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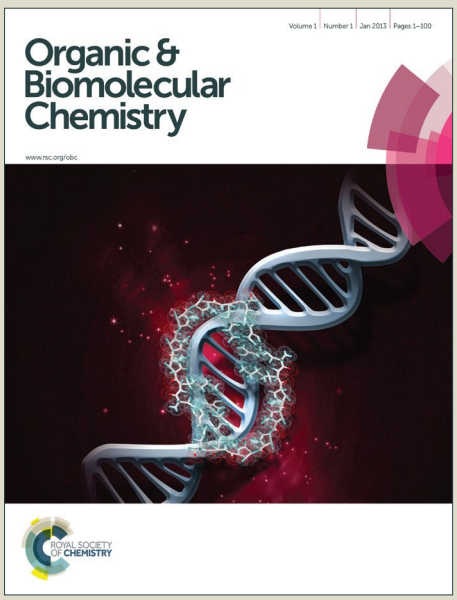

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Chemoenzymatic collective synthesis of optically active hydroxyl(methyl)tetrahydronaphthalene-based bioactive terpenoids†

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Starting from succinic anhydride and 2-methylanisole chemoenzymatic collective formal/total synthesis of several optically active tetrahydronaphthalene based bioactive natural products has been presented via advanced level common precursors; the natural product and antipode (–)/(+)-aristelegone B. Regioselective benzylic oxidations, stereoselective introduction of hydroxyl groups at the *α*-position of ketone moiety in *syn*-orientation, efficient enzymatic resolutions with high enantiomeric purity, stereoselective reductions, samarium iodide induced deoxygenations and tandem acylation-Wittig reactions; without racemization and/or eliminative aromatization were the key features. An attempted diastereoselective synthesis of (±)-vallapin has also been described.

Introduction

A large number of hydroxyl(methyl)tetrahydronaphthalene and methoxy(methyl)tetrahydronaphthalene class of natural products with broad range of biological activities have been known (Fig. 1).[1] Nature designs them starting from either farnesyl pyrophosphate or geranyl pyrophosphate via intramolecular cyclizations involving 1,2- and 1,3-hydride shifts followed by a regioselective oxidation pathway.[2] A postulated biogenetic transformation of farnesyl pyrophosphate to the potential precursor 7-hydroxycalamene with an appropriate fixing of positions of both methyl and hydroxyl/methoxy groups has been depicted in scheme 1. In a biogenetic process the fifteen carbon bearing crucial intermediate 7-hydroxycalamene further undergoes several requisite functional group transformations in a stereoselective fashion with or without the loss of isopropyl group, thus delivering a variety of enantiomerically pure bioactive natural products bearing twelve/fifteen carbon skeletons (Scheme 1). The (+)-aristelegone A, (–)-aristelegone B and (–)-aristelegone D have been isolated from *Aristolochia elegans*; while (+)-methylaristelegone A (antispasmodic) has been isolated from *Aristolochia constricta*.[3] The (+)-heritonin (toxic to fish), (+)-heritol (toxic to fish) and (–)-vallapin (pesticide) have been isolated from *Heritiera littoralis* and (+)-mutisianthol (antitumor) has been isolated from *Mutisia homoeantha*.[1e,4] The (–)-7-methoxy-1,2-dihydrocadalene and (–)-7-methoxycalamenene have been isolated from *Heteroscyphus planus* culture.[5] Several elegant product specific racemic as well as enantioselective total synthesis of above specified natural products have been reported;[6–10] except for the aristelegone D, 7-methoxy-1, 2-dihydrocadalene and vallapin. The science of collective total synthesis of bioactive natural products is very important for structure activity relationship studies

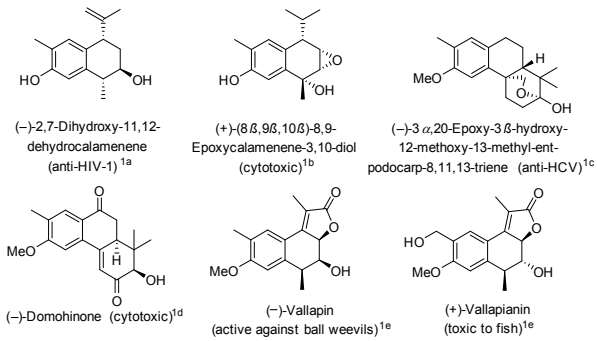

Fig. 1 Hydroxyl/methoxy(methyl)tetrahydronaphthalene based bioactive natural products.

from lead optimization and drug discovery point of view.[11] The substituted methoxy(methyl)tetrahydronaphthalene based compounds have very high propensity towards instantaneous oxidation, elimination and enolization processes due to the facile stability driven aromatizations and hence synthesis of such type of target compounds is a challenging task.[12] A concise retrosynthetic analysis of natural products portrayed in scheme 1 revealed that the 7-methoxy-6-methyltetralone would be a potential precursor to accomplish both racemic and chemoenzymatic collective total synthesis of all selected target compounds. In continuation with our studies on both cyclic anhydrides and derivatives to bioactive natural products[13] and efficient enzymatic resolutions,[14] we herein report the collective formal/total synthesis of nine optically active natural products (Schemes 1–4) and an attempted diastereoselective synthesis of (±)-vallapin via alternatively designed *β*-hydroxytetralone intermediate (Scheme 5).

Results and discussion

The 2-methylanisole (**1**) on Friedel-Crafts acylation with succinic anhydride (**2**) followed by Clemmensen reduction and acid-promoted intramolecular cyclization provided desired tetralone **3** in 62% yield over 3-steps (Scheme 2).[9a] Tetralone **3** on Wittig reaction exclusively formed the *exo*-methylene product **4** in 74% yield which

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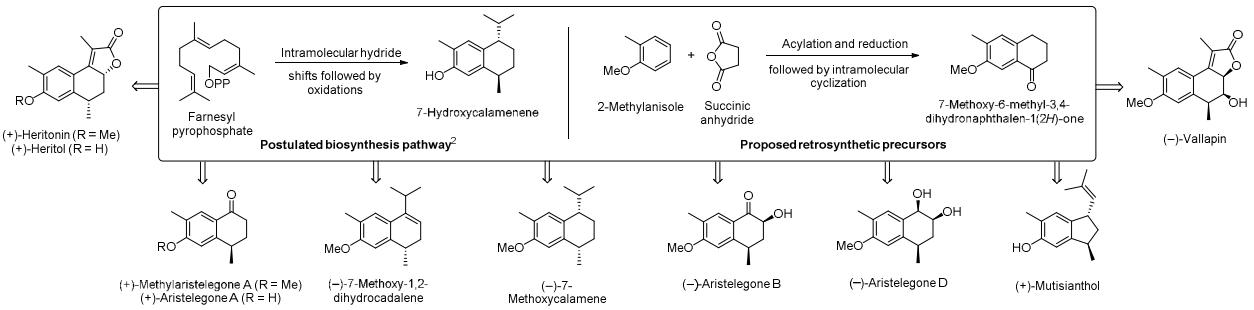
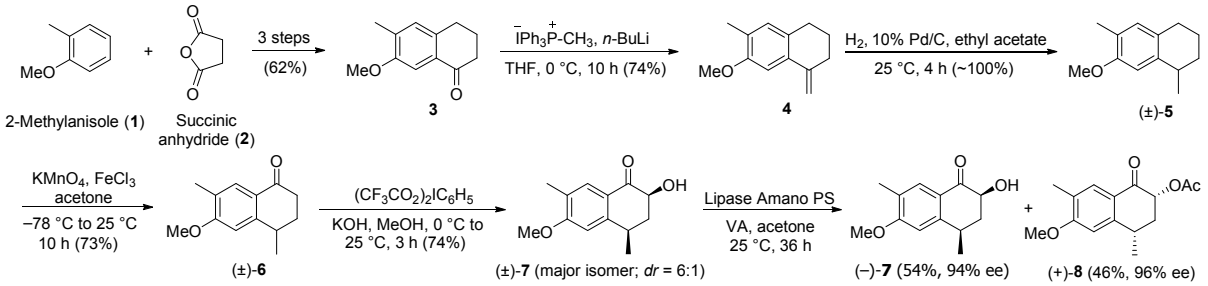


Scheme 1 Postulated brief biogenesis and proposed retrosynthetic precursors of the selected bioactive terpenoids.



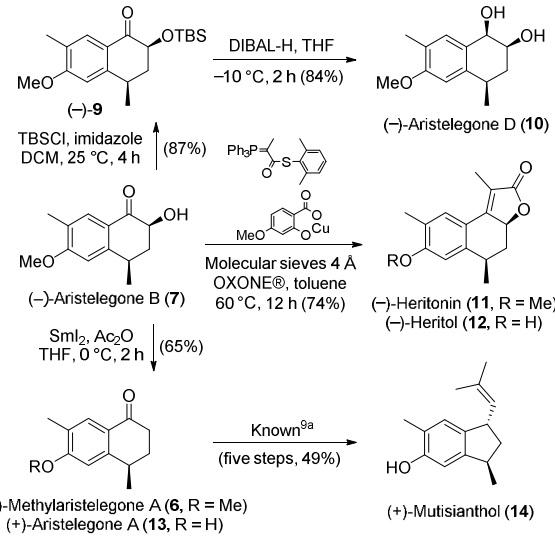
Scheme 2 Diastereoselective synthesis of the common precursor (±)-aristelegone B (**7**) and its efficient enzymatic resolution.

Table 1 Lipase Amano PS catalyzed resolution of (±)-aristelegone B (**7**)

entry	solvent	temp. (time)[a]	(–)-**7**: % yield (*ee*)[b]	(+)-**8**: % yield (*ee*)[b]	*E*
1	Benzene	25 °C (48 h)	42 (77)	48 (68)	12.0
2	Benzene-PE (1:1)	25 °C (48 h)	51 (67)	49 (50)	5.8
3	Acetone	25 °C (24 h)	67 (65)	33 (96)	96.7
4	Acetone	25 °C (36 h)	54 (94)	46 (96)	175.8
5	Acetone	25 °C (48 h)	49 (97)	51 (91)	89.0

[a] Reactions were monitored by HPLC; [b] chiral HPLC.

on catalytic hydrogenation over palladium on charcoal delivered the reduced product (±)-**5** in quantitative yield. $KMnO_4/FeCl_3$ promoted regioselective benzylic oxidation of (±)-tetrahydronaphthalene **5** furnished the (±)-methylaristelegone A (**6**) in 73% yield. Hypervalent iodine reagents are known to afford *α*-ketols with *α*-hydroxyl group attached to the more sterically hindered face of an enolate and mechanistically it takes place via the inversion of configuration.[7] Accordingly the base induced stereoselective *α*-hydroxylation of (±)-tetralone **6** with (bis(trifluoroacetoxy)iodo)benzene resulted into (±)-aristelegone B (**7**) as a desired major product (74%, *dr* = 6:1, by ^{1}H NMR). As represented in Table 1, we systematically studied the lipase Amano PS catalyzed stereoselective acylation of (±)-aristelegone B (**7**) using vinyl acetate (VA) as an acyl donor and obtained the optically active natural product (–)-aristelegone B (**7**) in 54% yield (94% *ee*, by HPLC) and (+)-acylaristelegone B (**8**) in 46% yield (96% *ee*, by HPLC). The obtained stereochemical outcome was further confirmed by comparison with reported analytical and spectral data for natural product (–)-**7**.[3a] Typically, synthesis of a natural product starting from the natural product belonging to same genesis are more concise, efficient and involve minimum protection-deprotection steps. The twelve carbon skeleton of naturally occurring aristelegone B bears well placed substituents



Scheme 3 Collective synthesis of enantiomerically pure terpenoids from (–)-aristelegone B (**7**).

and essential functional groups; hence it was planned to use (±)/(+)/(–)-**7**/**8** as pivotal building blocks to accomplish racemic/chiral pool based/stereoselective collective synthesis of target compounds from scheme 1.

The free hydroxyl group in (–)-aristelegone B (**7**) was initially protected as –OTBS to avoid its direct interaction with aluminium from DIBAL-H and also to increase the steric bulk of *β*-face to favor a hydride attack from an anticipated less hindered *α*-face (Scheme 3). TBS-protected (–)-hydroxytetralone **9** on DIBAL-H reduction directly delivered the natural product (–)-aristelegone D (**10**) in 84% yield. TLC results of above reaction clearly indicated that *O*-desilylation takes place during the workup procedures. The analytical and spectral data obtained for synthetic product was in

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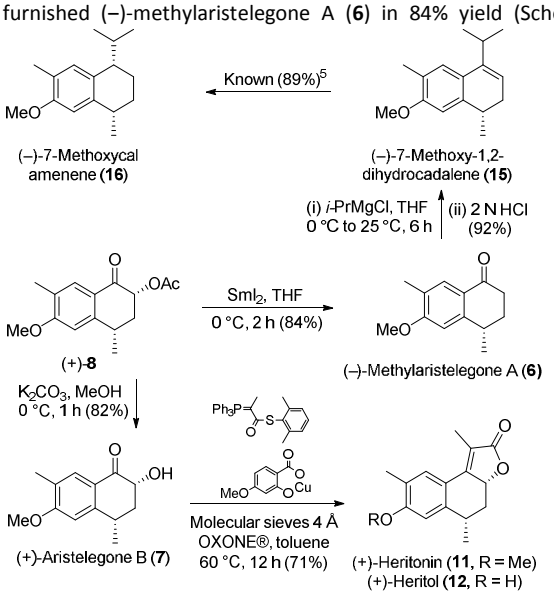
complete agreement with reported data for natural product[3a] and the chemoenzymatic first synthesis of (–)-aristelegone D (**10**) was accomplished in ten steps with 8% overall yield. (–)-Aristelegone B (**7**) underwent a smooth tandem acylation-Wittig reaction under the recently reported Matsuo and Shindo conditions[8b] and furnished an aimed product (–)-heritonin (**11**) in 74% yield (93% *ee*, by HPLC) via intramolecular cyclization. The above mentioned tandem acylation-Wittig reaction was moisture sensitive. Therefore freshly dried reagents were used under perfectly anhydrous reaction conditions to obtain the desired product in very good yield. It is noteworthy that starting material *α*-hydroxyketone, in situ formed corresponding *α*-acylated-ketone intermediate and the obtained product *γ*-lactone all three bear a sufficiently acidic methine proton; however the reaction was very clean and delivered the final product (–)-heritonin (**11**) without any racemization. The obtained analytical and spectral data for (–)-heritonin (**11**) was in complete agreement with reported data[8b,c] and it was synthesized in nine steps with 8% overall yield. $AlCl_3$ induced transformation of (–)-heritonin (**11**) to (–)-heritol (**12**) in 80% yield is known.[8c] The *α*-hydroxyl group was diastereoselectively introduced on (±)-methylaristelegone A (**6**) to use it as a handle for efficient enzymatic resolution and also as an appropriate functional group. Samarium iodide persuaded post resolution detachment of hydroxyl group in (–)-aristelegone B (**7**) via the corresponding acetate formed (+)-methylaristelegone A (**6**) in 65% yield. (+)-Methylaristelegone A (**6**) on treatment with BBr_3 provided (+)-aristelegone A (**13**) in 74% yield. Starting from (+)-methylaristelegone A (**6**), three-step synthesis of (–)-heritonin (**11**) via Reformatsky reaction and five-step synthesis of (+)-mutisianthol (**14**) via thallium(III) trinitrate catalyzed ring contraction pathways are well known.[8c,9a]

At this stage it was also decided to use the second enantiomerically pure building block (+)-**8** obtained in enzymatic resolution for synthesis of natural products. The samarium iodide influenced detachment of acetoxy group in compound (+)-**8** furnished (–)-methylaristelegone A (**6**) in 84% yield (Scheme 4).



Scheme 4 Synthesis of (–)-7-Methoxy-1,2-dihydrocadalene (**15**), (–)-7-Methoxycalamenene (**16**) and (+)-Heritonin (**11**).

Reaction of isopropylmagnesium bromide with (–)-methylaristelegone A (**6**) followed by acid catalyzed in situ dehydration of the formed intermediate tertiary alcohol yielded another natural product (–)-7-methoxy-1,2-dihydrocadalene (**15**) in 92% yield. The analytical and spectral data obtained for synthetic product was in complete agreement with reported data for natural product[5] and the chemoenzymatic first synthesis of (–)-7-methoxy-1,2-dihydrocadalene (**15**) was accomplished in ten steps with 8% overall yield. An enantioselective reduction of the actually isolated natural product (–)-**15** to form yet another natural product (–)-7-methoxycalamenene (**16**) is known.[5] Base-induced de-acylation of compound (+)-**8** to form (+)-aristelegone B (**7**) followed by its similarly performed tandem acylation-Wittig reaction provided the natural product (+)-heritonin (**11**) in 71% yield.

In the next part of study, chemoenzymatic total synthesis of (–)-vallapin (**27**) was initially planned again from same common precursor tetralone **3**. Tetralone **3** on treatment with $KMnO_4$/AcOH[15] in refluxing benzene furnished the required *α*-acetoxyketone (±)-**17** in 70% yield (Scheme 5). The ketone (±)-**17** on Wittig reaction exclusively formed yet another *exo*-methylene product (±)-**18** in 67% yield. As represented in Table 2, we also systematically studied the lipase Amano PS catalyzed stereoselective hydrolysis of acetate (±)-**18** and obtained the optically active products (+)-**18** in 44% yield (92% *ee*, by HPLC) and (+)-**19** in 56% yield (89% *ee*, by HPLC). Tentative stereochemical assignment of (+)-**18** and (+)-**19** was done on the basis of known Amano PS selectivity.[14] Anticipating high propensity of such type of substituted tetralone systems to aromatize and also from starting material availability point of view; it was essential to first standardize all reaction conditions and complete the diastereoselective synthesis of our target compound. Hydrolysis of acetate (±)-**18** to the corresponding alcohol (±)-**19** followed by TBDPS-protection provided silyl ether (±)-**20** in 78% yield over two steps. Diastereoselective reduction of exocyclic carbon–carbon double bond in compound (±)-**20** delivered the *syn*-disubstituted tetrahydronaphthalene (±)-**21** in ~100% isolated yield (*dr* = 9:1, by ^{1}H NMR). The bulk of –OTBDPS group in (±)-**20** directs *π*-lobes adsorption on palladium catalyst from opposite face to form the desired *cis*-isomer as a major product. Regioselective CrO_3 oxidation of benzylic methylene group in tetrahydronaphthalene (±)-**21** furnished the expected tetralone (±)-**22** in 66% yield. Fortunately during the course of CrO_3 oxidation in acetic acid we did not notice any desilylation and concomitant aromatization. The studied Wittig reaction of tetralone (±)-**22** to obtain product (±)-**24** and Reformatsky reaction of tetralone (±)-**22** to obtain (±)-**25** were unfortunately not successful (Fig. 2). An attempted Reformatsky reaction on (±)-**22**, instead formed the corresponding aromatized product **23** in 68% yield. An attempted desilylation of (±)-**22** also resulted in formation of same aromatized product **23** with 63% yield plausibly via the corresponding unstable *β*-hydroxyketone intermediate. Selective introduction of oxygen function on tetralone (±)-**22** by using $KMnO_4$/CH_3CH_2COOH in refluxing benzene offered the expected product (±)-**26** but in less than 10% yield. The well functionalized product (±)-**26** was very unstable and hence we could cautiously characterize an isolated crude product only by using ^{1}H NMR and HRMS data. We feel that much milder reaction conditions will be required to transform tetralone (±)-**22** or other similar type of intermediates to the desired target compound (±)-vallapin and it remains as a synthetic challenge.

Conclusions

In summary, we have described facile chemoenzymatic collective total synthesis of several tetrahydronaphthalene based optically active terpenoids. The late stage efficient enzymatic resolution

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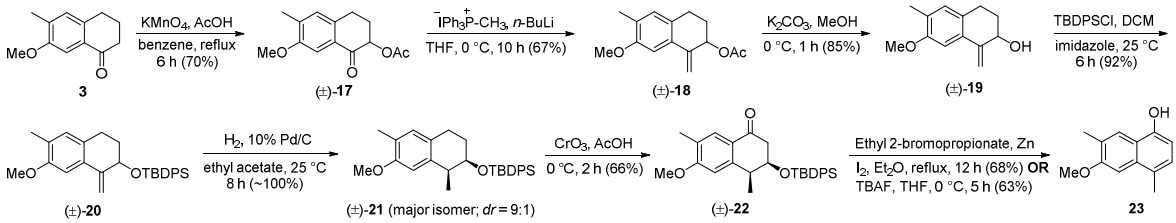
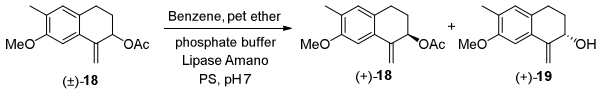


Scheme 5 Attempted diastereoselective synthesis of vallapin (**27**).

Table 2 Lipase Amano PS catalyzed resolution of (±)-acetate **18**



entry	temp. (time)[a]	(+)-18: % yield (*ee*)[b]	(+)-19: % yield (*ee*)[b]	*E*
1	35 °C (96 h)	55 (79)	45 (95)	94.6
2	40 °C (72 h)	55 (80)	45 (100)	497.0
3	45 °C (24 h)	54 (88)	46 (100)	590.3
4	45 °C (48 h)	44 (92)	56 (89)	56.2

[a] Reactions were monitored by HPLC; [b] chiral HPLC

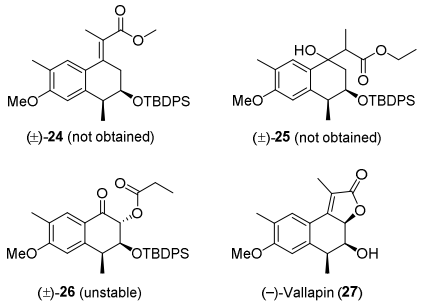


Fig. 2 Expected products from tetralone (±)-**22** for the synthesis of vallapin (**27**).

provides access to both (+)/(−)-isomers as potential building blocks. Remarkably stereoselective reactions were performed to accomplish the synthesis of several natural products from one single common precursor aristelegone B. Multistep total synthesis of both (+)-heritonin and (−)-heritonin have been accomplished and all synthetic pathways described herein will also be useful to mirror the total synthesis of their respective antipodes. Unfortunately all our attempts to complete first total synthesis of (±)-vallapin met with failure due to the inherent instability of advanced *β*-hydroxytetralone intermediate.

Experimental section

General information

Melting points are uncorrected. The IR spectra were recorded on an FT-IR spectrometer. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR, 500 MHz NMR and 700 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz), 500 NMR (125 MHz) and 700 MHz NMR (175 MHz) spectrometers. Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. Column chromatographic separations were carried out on silica gel (60–120 mesh and 230–400 mesh). Commercially available 2-methylanisole, methyltriphenylphosphonium iodide, $PhI(OCOCF_3)_2$, vinyl acetate, TBSCl, DIBAL-H, molecular sieves 4 Å, OXONE®, samarium diiodide solution (0.10 M in THF), boron tribromide solution (1 M in DCM), acetic anhydride, TBDPSCl, ethyl 2-bromopropionate, tetrabutylammonium fluoride solution and Zn metal were used. Amano PS enzymes form Amano Enzyme Japan and Sigma-Aldrich were used.

7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(*2H*)-one (3). Mp 54–55 °C; IR ($CHCl_3$) ν_{max} 1668, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 (quintet, J = 6 Hz, 2H), 2.25 (s, 3H), 2.60 (d, J = 8 Hz, 1H), 2.64 (d, J = 6 Hz, 1H), 2.86 (t, J = 6 Hz, 2H), 3.86 (s, 3H), 7.02 (s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 23.5, 28.7, 38.7, 55.3, 106.6, 130.7, 131.2, 133.6, 136.9, 156.5, 198.1; ESIMS (*m*/*z*) 191 $[M+H]^+$.

7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalene (4). To a stirred solution of methyltriphenylphosphonium iodide (8.01 g, 19.72 mmol) in anhydrous THF (35 mL) was added a solution of *n*-BuLi (12.33 mL, 19.72 mmol, 1.60 M in hexane) in dropwise fashion at 0 °C under argon atmosphere and the reaction mixture was stirred for 30 min. A solution of compound **3** (2.50 g, 13.14 mmol) in THF (10 mL) was added to the above reaction mixture at 0 °C and it was further stirred for 10 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (100 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:19) as an eluent afforded product **4** as viscous oil (1.83 g, 74%). IR ($CHCl_3$) ν_{max} 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.79 (quintet, J = 6 Hz, 2H), 2.12 (s, 3H), 2.40–2.50 (m, 2H), 2.68 (t, J = 6 Hz, 2H), 3.77 (s, 3H), 4.85 (s, 1H), 5.35 (s, 1H), 6.81 (s, 1H), 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 24.1, 29.5, 33.3, 55.3, 105.0, 106.6, 126.9, 129.3, 131.2, 132.8, 143.8, 156.0; ESIMS (*m*/*z*) 189 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O$ 189.1274, found 189.1272.

(±)-7-Methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene (5). To a stirred solution of compound **4** (1.50 g, 7.97 mmol) in ethyl acetate (25 mL) was added 10% Pd/C (50 mg) at 25 °C and the reaction mixture was subjected to hydrogenation under balloon pressure for 4 h. The reaction mixture was filtered through Celite bed and washed with ethyl acetate. The concentration of the filtrate in vacuo furnished pure product (±)-**5** as viscous oil (1.51 g, ~100%). IR ($CHCl_3$) ν_{max} 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (d, J = 8 Hz, 3H), 1.40–2.00 (m, 4H), 2.18 (s, 3H), 2.68 (t, J = 6 Hz, 2H), 2.90 (sextet, J = 6 Hz, 1H), 3.83 (s, 3H), 6.68 (s, 1H), 6.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.6, 23.0, 29.0, 31.6, 32.6, 55.4, 109.6, 124.0, 128.3, 131.1, 140.3, 155.8; ESIMS (*m*/*z*) 213 $[M+Na]^+$.

(±)-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (6). To a stirred solution of (±)-**5** (1.50 g, 7.88 mmol) in acetone (30 mL) were added $KMnO_4$ (12.46 g, 78.80 mmol) and $FeCl_3$ (3.20 g, 19.70

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mmol) and the reaction mixture stirred at −78 °C under argon atmosphere for 1 h. The reaction mixture was allowed to warm gradually to 25 °C and further stirred for 10 h. The resulting suspension was diluted with dichloromethane (30 mL), filtered and the residue was washed with dichloromethane (10 mL × 2). The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded product (±)-**6** as a white solid (1.17 g, 73%). Mp 108–109 °C; IR ($CHCl_3$) ν_{max} 1667, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40 (d, J = 6 Hz, 3H), 1.75–2.00 (m, 1H), 2.10–2.35 (m, 1H), 2.20 (s, 3H), 2.40–2.85 (m, 2H), 2.95–3.15 (m, 1H), 3.90 (s, 3H), 6.68 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.7, 20.8, 30.7, 33.0, 35.8, 55.4, 107.6, 124.8, 125.4, 129.6, 149.4, 162.2, 197.4; ESIMS (m/z) 205 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ 205.1223, found 205.1224.

(±)-2-Hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Aristelegone B, 7). A solution of the ketone (±)-**6** (1.10 g, 5.39 mmol) and KOH (3.02 g, 53.90 mmol) in MeOH (25 mL) was stirred at 0 °C under argon atmosphere for 10 min and $PhI(OCOCF_3)_2$ (2.78 g, 6.47 mmol) was added to the reaction mixture. It was stirred at the same temperature for 1 h and at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the obtained residue was dissolved in diethyl ether (50 mL). The organic layer was washed with sat. $NaHCO_3$, brine and dried over Na_2SO_4. The obtained product was purified by silica gel (230–400 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to afford the major product (±)-**7** as a white solid (0.75 g, 63%). Mp 102–103 °C; IR ($CHCl_3$) ν_{max} 3466, 1674, 1606 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46 (d, J = 8 Hz, 3 H), 1.76 (dd, J = 26 and 14 Hz, 1H), 2.22 (s, 3H), 2.49 (ddd, J = 12, 4 and 4 Hz, 1H), 3.16 (septet, J = 6 Hz, 1H), 3.92 (s, 3H), 3.95 (d, J = 2 Hz, 1H), 4.34 (ddd, J = 14, 4 and 2 Hz, 1H), 6.78 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.5, 31.6, 40.8, 55.5, 72.9, 107.0, 121.7, 126.1, 129.7, 149.0, 162.9, 198.5; ESIMS (m/z) 243 $[M+Na]^+$.

Amano PS Catalyzed Resolution of (±)-2-Hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (7). To a stirred solution of (±)-2-hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (**7**) (700 mg, 3.18 mmol) and vinyl acetate (1.35 g, 15.90 mmol) in acetone (20 mL) was added the enzyme Amano PS (50 mg, Sigma-Aldrich). The resulting reaction mixture was stirred at 25 °C for 36 h with monitoring the reaction progress by HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (30 mL). The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–dichoromethane (1:99) as an eluent afforded pure product (+)-**8** as viscous oil (383 mg, 46%) and (−)-**7** as a white solid (378 mg, 54%).

(+)-8: $[\alpha]^{25}_D$ +30.6 (*c* 0.20 $CHCl_3$, 96% *ee*); IR ($CHCl_3$) ν_{max} 1741, 1688, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.47 (d, J = 6 Hz, 3H), 2.00 (dd, J = 26 and 12 Hz, 1H), 2.21 (s, 3H), 2.23 (s, 3H), 2.37 (td, J = 12 and 8 Hz, 1H), 3.24 (septet, J = 6 Hz, 1H), 3.92 (s, 3H), 5.52 (dd, J = 12 and 8 Hz, 1H), 6.75 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.5, 20.9, 32.1, 38.0, 55.5, 74.0, 106.7, 124.0, 126.1, 130.0, 147.7, 162.7, 170.4, 192.2; ESIMS (m/z) 263 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ 263.1278, found 263.1273.

(−)-Aristelegone B (7): Mp 103–104 °C [lit. 103 °C][8g]; $[\alpha]^{25}_D$ −28.9 (*c* 0.14 $CHCl_3$, 94% *ee*); the obtained spectroscopic data was identical with the data for (±)-**7**.

(−)-(2*S*,4*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (9). To a stirred solution of alcohol (−)-**7** (50 mg, 0.22 mmol) in dichloromethane (5 mL) were added imidazole (18 mg, 0.26 mmol) and TBSCl (40 mg, 0.26 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and further stirred for 4 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:19) as an eluent afforded pure product (**−**)-**9** as viscous oil (66 mg, 87%). $[\alpha]^{25}_D$ −64.1 (*c* 0.10 $CHCl_3$); IR ($CHCl_3$) ν_{max} 1689, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 3H), 0.23 (s, 3H), 0.95 (s, 9H), 1.44 (d, J = 8 Hz, 3H), 1.94 (q, J = 12 Hz, 1H), 2.19 (s, 3H), 2.29 (td, J = 12 and 8 Hz, 1H), 3.12 (septet, J = 8 Hz, 1H), 3.89 (s, 3H), 4.35 (dd, J = 12 and 4 Hz, 1H), 6.73 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.4, −4.3, 15.7, 18.6, 20.7, 25.9, 32.4, 42.0, 55.4, 74.9, 106.7, 124.4, 125.8, 129.9, 147.9, 162.2, 197.0; ESIMS (m/z) 357 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{31}O_3Si$ 335.2037, found 335.2031.

(−)-(1*R*,2*S*,4*R*)-6-Methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene-1,2-diol (Aristelegone D, 10). To a stirred solution of (−)-**9** (50 mg, 0.15 mmol) in THF (4 mL) was added DIBAL solution (0.16 mL, 0.16 mmol, 1 M in hexane) in dropwise fashion at −10 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with saturated NH_4Cl solution and the reaction mixture was concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:3) as an eluent afforded pure product (**−**)-**10** as a white solid (28 mg, 84%). Mp 124–125 °C [lit. 126–127 °C][3a]; $[\alpha]^{25}_D$ −67.8 (*c* 0.27 $CHCl_3$) {lit. $[\alpha]^{25}_D$ −70.6 (*c* 0.017 $CHCl_3$)}[3a]; IR ($CHCl_3$) ν_{max} 3430, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 8 Hz, 3H), 1.72 (q, J = 12 Hz, 1H), 1.85–2.05 (m, 1H), 2.00–2.60 (br s, 2H), 2.20 (s, 3H), 2.90 (septet, J = 2 Hz, 1H), 3.84 (s, 3H), 3.89 (td, J = 12 and 4 Hz, 1H), 4.63 (d, J = 2 Hz, 1H), 6.75 (s, 1H), 7.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 21.4, 32.5, 35.0, 55.3, 69.7, 70.2, 107.7, 125.4, 127.8, 132.7, 139.9, 158.2; ESIMS (m/z) 245 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_3$ 221.1172, found 221.1172.

(−)-(3a*S*,5*R*)-7-Methoxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3a*H*)-one (Heritonin, 11). To a stirred solution of the (−)-aristelegone B (**7**) (88 mg, 0.40 mmol) in toluene (4 mL) was added Cu(II) catalyst (5 mol %), Wittig reagent (272 mg, 0.60 mmol), molecular sieves 4 Å (200 mg, 500 mg/mmol) and OXONE® (369 mg, 1.20 mmol) under argon atmosphere. The reaction mixture was stirred at 60 °C for 12 h until disappearance of the starting material, then xylene (6 mL) was added to the reaction mixture and the whole reaction mixture was stirred at 138 °C for 1 h. The reaction mixture was allowed to reach 25 °C, filtered through Celite bed and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel (60–120) column chromatographic purification using ethyl acetate–petroleum ether (1:19) as an eluent to afford pure product (**−**)-**11** as a white solid (76 mg, 74%). Mp 110–112 °C [lit. 115–116 °C][8c]; $[\alpha]^{25}_D$ −299.2 (*c* 0.25 $CHCl_3$, 93% *ee*) {lit. $[\alpha]^{25}_D$ −312.97 (*c* 1.3 $CHCl_3$)}[8c]; IR ($CHCl_3$) ν_{max} 1738, 1651, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 1.46 (d, J = 7 Hz, 3H), 1.48 (q, J = 14 Hz, 1H), 2.14 (s, 3H), 2.25 (s, 3H), 2.64 (dt, J = 14 and 7 Hz, 1H),

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3.14 (septet, *J* = 7 Hz, 1H), 3.89 (s, 3H), 4.92 (dd, *J* = 14 and 7 Hz, 1H), 6.86 (s, 1H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 9.9, 16.0, 21.7, 32.0, 38.7, 55.3, 78.1, 108.4, 115.9, 120.7, 125.7, 129.6, 142.2, 156.7, 159.6, 175.6; HRMS (ESI) calcd for $C_{16}H_{19}O_3$ 259.1329, found 259.1326.

(+)-(*R*)-6-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Methylaristelegone A, 6). To a stirred solution of (−)-aristelegone B (**7**) (50 mg, 0.22 mmol) in THF (2 mL) was added acetic anhydride (45 mg, 0.44 mmol) followed by a solution of samarium diiodide (8.80 mL, 0.88 mmol, 0.10 M in THF) in dropwise fashion at 0 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (10 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:9) as an eluent afforded pure product (+)-**6** as a white solid (30 mg, 65%). Mp 109–110 °C [lit. 107–108 °C][6b]; $[\alpha]^{25}_D$ +21.3 (*c* 0.25 $CHCl_3$) {lit. $[\alpha]^{12}_D$ +26.5 (*c* 2.4 $CHCl_3$)}[6b]; the obtained spectroscopic data was identical with the data for (±)-**6**.

(+)-(*R*)-6-Hydroxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Aristelegone A, 13). To a stirred solution of (+)-methylaristelegone A (**6**) (25 mg, 0.12 mmol) in DCM (2 mL) was added solution of a boron tribromide (0.30 mL, 0.30 mmol, 1 M in DCM) in dropwise fashion at −78 °C and the reaction mixture was stirred under argon atmosphere for 1 h. The reaction mixture was allowed to reach 25 °C and stirred further for 12 h. The reaction was quenched with ice cold water and stirred for 30 min. The reaction mixture was extracted with DCM (7 mL × 2) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:2) as an eluent afforded pure product (+)-**13** as a white solid (17 mg, 74%). Mp 148–150 °C [lit. 150–151 °C][3a]; $[\alpha]^{25}_D$ +13.6 (*c* 0.28 $CHCl_3$) {lit. $[\alpha]^{25}_D$ +15.4 (*c* 0.24 $CHCl_3$)}[3a]; IR ($CHCl_3$) ν_{max} 3218, 1651, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 (d, *J* = 5 Hz, 3H), 1.82−1.90 (m, 1H), 2.16−2.24 (m, 1H), 2.26 (s, 3H), 2.57 (ddd, *J* = 20, 10 and 5 Hz, 1H), 2.76 (ddd, *J* = 20, 10 and 5 Hz, 1H), 2.99 (sextet, *J* = 10 Hz, 1H), 6.64 (br s, 1H), 6.75 (s, 1H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 20.5, 30.8, 32.6, 36.2, 112.8, 123.0, 124.9, 130.6, 149.7, 159.5, 198.4; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ 191.1067, found 191.1070.

(–)-(*S*)-6-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Methylaristelegone A, 6). To a stirred solution of acetoxy ketone (+)-**8** (100 mg, 0.38 mmol) in THF (4 mL) was added solution of samarium diiodide (7.60 mL, 0.76 mmol, 0.10 M in THF) in dropwise fashion at 0 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (10 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:9) as an eluent afforded pure product (−)-**6** as a white solid (65 mg, 84%). Mp 109–111 °C [lit. 115–116 °C][9a]; $[\alpha]^{25}_D$ −22.4 (*c* 0.25 $CHCl_3$) {lit. $[\alpha]^{25}_D$ −18.4 (*c* 1.18 $CHCl_3$)}[9a]; the obtained spectroscopic data was identical with the data for (±)-**6**.

(–)-(*S*)-4-Isopropyl-7-methoxy-1,6-dimethyl-1,2-dihydronaphthalene (15). To a stirred solution of (–)-methylaristelegone A (**6**) (50 mg, 0.24 mmol) in THF (4 mL) was added solution of isopropylmagnesium chloride (0.14 mL, 0.28 mmol, 2 M in THF) in dropwise fashion at 0 °C and the reaction mixture was stirred at the 25 °C under argon atmosphere for 6 h. The reaction was quenched with 2 N HCl and stirred for 30 min. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:49) as an eluent afforded pure product (–)-**15** as viscous oil (52 mg, 92%). $[\alpha]^{25}_D$ −57.8 (*c* 0.37 $CHCl_3$); IR ($CHCl_3$) ν_{max} 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 8 Hz, 3H), 1.19 (d, *J* = 8 Hz, 3H), 1.22 (d, *J* = 8 Hz, 3H), 2.07 (dt, *J* = 16 and 8 Hz, 1H), 2.24 (s, 3H), 2.37−2.46 (m, 1H), 2.81 (sextet, *J* = 8 Hz, 1H), 2.95 (septet, *J* = 8 Hz, 1H), 3.87 (s, 3H), 5.67 (t, *J* = 4 Hz, 1H), 6.72 (s, 1H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 19.9, 22.0, 22.4, 28.1, 30.9, 32.6, 55.4, 108.6, 116.8, 123.4, 125.4, 126.5, 141.1, 141.5, 156.3; HRMS (ESI) calcd for $C_{16}H_{23}O$ 231.1743, found 231.1743.

(+)-(2*R*,4*S*)-2-Hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Aristelegone B, 7). To a stirred solution of acetoxy ketone (+)-**8** (200 mg, 0.76 mmol) in methanol (5 mL) was added K_2CO_3 (5 mg) at 0 °C and the reaction mixture was further stirred under argon atmosphere for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:9) as an eluent afforded pure product (+)-**7** as a white solid (137 mg, 82%). Mp 102–103 °C [lit. 103 °C][8g]; $[\alpha]^{25}_D$ +29.2 (*c* 0.18 $CHCl_3$, 92% *ee*); the obtained spectroscopic data was identical with the data for (±)-**7**.

(+)-(3a*R*,5*S*)-7-Methoxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3a*H*)-one (Heritonin, 11). To a stirred solution of the (+)-aristelegone B (**7**) (88.0 mg, 0.40 mmol) in toluene (4 mL) was added Cu(II) catalyst (5 mol %), Wittig reagent (272 mg, 0.60 mmol), molecular sieves 4 Å (200 mg, 500 mg/mmol) and OXONE® (369 mg, 1.20 mmol) under argon atmosphere. The reaction mixture was stirred at 60 °C for 12 h until disappearance of the starting material, then xylene (6 mL) was added to the reaction mixture and the whole reaction mixture was stirred at 138 °C for 1 h. The reaction mixture was allowed to reach 25 °C, filtered through Celite bed and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel (60−120) column chromatographic purification using ethyl acetate−petroleum ether (1:19) as an eluent to afford pure product (+)-**11** as a white solid (72 mg, 71%). Mp 111–113 °C [lit. 115–116 °C][4a]; $[\alpha]^{25}_D$ +298.1 (*c* 0.32 $CHCl_3$); the obtained spectroscopic data was identical with the data for (−)-**11**.

(±)-7-Methoxy-6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl acetate (17). A solution of $KMnO_4$ (1.25 g, 78.84 mmol) in benzene–acetic acid (10:1, 250 mL) was stirred under reflux (Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (30–45 min). To this solution was added compound **3** (5.00 g, 26.28 mmol) and reflux was continued. The reaction was monitored by TLC and after 6 h it was diluted with diethyl ether and neutralized with aq. $NaHCO_3$. The resulting organic phase was dried over Na_2SO_4 and concentrated under vacuo. The crude product was purified by silica gel (60−120) column chromatographic purification using ethyl acetate−petroleum ether (1:3) as an eluent to afford pure product

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(±)-**17** as viscous oil (4.56 g, 70%). IR ($CHCl_3$) ν_{max} 1775, 1746, 1692, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.10–2.42 (m, 2H), 2.21 (s, 3H), 2.23 (s, 3H), 2.86–3.18 (m, 2H), 3.83 (s, 3H), 5.49 (dd, J = 12 and 6 Hz, 1H), 7.00 (s, 1H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.5, 20.8, 27.0, 29.4, 55.4, 74.5, 107.0, 130.2, 130.6, 134.5, 135.6, 156.7, 170.2, 192.7; ESIMS (*m*/*z*) 271 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{17}O_4$ 249.1121, found 249.1120.

(±)-7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl acetate (18). To a stirred solution of methyltriphenylphosphonium iodide (8.10 g, 19.93 mmol) in anhydrous THF (40 mL) was added a solution of *n*-BuLi (12.45 mL, 19.93 mmol, 1.60 M in hexane) in dropwise fashion at 0 °C under argon atmosphere and the mixture was stirred for 30 min. A solution of compound (±)-**17** (4.50 g, 18.12 mmol in 20 ml THF) was added to the above reaction mixture at 0 °C and it was further stirred for 10 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (150 mL), washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded product (±)-**18** as a white solid (2.99 g, 67%). Mp 52–54 °C; IR ($CHCl_3$) ν_{max} 1736, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.95–2.18 (m, 2H), 2.09 (s, 3H), 2.21 (s, 3H), 2.70–3.05 (m, 2H), 3.86 (s, 3H), 5.25 (s, 1H), 5.61 (s, 1H), 5.66 (dd, J = 6 and 4 Hz, 1H), 6.92 (s, 1H), 7.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 21.4, 25.1, 28.7, 55.3, 72.8, 105.4, 109.9, 127.6, 127.8, 130.8, 130.9, 141.5, 156.3, 170.5; HRMS (ESI) calcd for $C_{15}H_{18}O_3Na$ 269.1148, found 269.1147.

Amano PS catalyzed resolution of (±)-7-methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl acetate (18). To a stirred solution of allyl acetate (±)-**18** (1.00 g, 4.05 mmol) in a mixture of petroleum ether and benzene (1:2, 30 mL) were successively added the phosphate buffer (pH 7, 20 mL) and enzyme Amano PS (50 mg, Amano Enzyme Japan). The resulting reaction mixture was stirred at 45 °C for 48 h with monitoring the reaction progress by HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded pure product (+)-**18** as a white solid (2.99 g, 44%) and (+)-**19** also as a white solid (329 mg, 56%).

(+)-18: $[\alpha]^{25}_D$ +2.8 (*c* 1.75 $CHCl_3$, 92% *ee*); the obtained spectroscopic data was identical with the data for (±)-**18**.

(+)-19:$[\alpha]^{25}_D$ +3.2 (*c* 0.40 $CHCl_3$, 89% *ee*); the obtained spectroscopic data was identical with the data for (±)-**19**.

(±)-7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-ol (19). To a stirred solution of acetate (±)-**18** (1.50 g, 6.08 mmol) in methanol (10 mL) was added K_2CO_3 (20 mg) at 0 °C and the reaction mixture was further stirred under argon atmosphere for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:2) as an eluent afforded pure product (±)-**19** as a white solid (1.05 g, 85%). Mp 85–87 °C; IR ($CHCl_3$) ν_{max} 3430, 1644, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.69 (br s, 1H), 1.85–2.15 (m, 2H), 2.20 (s, 3H), 2.68–3.07 (m, 2H), 3.86 (s, 3H), 4.51 (dd, J = 8 and 4 Hz, 1H), 5.27 (s, 1H), 5.55 (s, 1H), 6.91 (s, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 25.4, 31.7, 55.4, 70.9, 105.6, 107.2, 127.5, 128.1, 131.0 (2 C), 146.6, 156.3; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ 205.1223, found 205.1224.

(±)-*tert*-Butyl((7-methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)diphenylsilane (20). To a stirred solution of alcohol (±)-**19** (1.00 g, 4.89 mmol) in dichloromethane (20 mL) were added imidazole (366 mg, 5.38 mmol) and TBDPSCl (1.48 g, 5.38 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and further stirred for 6 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (40 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:49) as an eluent afforded pure product (±)-**20** as a white solid (1.99 g, 92%). Mp 108–109 °C; IR ($CHCl_3$) ν_{max} 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 9H), 1.65–2.00 (m, 2H), 2.17 (s, 3H), 2.45–2.65 (m, 1H), 2.80–3.00 (m, 1H), 3.84 (s, 3H), 4.48 (dd, J = 8 and 4 Hz, 1H), 5.15 (s, 1H), 5.37 (s, 1H), 6.82 (s, 1H), 6.96 (s, 1H), 7.25–7.50 (m, 6H), 7.62 (dd, J = 8 and 2 Hz, 2H), 7.72 (dd, J = 8 and 2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 19.4, 26.1, 27.0, 32.7, 55.4, 72.5, 105.9, 107.1, 126.9, 127.4, 127.6, 128.0, 129.5, 129.6, 130.8, 132.2, 134.0, 134.6, 135.9 (2 C), 146.4, 156.1; HRMS (ESI) calcd for $C_{29}H_{33}O_2Si$ 441.2244, found 441.2245.

(±)-*tert*-Butyl((7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)diphenylsilane (21). To a stirred solution of compound (±)-**20** (1.50 g, 3.38 mmol) in ethyl acetate (25 mL) was added 10% Pd/C (25 mg) at 25 °C and the reaction mixture was subjected to hydrogenation under balloon pressure for 8 h. The reaction mixture was filtered through Celite bed and washed with ethyl acetate. The concentration of the filtrate in vacuo furnished diastereomeric mixture of compound (±)-**21** as a white solid with ~9:1 ratio (by ^1H NMR) (1.51 g, ~100%). Mp 110–113 °C; IR ($CHCl_3$) ν_{max} 1602 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 9H), 1.32 (d, J = 8 Hz, 3 H), 1.55–1.70 (m, 1H), 1.80–2.05 (m, 1H), 2.11 (s, 3H), 2.28–2.55 (m, 1H), 2.57–2.75 (m, 1H), 2.83–3.00 (m, 1H), 3.77 (s, 3H), 4.04–4.17 (m, 1H), 6.48 (s, 1H), 6.73 (s, 1H), 7.25–7.50 (m, 6H), 7.65–7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 17.4, 19.4, 26.6, 27.0, 27.5, 39.6, 55.4, 71.8, 110.5, 124.5, 126.3, 127.47, 127.54, 129.5, 129.6, 130.5, 134.3, 134.8, 135.8, 139.9 (2 C), 155.9; ESIMS (*m*/*z*) 467 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{36}O_2NaSi$ 467.2377, found 467.2371.

(±)-3-((*tert*-Butyldiphenylsilyl)oxy)-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (22). To a stirred solution of (±)-**21** (1.00 g, 2.24 mmol) in acetic acid (20 mL) was added a solution of CrO_3 (292 mg, 2.92 mmol) in AcOH plus H_2O (8:2, 8 mL) in dropwise fashion at 0 °C. The reaction mixture was further stirred for 2 h, diluted with water and carefully neutralized by addition of a saturated solution of $NaHCO_3$. The reaction mixture was extracted with diethyl ether (25 mL × 3) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded diastereomerically pure product (±)-**22** as viscous oil (680 mg, 66%). IR ($CHCl_3$) ν_{max} 1728, 1667, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.09 (s, 9H), 1.37 (d, J = 8 Hz, 3 H), 2.15 (s, 3H), 2.59 (dd, J = 18 and 6 Hz, 1 H), 2.83 (dd, J = 18 and 12 Hz, 1 H), 3.03 (quintet, J = 6 Hz, 1H),

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3.86 (s, 3H), 4.32 (td, *J* = 12 and 4 Hz, 1H), 6.53 (s, 1H), 7.30–7.50 (m, 6H), 7.60–7.80 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6, 19.2, 26.5, 26.9, 40.6, 42.7, 55.5, 69.8, 108.7, 124.1, 125.9, 127.7, 129.3, 129.6, 129.79, 129.83, 133.6, 133.7, 134.8, 135.7, 148.1, 162.5, 195.9; ESIMS (*m*/*z*) 481 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{35}O_3Si$ 459.2350, found 459.2348.

6-Methoxy-4,7-dimethylnaphthalen-1-ol (23). *Method A*: To a stirred slurry of keto compound (±)-**22** (100 mg, 0.21 mmol), activated Zn (27 mg, 0.42 mmol) and a catalytic amount of iodine in anhydrous diethyl ether (10 mL) was slowly added a solution of ethyl 2-bromopropionate (76 mg, 0.42 mmol) in anhydrous diethyl ether (2 mL) at 25 °C under argon atmosphere. Reaction mixture further refluxed for 12 h, quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded pure product **23** as an orange oil (30 mg, 68%). *Method B*: To a stirred solution of keto compound (±)-**22** (100 mg, 0.21 mmol) in anhydrous THF (10 mL) was slowly added a solution of tetrabutylammonium fluoride (0.23 mL, 0.23 mmol, 1 M in THF) at 0 °C. Reaction mixture was further stirred for 5 h at same temperature and quenched with saturated NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded pure product **23** as an orange oil (27 mg, 63%). IR ($CHCl_3$) ν_{max} 3415, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 2.58 (s, 3H), 3.99 (s, 3H), 5.37 (br s, 1H), 6.59 (d, *J* = 8 Hz, 1H), 7.07 (d, *J* = 8 Hz, 1H), 7.11 (s, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.9, 19.1, 55.2, 101.3, 106.1, 119.3, 123.1, 125.0, 125.8, 127.2, 133.6, 149.5, 157.2; ESIMS (*m*/*z*) 203 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ 203.1067, found 203.1066.

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