809, 458 ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 15.5 Hz, 1H), 7.86 (d, *J* = 15.5 Hz, 1H), 7.61 (d, *J* = 4.0 Hz, 2H), 7.42 - 7.37 (m, 3H), 6.08 (s, 1H), 4.24 (d, *J* = 5.2 Hz, 1H), 3.84 (s, 3H), 3.14 (dd, *J* = 11.2, 5.4 Hz, 1H), 1.87 - 1.81 (m, 2H), 1.77 - 1.72 (m, 1H), 1.61 (s, 3H),

1.57 (br. s, 1H), 1.45 - 1.38 (m, 2H), 1.13 (t, *J* = 11.5 Hz, 1H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.1, 166.7, 162.1, 161.5, 143.4, 135.3, 130.3, 128.9, 128.4, 125.8, 113.3, 103.3, 93.0, 92.3, 69.4, 55.5, 46.5, 39.5, 35.4, 28.3, 27.1, 21.8, 17.2, 15.4; HRMS: m/z calcd for $C_{26}H_{31}O_5$ $[M+H]^+$: 423.2171; found: 423.2172.

(–)-adunctin E (15) and (–)-*epi*-adunctin E (16)

To a magnetically stirred solution of (+)-methyllinderatin (**5**) (100 mg, 0.24 mmol) in acetonitrile was added rose bengal (5 mg, 4.9 μmol). The temperature of reaction was maintained at 10 ^{o}C (by putting cold water). The reaction mixture was then continuously purged with O_2 balloon (by inserting another open needle into the septa of RB) and then exposed to 150 W sodium lamp. After consumption of starting material indicated by TLC, sodium lamp was removed and silica gel (230 – 400 mesh size, 500 mg) was added to the reaction mixture and stirred at rt for additional 1 hr. Reaction mixture then concentrated under reduced pressure and extracted with ethyl acetate (2 × 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using monoglyme-hexane (1:7) as eluent furnished (–)-*epi*-adunctin E (**16**) (27 mg, 26%) as white solid; *Rf* = 0.55 (monoglyme-hexane 1:4); M.p.: 111-112 ^{o}C; $[\alpha]_D^{20}$ –38 (*c* 0.2, MeOH); IR (neat): ν_{max}/cm^{-1} 3384 (br.), 2926, 2874, 1622, 1598, 1358, 1184, 817, 699; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.16 (m, 5H), 5.99 (s, 1H), 4.45 (d, *J* = 4.6 Hz, 1H), 3.75 (s, 3H), 3.36 - 3.29 (m, 2H), 3.00 – 2.95 (m, 2H), 2.91 (d, *J* = 4.0 Hz, 1H), 1.82 - 1.77 (m, 1H), 1.74 - 1.66 (m, 1H), 1.63 - 1.51 (m, 2H), 1.32 (s, 3H), 1.15 - 1.05 (m, 2H), 0.81 (d, *J* = 6.3 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 203.7, 165.9, 162.0, 161.7, 141.5, 128.9, 128.6, 126.6, 113.2, 103.1, 93.3, 89.5, 82.2, 55.9, 47.2, 44.5, 41.4, 31.0, 30.6, 27.2, 22.1, 21.6, 19.8, 15.6; HRMS: m/z calcd for $C_{26}H_{33}O_6$ $[M+H]^+$: 441.2277; found: 441.2273. Further elution of the column with monoglyme-hexane (1:7) gave (–)-adunctin E (**15**) (54

mg, 50%) as a white solid; *Rf* = 0.50 (monoglyme -hexane 1:4); M.p.: 100-103 ^{o}C; $[\alpha]_D^{20}$ –17.1 (*c* 0.65, MeOH); IR (neat): ν_{max}/cm^{-1} 3393 (br.), 2931, 2870, 1631, 1602, 1369, 1205, 813, 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 - 7.20 (m, 5H), 6.04 (s, 1H), 4.49 (d, *J* = 5.2 Hz, 1H), 3.81 (s, 3H), 3.43 - 3.30 (m, 2H), 3.08 (dd, *J* = 11.5, 5.7 Hz, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 2.00 (d, *J* = 14.9 Hz, 1H), 1.86 - 1.80 (m, 1H), 1.62 - 1.54 (m, 1H), 1.43 (s, 3H), 1.38 - 1.30 (m, 2H), 1.08 (t, *J* = 11.5 Hz, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 165.2, 161.8, 161.6, 141.2, 128.4, 128.3, 126.0, 112.9, 102.6, 92.8, 87.6, 80.9, 55.5, 46.3, 43.7, 39.7, 31.9, 30.1, 27.1, 22.0, 21.8, 17.1, 15.4; HRMS: m/z calcd for $C_{26}H_{33}O_6$ $[M+H]^+$: 441.2277; found: 441.2271.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C spectra for all new compounds and X-ray crystal data of compound **15** (CIF file). This material is available free of charge via the internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: ddethe@iitk.ac.in.

Notes

The authors declare no competing financial interest.

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