JOC The Journal of Organic Chemistry

Note

Total Synthesis of Adunctin B

Dattatraya Hanumant Dethe, and Balu D. Dherange

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00015 • Publication Date (Web): 20 Feb 2018

ACS Publications

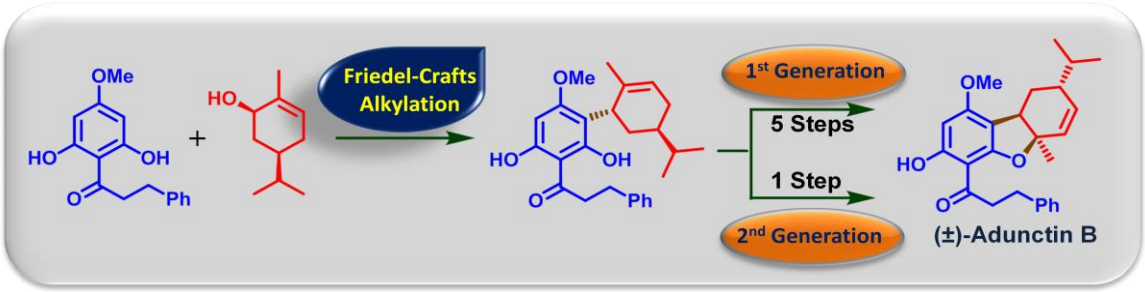
The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Total Synthesis of Adunctin B

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: Total synthesis of (±)-adunctin B, a natural product isolated from *Piper aduncum* (Piperaceae) has been achieved using two different strategies, in seven and three steps. The efficient approach features highly atom economical and diastereoselective Friedel-Crafts acylation, alkylation reaction and palladium catalyzed Wacker type oxidative cyclization.

The Piperaceae (pepper family) is one of the largest family of flowering plants. The family constitutes roughly 3,600 species. The distribution of Piperaceae family is pantropical in nature and contains all variety of species from shrubs, herbs to trees. A monoecious shrub *Piper aduncum*, L. (Piperaceae) distributed in Malesia, Papua New Guinea and large part of tropical America, is used for the treating fresh wounds, diarrhoea,[1] dysentery, and as a haemostatic agent.[2] Sticher and co-workers[3] isolated adunctin A-E (**1**-**5**) along with known methyllindaretin[4] from the leaves of *Piper adunctum*. Spectral analysis (1D, 2D and single crystal X-ray) established the structure of adunctin A (**1**) as monoterpene-substituted

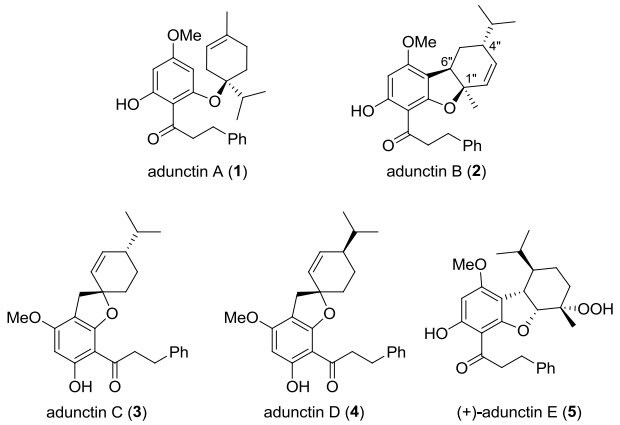
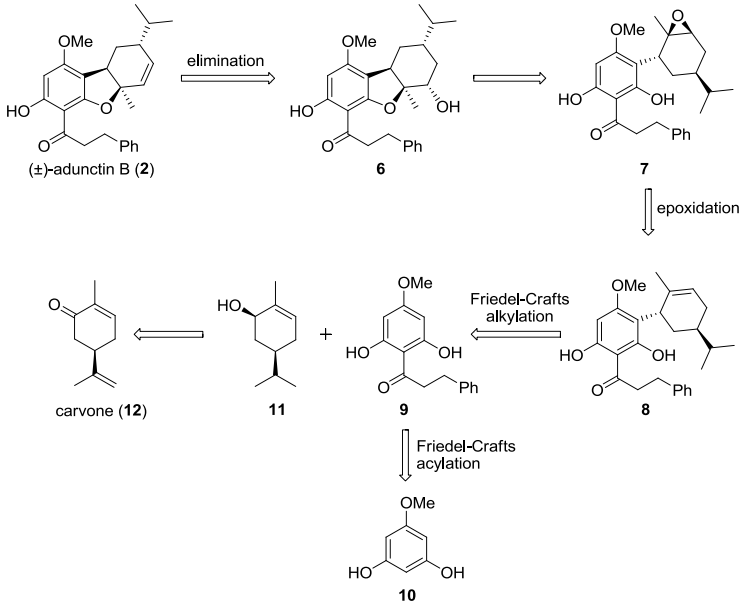


Figure 1. Structures of adunctin B (**2**) and related natural products

dihydrochalcone, adunctin C (**3**), and D (**4**) as spirobenzofuran derivative, whereas adunctin B (**2**) and E (**5**) as cinnamoyl-hexahydrodibenzofuran derivatives (Figure 1). Adunctin B (**2**) has three stereocentres at 1", 4" and 6" positions. It showed antibacterial effects toward *Micrococcus luteus* at a concentration of 3.5 μg/mL.[3]

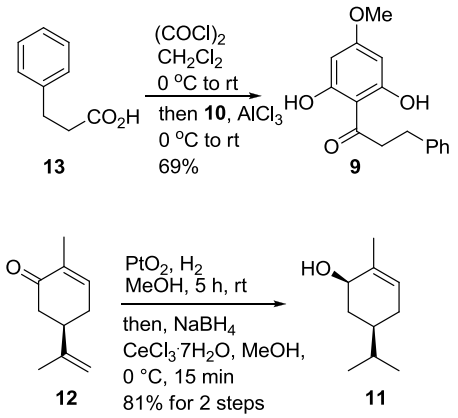
The first racemic synthesis of adunctin B (**2**) was reported by Arimitsu et al.[5] in 2011 from commercially available 4,6-dimethoxysalicylaldehyde with 1.22% overall yield in 16 steps, using coumarin rearrangement strategy, previously developed in their lab. Encouraged by our recent syntheses of methyllinderatin, linderol A and adunctin E,[6] we became interested in the total synthesis of adunctin B. Herein, we report concise total synthesis of (±)-adunctin B (**2**) using highly atom economic and diastereoselective Friedel-Crafts reaction, followed by palladium catalyzed Wacker-type oxidative cyclization.

Our retrosynthetic analysis of adunctin B (**2**) is depicted in Scheme 1. It was envisioned that synthesis of adunctin B (**2**) could be achieved from alcohol **6** by dehydration to generate the requisite double bond. The nucleophilic attack of phenolic OH group on epoxide **7**, under basic conditions would lead to the formation of tricyclic compound **6**. Epoxidation on alkene **8** using *m*-CPBA would generate epoxide **7**. The Friedel-Crafts alkylation of electron rich dihydrochalcone **9** and dihydrocarveol **11** should furnish the key intermediate **8**. Dihydrochalcone **9** could be prepared from commercially available 5-methoxyresorcinol (**10**) while, dihydrocarveol **11** could be obtained from carvone (**12**).



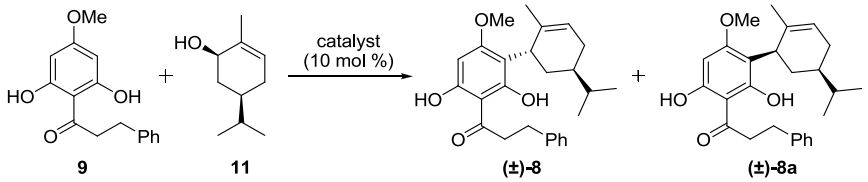
Scheme 1. Retrosynthetic analysis for adunctin B (2)

The synthesis commenced with preparation of dihydrochalcone derivative **9**, which was previously synthesized in 4-5 steps, using protection-deprotection protocol.[6,7] We developed an alternate, protecting group free, one pot synthesis where, the commercially available acid **13** was converted to corresponding acid chloride using oxalyl chloride, followed by addition of 5-methoxyresorcinol (**10**) and $AlCl_3$ afforded required dihydrochalcone **9** as a single regioisomer in 69% yield (Scheme 2). The dihydrocarveol **11** was prepared from carvone (**12**) in one pot by regioselective double bond reduction using Adam's catalyst,[8] followed by Luche reduction[9] in 81% yield.



Scheme 2. Synthesis of dihydrochalcone 9 and dihydrocarveol 11

Table 1. Optimization table for acid catalyzed Friedel-Crafts alkylation reaction

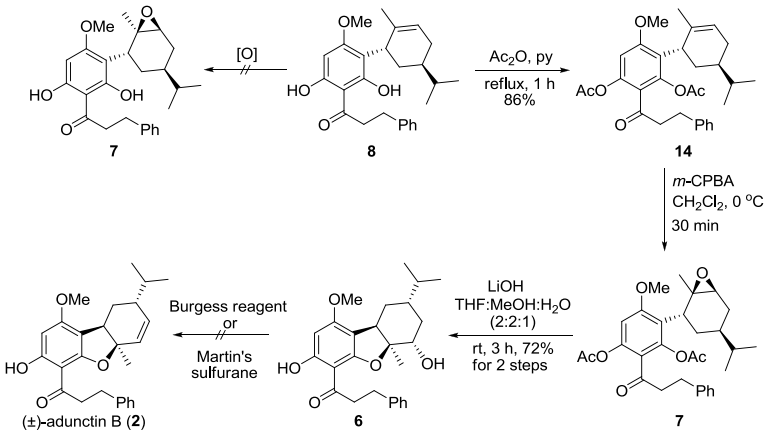


entry	catalyst	solvent	temp	time (h)	yield [%][a] (**8**+**8a**)	ratio (**8**:**8a**)
1	*p*-TSA	toluene	reflux	1	32	4:1
2	$Cu(OTf)_2$	toluene	reflux	2	07	5:1
3	$Cu(OTf)_2$	EtOAc	rt	2	22	5:1
4	$Cu(OTf)_2$	CH_2Cl_2	rt	1	34	5:1
5	$FeCl_3$	CH_2Cl_2	rt	1	41	4:1
6	$Bi(OTf)_3$	CH_2Cl_2	rt	1	28	5:1
7	$Sc(OTf)_3$	CH_2Cl_2	rt	1	52	6:1
8	$BF_3{\cdot}OEt_2$	CH_2Cl_2	rt	0.5	79	6:1

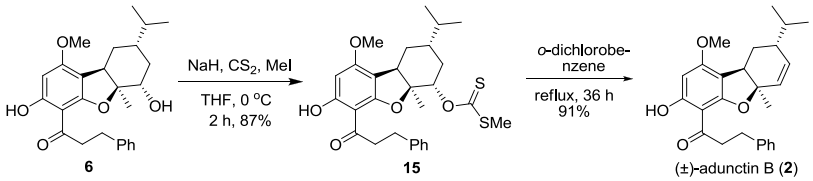
[a]Isolated yields.

With the required substrates **9** and **11** in hand, the key Friedel-Crafts alkylation reaction was investigated. Various Lewis/Brønsted acids were screened for this purpose (Table 1). Initially, when the mixture of arene **9** and dihydrocarveol **11** was treated with *p*-TSA in refluxing toluene, led to the formation of the mixture of compounds **8** and **8a** in 4:1

diastereomeric ratio with 32% yield. When the reaction was carried out using $Cu(OTf)_2$ in toluene, generated the products **8** and **8a** merely in 7% yield (Table 1, entry 2). When the same reaction was carried out using ethyl acetate as a reaction solvent, generated the products **8** and **8a** in 22% yield (entry 3), while use of dichloromethane led to the formation of desired products with 34% yield, in 5:1 diastereomeric ratio (Table 1, entry 4), hence it was decided to carry out further catalyst screening in dichloromethane. Among the other catalysts screened namely, $FeCl_3$, $Bi(OTf)_3$, $Sc(OTf)_3$ and $BF_3{\cdot}OEt_2$, the highest yield of the products **8** and **8a** was obtained with 10 mol % $BF_3{\cdot}OEt_2$ in dichloromethane (Table 1, entry 8) in 6:1 diastereomeric ratio and 79% yield. Diastereomers **8** and **8a** were carefully separated by silica gel column chromatography. As expected compounds **8** and **8a** showed zero optical rotation since allyl alcohol **11** on treatment with Lewis acid generates the meso symmetric allylic carbocation and the nucleophilic attack of aromatic ring could be possible from both sides. Desymmetrization of the meso symmetric alllylic carbocation was attempted using (1*S*)-(+)-10-camphor sulphonic acid, which generated racemic compounds **8** and **8a**, and Tsuji Trost reaction condition, where no any product formation was observed.



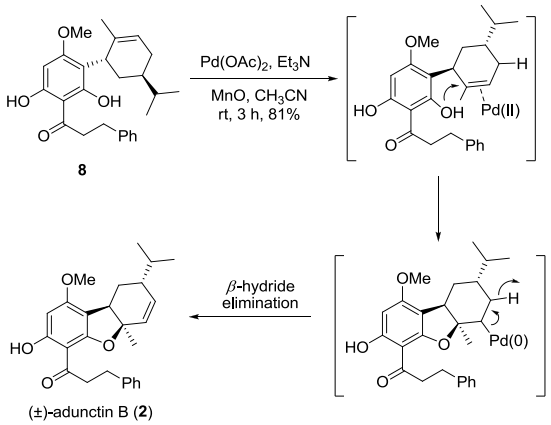
Scheme 3. Attempted synthesis of (±)-adunctin B (2)



Scheme 4. Completion of total synthesis of (±)-adunctin B (2)

The next task was epoxidation of alkene **8**. Our initial attempts to epoxidise alkene **8** using *m*-CPBA, DMDO, NO_2,[10] $MnSO_4$,[11] or $VO(acac)_2$[12] resulted in either decomposition of starting material or no reaction with recovery of starting material (Scheme 3). It was thought that the aromatic ring in compound **8a** is highly electron rich and hence inclined to oxidation under above conditions, therefore it was decided to protect phenolic OH group of compound **8** as its acetate. Thus, acetylation of the compound **8** using acetic anhydride in pyridine afforded acetate **14** in 86% yield. Diastereoselective epoxidation of alkene **14** using *m*-CPBA generated epoxide **7** as a single diastereomer. Due to the bulkyness of aromatic ring of compound **8**, epoxidation exclusively took place from less hindered β side. Epoxide **7** on treating with lithium hydroxide resulted in hydrolysis of acetate groups and the subsequent nucleophilic attack of the phenoxide on epoxide furnishd the tricyclic intermediate **6** in 72% yield over two steps. At this stage, the attempted dehydration of alcohol **6** using Burgess or Martin's sulfurane reagents were unsuccessful (Scheme 3). Finally we relied on Barton's dehydration protocol. Thus, alcohol **6** was converted to corresponding xanthate **15** using NaH, CS_2 and MeI in 87% yield. The xanthate **15** on refluxing in *o*-dichlorobenzene for 36 h afforded the natural product (±)-adunctin B (**2**) in 91% yield (Scheme 4). The spectral data (^1H, ^{13}C, IR and HRMS) of synthetic (±)-adunctin B (**1**) was in complete agreement with the isolated one.[3]

Interestingly, the compound **8** on treatment with $Pd(OAc)_2$, MnO and Et_3N in acetonitrile[13] directly generated adunctin B (**2**) in 81% yield, by nucleophic attack of



Scheme 5. Second generation total synthesis of (±)-adunctin B (2)

phenolic-OH on to the olefin activated by palladium followed by *β*-hydride elimination reaction to generate the requisite double bond, as shown in scheme 5.

In summary, total synthesis of (±)-adunctin B was achieved using two different strategies. Friedel-Crafts acylation enabled one step synthesis of dihydrochalcone **9** from commercially available 5-methoxy resorcinol, which was then converted to adunctin B by catalytic, diastereoselective Friedel-Crafts alkylation, epoxidation and dehydration using Barton's protocol in 6 steps with 23% overall yield. Alternatively, Wacker-type oxidative cyclization reaction was explored to convert alkene **8** into adunctin B in single step, thus reducing the number of steps by fivefold compared to the earlier Yamashita's report. The modular strategy will enable the synthesis of related natural products and various analogues thereof.

EXPERIMENTAL SECTION

General Experimental Methods: 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. 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-TofPremier-HAB213 and Q-Tof-Premier-ESI-MS instruments. Melting points measurements were made using a hot stage apparatus. 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.

1-(2,6-dihydroxy-4-methoxyphenyl)-3-phenylpropan-1-one (**9**): To a magnetically stirred solution of acid **13** (8.57 g, 57.09 mmol) in CH_2Cl_2 (40 mL) was added oxalyl chloride (7.34 mL, 85.6 mmol) dropwise for 15 min. The reaction was stirred at same temperature for additional 15 min and then allowed to come to room temperature. After completion of reaction, indicated by TLC, reaction solvent and excess oxalyl chloride were distilled off by distillation. Reaction mixture again cooled to 0 °C, added CH_2Cl_2 (50 mL), 5-methoxyresorcinol (**10**) (4 g, 28 mmol) and $AlCl_3$ (7.61 g, 57.1 mmol). The reaction was left to slowly warm to room-temperature for overnight. After completion of reaction, indicated by TLC, CH_2Cl_2 was removed with a steady stream of nitrogen. Crushed ice was then added

until the reaction was quenched (*caution*: addition of ice was exothermic). The quenched reaction mixture was then transferred to a separating funnel with EtOAc (200 mL) and was extracted with 1 M HCl (2 × 50 mL) followed by brine (1 × 50 mL). Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:11) as eluent furnished dihydrochalcone **9** (5.4 g, 69%) as a pale yellow solid; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.29 (s, 2H), 7.35 - 7.07 (m, 5H), 5.92 (s, 2H), 3.70 (s, 3H), 3.28 (t, *J* = 7.8 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 205.0, 166.0, 164.5, 142.1, 128.9, 128.8, 126.3, 105.1, 93.8, 55.9, 45.7, 30.6.

(1*R*,5*R*)-5-isopropyl-2-methylcyclohex-2-enol (**11**): To a magnetically stirred solution of carvone (**12**) (5 g, 33.29 mmol) in methanol (50 mL) was added PtO_2 (15 mg, 66.57 µmol) and reaction was continued at same temperature under hydrogen bladder pressure. The reaction was monitored by ^{1}H NMR of crude sample. After completion of reaction (indicated by ^{1}H NMR of crude sample), reaction mixture was filtered through celite pad and concentrated under reduced pressure. To a magnetically stirred solution of above crude compound in MeOH (50 mL) was added $CeCl_3{\cdot}7H_2O$ (1.22 g, 3.3 mmol), cooled to 0 °C. After 10 min, $NaBH_4$ (621 mg, 16.4 mmol) was added portionwise for 5 min and reaction was 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 × 50 mL). Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished alcohol **11** (4.1 g, 81%) as a colourless liquid; R_f = 0.4 (EtOAc-hexane 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.46 (d, *J* = 3.6 Hz, 1H), 4.20 - 4.10 (m, 1H), 2.11 (tdd, *J* = 2.1, 5.9, 11.9 Hz, 1H), 2.00 - 1.90 (m, 1H), 1.77 - 1.69 (m, 1H), 1.73 (s, 3H), 1.53 - 1.37 (m, 2H), 1.16 (dt, *J* = 10.2, 12.2 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.6, 124.7, 71.7, 40.1, 37.4, 32.5, 29.5, 20.0, 19.7, 19.1.

rac-1-(2,6-dihydroxy-3-((1*S*,5*R*)-5-isopropyl-2-methylcyclohex-2-enyl)-4-methoxyphenyl)-3-phenylpropan-1-one (**8**) and *rac*-1-(2,6-dihydroxy-3-((1*R*,5*R*)-5-isopropyl-2-methylcyclohex-2-enyl)-4-methoxyphenyl)-3-phenylpropan-1-one (**8a**): To a magnetically stirred solution of compound **9** (1 g, 3.67 mmol) and **11** (736 mg, 4.77 mmol) in CH_2Cl_2 (20 mL) was added $BF_3{\cdot}OEt_2$ (52 mg, 0.37 mmol) at room temperature. The resulting reaction mixture was stirred at rt for 30 min. After completion of reaction indicated by TLC, the reaction was quenched using saturated solution of Na_2CO_3 (5 mL) and then extracted with CH_2Cl_2 (2 × 15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished (±)-**8** (1.02 g, 68%) as a colourless liquid; R_f = 0.6 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 3337, 2956, 2930, 2870, 1628, 1453, 1206, 1075, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 13.79 (s, 1H), 7.98 (s, 1H), 7.36 - 7.13 (m, 5H), 6.07 (s, 1H), 5.93 (br. s, 1H), 3.83 (s, 3H), 3.76 (br. s., 1H), 3.36 (dt, *J* = 7.6 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.24 (br d, *J* = 18.1 Hz, 1H), 1.98 - 1.90 (m, 1H), 1.72 (s, 3H), 1.68 - 1.62 (m, 2H), 1.51 - 1.40 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.5, 165.5, 164.0, 159.5, 142.3, 136.9, 129.2, 128.9, 128.7, 126.2, 107.8, 105.7, 92.6, 56.2, 46.5, 36.6, 35.5, 34.1, 31.6, 31.1, 29.2, 22.8, 20.5, 19.9; **HRMS**: m/z calcd for $C_{26}H_{31}O_4$ $[M–H]^-$: 407.2228; found: 407.2229. Further elution of the column with EtOAc-hexane (1:49) as eluent furnished (±)-**8a** (170 mg, 11%) as a colourless liquid; R_f = 0.55 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 3339, 2958, 2936, 2869, 1620, 1458, 1200, 1078, 681; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 13.64 (s, 1H), 7.33 - 7.16 (m, 5H), 6.86 (s, 1H), 6.07 (s, 1H), 5.89 (br. d, *J* = 5.1 Hz, 1H), 3.91 (br s, 1H), 3.82 (s, 3H), 3.38 (t, *J* = 8.0 Hz, 2H), 2.99 (t, *J* = 8.0 Hz, 2H), 2.15 (br. d, *J* = 17.4 Hz, 1H), 1.95 - 1.83 (m, 2H), 1.55 (br. s, 3H), 1.52 - 1.42 (m, 2H), 1.30 - 1.22 (m, 1H), 0.89 (d, *J* = 2.9 Hz, 3H), 0.88 (d, *J* = 2.9Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.3, 165.3, 163.5, 158.5, 142.3, 136.1, 128.9, 128.7, 126.2, 108.9, 105.6, 92.6, 56.2, 46.4,

40.6, 36.5, 33.1, 32.6, 30.9, 29.3, 21.4, 20.2, 19.8; **HRMS**: m/z calcd for $C_{26}H_{31}O_4$ $[M–H]^-$: 407.2228; found: 407.2225.

rac-4-((1*S*,5*R*)-5-isopropyl-2-methylcyclohex-2-enyl)-5-methoxy-2-(3-phenylpropanoyl)-1,3-phenylene diacetate (**14**): To a magnetically stirred solution of **8** (400 mg, 979 µmol) in pyridine (2 mL) was added acetic anhydride (370 µL, 3.92 mmol) drop-wise and the resulting mixture was then heated to 80 °C. After completion of reaction, indicated by TLC, the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with saturated $CuSO_4$ solution, brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:19) as eluent furnished **14** (414 mg, 86%) as a colourless liquid; R_f = 0.5 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 2957, 1774, 1695, 1606, 1367, 1191, 1045; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.30 - 7.16 (m, 5H), 6.56 (s, 1H), 5.44 (br. s, 1H), 3.82 (br. s, 3H), 3.80 - 3.60 (br. s, 1H), 3.10 - 3.02 (m, 2H), 2.99 - 2.88 (m, 2H), 2.13 (s, 3H), 2.04 (br. s, 3H), 2.00 - 1.93 (m, 1H), 1.75 (br. s, 2H), 1.59 - 1.54 (m, 1H), 1.43 (br. s, 3H), 1.39 - 1.34 (m, 1H), 1.31 - 1.25 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 200.5, 169.1, 169.0, 159.9, 147.2, 147.0, 141.6, 135.1, 128.8, 128.8, 126.3, 124.5, 121.6, 121.5, 103.2, 56.4, 45.4, 37.7, 34.4, 32.4, 30.1, 29.4, 28.7, 22.6, 21.3, 20.9, 20.8, 14.4; **HRMS**: m/z calcd for $C_{30}H_{37}O_6$ $[M+H]^+$: 493.2585;; found: 493.2593.

rac-1-((5a*S*,6*S*,8*S*,9a*R*)-3,6-dihydroxy-8-isopropyl-1-methoxy-5a-methyl-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-4-yl)-3-phenylpropan-1-one (**6**): To a magnetically stirred solution of the compound **14** (400 mg, 812 µmol) in anhydrous CH_2Cl_2 (5 mL), was added $NaHCO_3$ (34 mg, 0.4 mmol) at 0 °C. After 5 min *m*-CPBA (272 mg, 1.22 mmol) was added and the reaction mixture was stirred for next 30 min. A saturated solution of Na_2SO_3 was added and stirred for additional 15 min at rt, extracted with CH_2Cl_2 and organic layer was

then washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude epoxide as a colourless liquid. To a magnecically stirred solution of above crude epoxide in THF (3 mL), MeOH (3 mL) and water (1.5 mL) was added LiOH (58 mg, 2.43 mmol) at room temperature. After completion of reaction, indicated by TLC, the reaction mixture concentrated under reduced pressure, extracted with ethyl acetate (2 × 5 mL), washed with brine, dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:24) as eluent furnished **6** (250 mg, 72% for 2 steps) as a colourless oil; R_f = 0.5 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 3476 (br.), 2956, 2931, 2870, 1632, 1599, 1413, 1206, 1073, 811, 699; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 - 7.20 (m, 5H), 5.99 (s, 1H), 3.85 - 3.80 (m, 1H), 3.79 (s, 3H), 3.40 (br. s, 1H), 3.35 - 3.23 (m, 2H), 3.03 - 2.96 (t, *J* = 7.7 Hz, 2H), 2.55 (d, *J* = 10.4Hz, 1H), 1.78 (d, *J* = 15.4 Hz, 1H), 1.54 (s, 3H), 1.48 (dd, *J* = 12.9, 6.6 Hz, 1H), 1.28 (dd, *J* = 7.9, 3.4 Hz, 2H), 1.12 - 1.01 (m, 1H), 0.88 (d, *J* = 6.6, 3H), 0.86 (d, *J* = 6.6, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 203.9, 166.2, 162.9, 161.5, 141.7, 128.8, 128.7, 126.4, 108.6, 103.1, 95.0, 92.9, 74.1, 55.8, 47.5, 44.6, 38.6, 34.4, 32.4, 31.2, 27.5, 20.1, 20.0, 18.2; **HRMS**: m/z calcd for $C_{26}H_{33}O_5$ $[M+H]^+$: 425.2323; found: 425.2325.

rac-O-(2*S*,4*S*,4a*S*,9b*R*)-7-hydroxy-2-isopropyl-9-methoxy-4a-methyl-6-(3-phenylpropanoyl)-1,2,3,4,4a,9b-hexahydrodibenzo[b,d]furan-4-yl *S*-methyl carbonodithioate (**15**): To a magnetically stirred solution of **6** (150 mg, 353 µmol) in anhydrous THF (2 mL), cooled to 0 °C, was added NaH (28 mg, 706 µmol). The reaction mixture was stirred at same temperature for 30 min, then added CS_2 (42 µL, 706 µmol) and stirred for additional 15 min, followed by addition of MeI (43 µL, 706 µmol) and stirred at same temperature. After completion of reaction, indicated by TLC, the reaction mixture concentrated under reduced pressure, extracted with ethyl acetate (2 × 5 mL), washed with brine, dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:24)

as eluent furnished xanthate **15** (158 mg, 87%) as a colourless oil; R_f = 0.4 (EtOAc-hexane 1:9); **IR** (neat): ν_{max}/cm^{-1} 2956, 2932, 2867, 1631, 1600, 1369, 1218, 1205, 1056, 811; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 13.34 (s, 1H), 7.28 - 7.17 (m, 5H), 6.02 (s, 1H), 5.91 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.81 (s, 3H), 3.49 - 3.42 (m, 1H), 3.26 - 3.17 (m, 2H), 2.97 - 2.92 (m, 2H), 2.62 (dd, *J* = 13.2, 2.3 Hz, 1H), 2.41 (s, 3H), 2.04 - 1.96 (m, 1H), 1.65 (s, 3H), 1.53 - 1.49 (m, 1H), 1.42 - 1.33 (m, 2H), 1.26 - 1.21 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 215.8, 203.9, 166.3, 162.6, 161.2, 141.8, 128.7, 128.6, 126.1, 107.8, 103.1, 93.2, 92.5, 85.1, 55.8, 48.3, 44.3, 38.0, 32.3, 31.3, 30.4, 27.1, 20.1, 19.8 (2C), 19.2; **HRMS**: m/z calcd for $C_{28}H_{35}O_5S_2$ $[M+H]^+$: 515.1926; found: 515.1921.

(±)-adunctin B (**2**): A magnetically stirred solution of xanthate **15** (100 mg, 194 μmol) was refluxed in *o*-dichlorobenzene. After completion of reaction indicated by TLC, concentrated under reduced pressure and purification of the residue on silica gel column using EtOAc-hexane (1:29) as eluent furnished (±)-adunctin B (**2**) (72 mg, 91%) as a white solid; R_f = 0.5 (EtOAc-hexane 1:9); **M.p.**: 63-65 °C; **IR** (neat): ν_{max}/cm^{-1} 2957, 2925, 2853, 1728, 1629, 1600, 1444, 1268, 1206, 1148, 1060, 811, 698; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.37 (br. s, 1H), 7.33 - 7.18 (m, 5H), 5.98 (s, 1H), 5.86 (dd, *J* = 10.1, 2.3 Hz, 1H), 5.61 (dd, *J* = 10.1, 2.3 Hz, 1H), 3.82 (s, 3H), 3.41 (t, *J* = 4.6 Hz, 1H), 3.29 (t, *J* = 7.7 Hz, 2H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.27 (dt, *J* = 13.4, 4.7 Hz, 1H), 1.91 - 1.87 (m, 1H), 1.64 - 1.58 (m, 2H), 1.57 (s, 3H), 0.89 (d, *J* = 4.6 Hz, 3H), 0.90 (d, *J* = 4.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 203.7, 165.8, 162.6, 161.6, 141.5, 135.3, 129.2, 128.4 (2C), 125.9, 107.8, 102.4, 92.1, 89.0, 55.5, 44.3, 44.1, 38.0, 31.4, 30.9, 26.4, 26.0, 19.8, 19.6; **HRMS**: m/z calcd for $C_{26}H_{31}O_4$ $[M+H]^+$: 407.2217; found: 407.2224.

Alternate route: To a magnetically stirred solution of the compound **8** (100 mg, 244 μmol) in anhydrous acetonitrile (2 mL), was added triethyl amine (68 μL, 489 μmol), MnO (52 mg,

734 µmol) and $Pd(OAc)_2$ (5.5 mg, 24.4 μmol) at rt. The reaction mixture then stirred at same temperature for 3 h. After completion of reaction, indicated by TLC, the reaction mixture was filtered through celite pad, washed with EtOAc. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished (±)-adunctin B (**2**) (81 mg, 81%) as a white solid.

(Note: Prolonged reaction time (>3 h) results in the isomerization of double bond.)

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Details of the characterization data for all new compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENT

B.D.D. thanks CSIR, New Delhi for the award of research fellowship. Financial support from CSIR, New Delhi (Project No. CSIR/CHM/2016336) is gratefully acknowledged.

REFERENCES

(1) Macedo, J. C. B.; Oviedo, **S.** G. *Bol.* Soc. *Quim. Peru* **1987**, 53, 228.

(2) Diaz, P. P.; Maldonado, E.; Ospina, E. *Rev. Latinoam. Quim.* **1984**, *15*, 136.

(3) Orjala, J.; Wright, A. D.; Erdelmeier, C. A. J.; Sticher, O.; Rali, T. *Helv. Chim. Acta*. **1993**, *76*, 1481.

(4) Ichino, K. *Phytochemistry* **1989**, *28*, 955.

(5) (a) Arimitsu, K.; Nomura, S.; Iwasaki, H.; Ozeki, M.; Yamashita, M. *Tetrahedron Lett.* **2011**, *52*, 7046; (b) Nomura, S.; Arimitsu, K.; Yamaguchi, S.; Kosuga, Y.; Kakimoto, Y.; Komai, T.; Hasegawa, K.; Nakanishi, A.; Miyoshi, T.; Iwasaki, H.; Ozeki, M.; Kawasaki, I.; Kurume, A.; Ohta, S.; Yamashita, M. *Chem. Pharm. Bull.* **2012**, *60*, 94.

(6) Dethe, D. H.; Dherange, B. D. *J. Org. Chem.* **2015**, *80*, 4526.

(7) (a) Chen, Y.-H.; Wang, W.-H.; Wang, Y.-H.; Lin, Z.-Y.; Wen, C.-C.; Chern, C.-Y. *Molecules* **2013**, *18*, 2052. (b) Ali, M. A.; Kondo, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1130.

(8) Kitahara, T; Kurata, H; Matsuoka, T; Mori, K. **1985**, *41*, 5475.

(9) Nugent, J.; Matousova, E.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2017**, *82*, 12569.

(10) Bosch, E.; Kochi, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 1319.

(11) Lane, B. S.; Vogt, M.; DeRose, V. J.; Burgess, K. *J. Am. Chem. Soc.* **2002**, *124*, 11946.

(12) Bhaduri, S.; Khwaja, H.; Khanwalkar, V. *J. Chem. Soc., Dalton Trans.* **1982**, 445.

(12) (a) Pearson, A. J.; Hsu, S.-Y. *J. Org. Chem.* **1986**, *51*, 2505. (b) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045.

(13) (a) Takahiro, H.; Shinji, Y.; Shun-Ichi, M.; Akio, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3662. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.*, **1978**, *100*, 5800. (c) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2892.