JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Enantioselective Total Syntheses of (+)-Hostmanin A, (−)-Linderol A, (+)-Methyllinderatin and Structural Reassignment of Adunctin E

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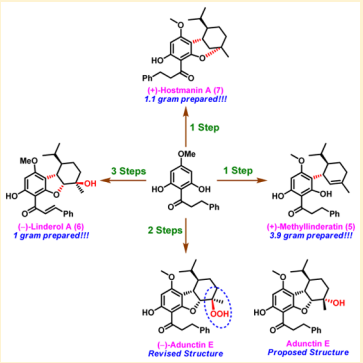
Supporting Information

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, and diarrhea and as a hemostatic agent. Investigation of the 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 a 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 have structures similar to those 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 toward *M. luteus* at concentrations of 3.5, 2.4, and 2.5 μg, respectively.

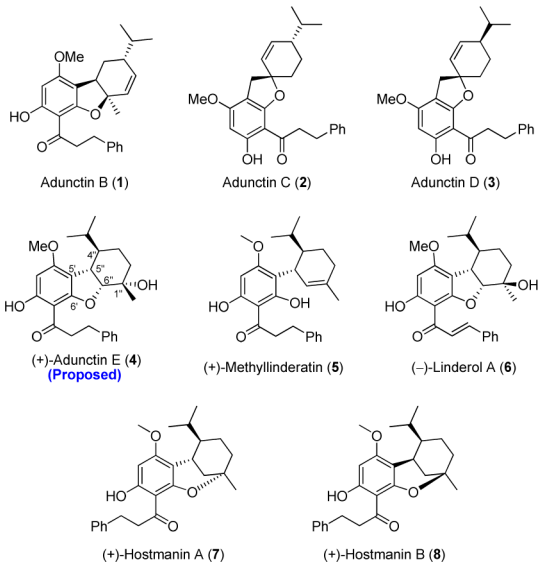


Figure 1. Adunctins and related natural products.

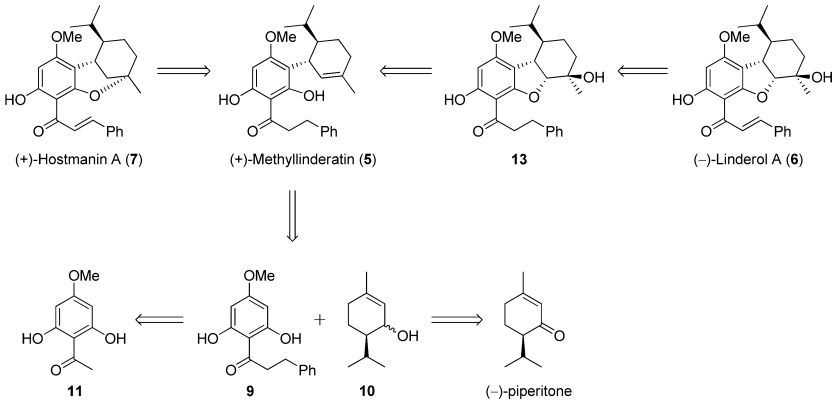
(−)-Methyllinderatin (**5**) also showed potent antiplasmodial activity with an IC_{50} value of 5.64 μM against chloroquine sensitive and resistant strains of *Plasmodium falciparum* (F32, FcB1). The activity of (−)-methyllinderatin (**5**) was confirmed in vivo against *Plasmodium vinckeipetteri* in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

Received: February 19, 2015
Published: April 10, 2015

DOI: 10.1021/acs.joc.5b00331
J. Org. Chem. 2015, 80, 4526−4531

Scheme 1. Retrosynthetic Analysis



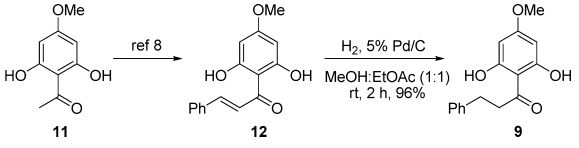
strategy in a 20 step long linear sequence, followed by an asymmetric version by a chiral auxiliary approach.[5f] Later, in 2011, Yamashita and co-workers[5j,k] reported the first total synthesis of (±)-aduncin B (**1**) in a 15 step long linear sequence. In 2007, Ohta and co-workers[5g] reported the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

Most of the previously reported syntheses[5] of aduncin B (**1**) and linderol A (**6**) are racemic, tedious (15−20 step long linear sequences) and are not stereoselective. Herein, we report protecting group free,[6] concise, and gram-scale enantioselective total syntheses of (+)-methyllinderatin (**5**), (+)-hostmanin A (**7**), and (−)-linderol A (**6**) and the structural reassignment of aduncin E (**4**).

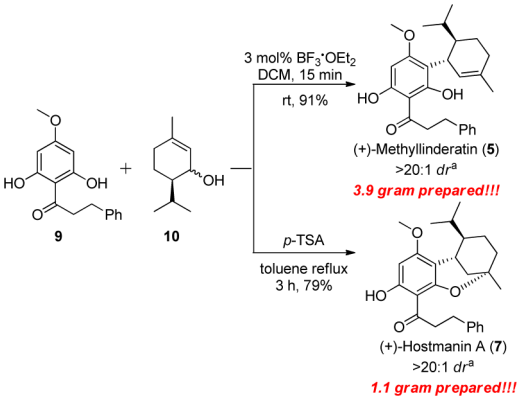
RESULT AND DISCUSSION

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 route had the advantage of optimum convergency, and it was presumed that the stereochemical outcome of the Friedel−Crafts coupling reaction would be governed by the bulky isopropyl group at the 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 a known protocol,[8] followed by reduction of the double bond of **12** by 5% Pd/C, under a hydrogen atmosphere to afford the required dihydrochalcone **9** in 96% yield (Scheme 2). The piperetol (**10**) was obtained by reduction of the 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 the 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 a >20:1 diastereomeric ratio (only major diastereomer is shown in Scheme 3). The spectral data (^{1}H, ^{13}C, IR, and HRMS) and optical rotation {$[\alpha]_D$ +41.2 (*c* 0.4, $CHCl_3$)} were in complete agreement with those of natural (+)-methyllinderatin (**5**)[2] {lit[2] $[\alpha]_D$ +41.0 (*c* 0.4, $CHCl_3$)}. The one step synthesis of (+)-Hostmanin A (**7**) was also achieved. Thus, the reaction of dihydrochalcone derivative **9** with alcohol **10** in the 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)} were identical to those reported for the natural product[4] (Scheme 3).

Scheme 2. Preparation of Starting Material



Scheme 3. Total Synthesis of (+)-Methyllinderatin (5) and (+)-Hostmanin A (7)

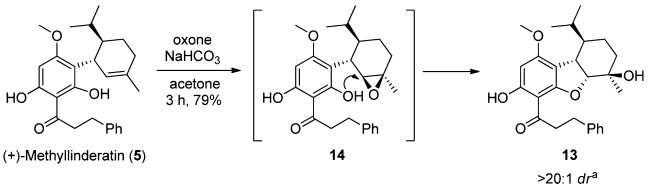


[a] *dr* = *anti/syn* determined via ^{1}H NMR spectroscopy.

Next, we turned our attention toward the 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 the double bond, followed by opening of epoxide **14** by the adjacent phenolic-OH group, as shown in Scheme 4. Conversion of tricyclic intermediate **13** to linderol A (**6**) required the formation of a double bond at the benzylic position. After trying various conditions, 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 (^{1}H, ^{13}C, IR,

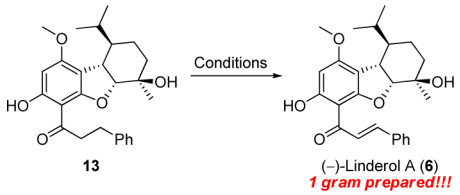
DOI: 10.1021/acs.joc.5b00331
J. Org. Chem. 2015, 80, 4526−4531

Scheme 4. Toward the Total Synthesis of (−)-Linderol A (6)



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

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%

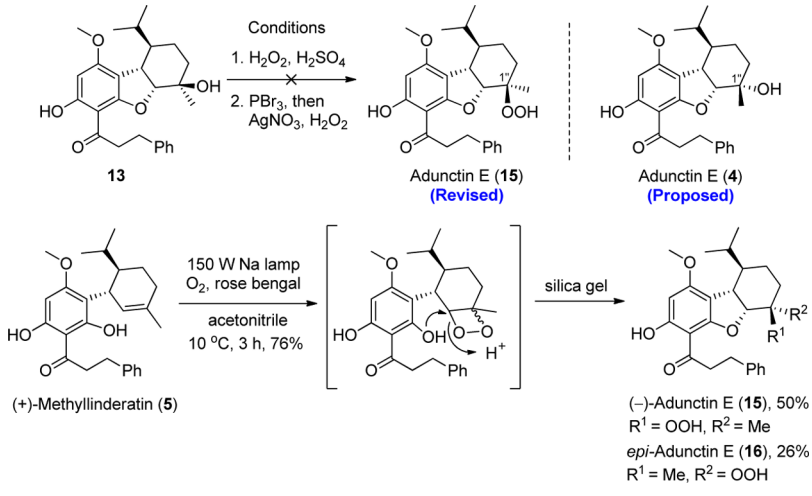
[a]Isolated yields. [b]Decomposition of starting material. [c]Recovered starting material.

and HRMS) and optical rotation {$[\alpha]_D$ −23.4 (*c* 0.42, $CHCl_3$)} of synthetic linderol A (**6**) were in complete agreement with those of 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 toward 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 Sticher group[1] was incorrect. After careful comparison of ^{1}H and ^{13}C NMR spectral data, we found that the major difference is that adunctin E (**4**) has a 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 the 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 the 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 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. On the basis of the 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 the revised structure of adunctin E (**15**). Our initial attempt to convert the hydroxyl group of compound **13** to hydroperoxide by using H_2O_2 under acidic conditions as well as by using PBr_3, followed by H_2O_2 in the presence of $AgNO_3$, was unsuccessful. Next, we relied on [2 + 2] cycloaddition of (+)-methyllinderatin (**5**) with singlet oxygen, followed by a ring-opening protocol. Thus, [2 + 2] cycloaddition reaction of (+)-methyllinderatin (**5**) with singlet oxygen using a sodium lamp in the presence of rose bengal directly afforded a diastereomeric mixture of hydroperoxides **15** and **16** in a 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 the 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*, 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 the proposed structure of adunctin E (**4**) (see Scheme 5). Using the same strategy, natural (+)-adunctin E (**15**) could be synthesized from dihydrochalcone derivative **9** and *ent*-**10**. Thus, the total synthesis of the 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

Scheme 5. Total Synthesis of Revised Structure of Adunctin E (15)



DOI: 10.1021/acs.joc.5b00331
J. Org. Chem. 2015, 80, 4526−4531

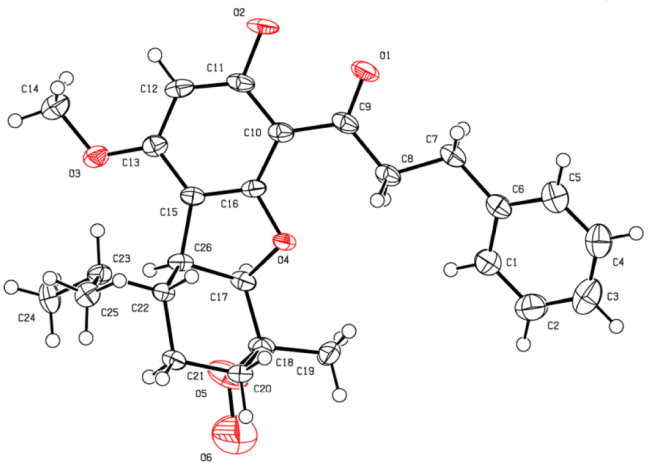


Figure 2. ORTEP diagram of (−)-aduncin E (**15**). Thermal ellipsoids are drawn at the 50% probability level.

syntheses of four natural products, namely, (+)-methyllinderatin, (+)-hostmanin A, (−)-linderol A, and (−)-aduncin E, using a modified Friedel−Crafts reaction, and a 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 a 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 a *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 recording IR spectra. NMR spectra were recorded on either 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) or 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; R_f = 0.30 (EtOAc−hexane 1:4); mp: 173−176 °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 $CeCl_3$·$7H_2O$ (4.89 g, 13.14 mmol), cooled to 0 °C. After 10 min, $NaBH_4$ (497 mg, 13.14 mmol) was added portionwise for 5 min, and the reaction was allowed to stir at the same temperature. After completion of reaction indicated by TLC, the reaction was quenched by water, and the reaction mixture was 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 colorless liquid; R_f = 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·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; R_f = 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; ^{1}H 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 °C for 3 h. After completion of reaction indicated by TLC, the reaction was quenched by a 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; R_f = 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-((5aR,6R,9R,9aS)-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 was then cooled to 0 °C and stirred for 10 min. Then, a solution of oxone (6.02 g, 9.8 mmol) (prepared by dissolving oxone in 25 mL water) was added dropwise. The reaction continued at the same temperature for an additional 30 min and then was slowly allowed to come to room temperature. After completion of reaction, indicated by TLC, the reaction mixture was 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 a yellow solid; R_f = 0.55 (EtOAc−hexane 1:4); mp: 143−145 °C; $[\alpha]_D^{25}$ −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, $CDCl_3$):

DOI: 10.1021/acs.joc.5b00331
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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) dropwise. The resulting solution was stirred at 0 °C for 10 min and then at room temperature for an additional 1 h. The reaction mixture was quenched with a saturated $NaHCO_3$ solution, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and 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 and 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 and 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; R_f = 0.50 (EtOAc−hexane 1:4); mp: 180−182 °C; $[\alpha]_D^{20}$ −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 °C (by putting cold water). The reaction mixture was then continuously purged with an O_2 balloon (by inserting another open needle into the septa of RB) and then exposed to a 150 W sodium lamp. After consumption of starting material indicated by TLC, the sodium lamp was removed and silica gel (230−400 mesh size, 500 mg) was added to the reaction mixture, which was stirred at rt for an additional 1 h. The reaction mixture was 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 a white solid; R_f = 0.55 (monoglyme−hexane 1:4); mp: 111−112 °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; R_f = 0.50 (monoglyme−hexane 1:4); mp: 100−103 °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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Jiten K. Bera, Mr. Prosenjit Daw, and Mr. Kuldeep Singh for their help in X-ray analysis. B.D.D. thanks CSIR, New Delhi. Financial support from DST, New Delhi (Project No. SB/S1/OC-01/2014), is gratefully acknowledged.

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