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Graphical Abstract

Stereodivergent approach to Alzheimer's therapeutic agent (*R*)-(-) and (*S*)-(+)-arundic acid employing chiral 4-pentenol derivatives as building blocks

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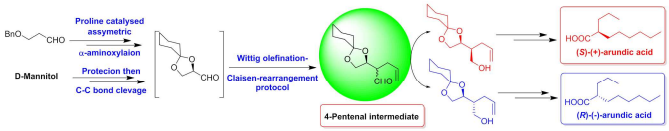

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ABSTRACT

An efficient stereodivergent total synthesis of anti-Alzheimer agent (*R*)-(-) and (*S*)-(+)-arundic acid has been achieved from both chiral and nonchiral materials. This strategy features an efficient approach to separable diastereomeric C-2 chiral 4-pentenol intermediates employing proline catalysed asymmetric α-aminooxylation and [3,3] sigmatropic Claisen rearrangement are the highlights of present synthesis.

1. Introduction

Alzheimer's disease (AD) is chronic neurodegenerative process, which causes a progressive dysfunction of central nervous system. It affects parts of brain characterized by control of thought, memory and language. It reduces appetite or the ability to recognize and also associated with disorientation, mood swings, loss of motivation and behavioral issues, which becomes major concern for human health.[1] Although, a great efforts has been devoted to study of its origin, fight and prevention, only palliative treatments have been developed so far. Few medications are currently used to treat the cognitive problems of AD, which includes use of acetylcholinsterase inhibitors (tacrine, rivastigmine, galanthamine donepezil) and NMDA receptor antagonist (memantine)[2] but unfortunately in most of the cases benefit from their use is very small.[3] Research into fighting this ever-growing disease is towards development of new therapeutic drugs and synthesis of analogues of this class.

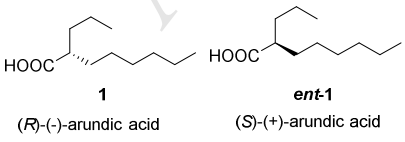


Figure. 1 Arundic acids

(*R*)-(-)-arundic acid (**Fig. 1**) was discovered as a novel emerging compound as neuroprotective agent as well as it is necessary for the treatment of spinal cord injury (SCI) in combination with other drugs.[4a] The phase II clinical trials of arundic acid for the treatment of acute ischemic stroke and clinical development in other neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and Parkinson's disease are recently completed.[4b,4c] Arundic acid clinically identified as useful drug which attenuates retinal ganglion cell death by increasing glutamate/aspartate transporter expression.[4d]

The interesting biological activities of (*R*)-(-)-arundic acid prompted many synthetic efforts, which resulted in several racemic and asymmetric total syntheses. The strategies used for syntheses relied on recemates resolution,[5] asymmetric alkylation,[6] use of chiral auxiliaries,[7] photochemical diastereoselective deconjugation,[8] crotylation using metal,[9] [3,3] sigmatropic Johnson–Claisen rearrangement[10] and recently used Pd/Cu catalyzed cross-coupling reaction.[11] Although, a range of different approaches has been developed, a concise synthesis of arundic acid from commercially available material with better overall yield remains a worthy objective.

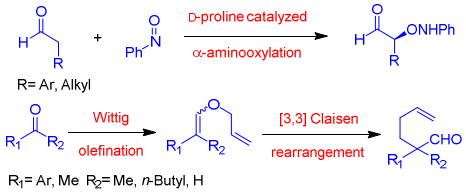
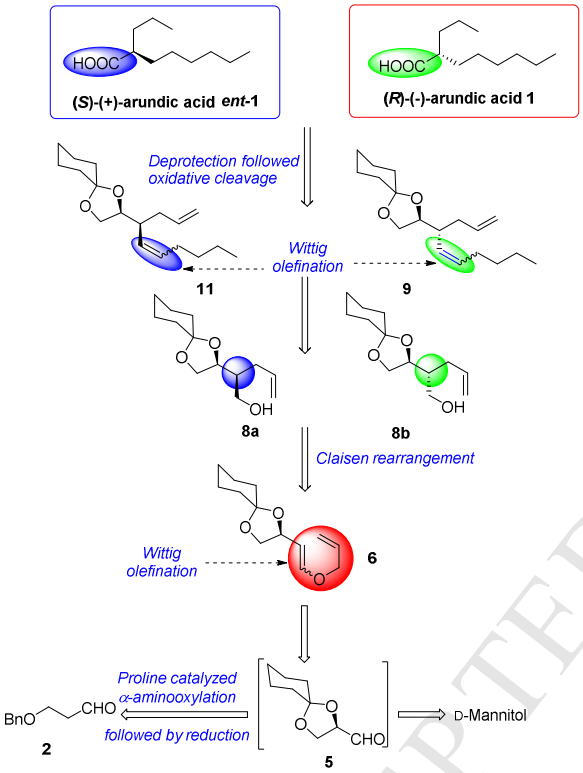


Figure. 2 General scheme for Wittig olefination-Claisen rearrangement protocol

As part of our on-going research programs on the total synthesis of bioactive natural products and heterocycles,[12-14] we were encouraged to pursue the total synthesis of both

enantiomers of arundic acid. Herein, we describe a concise and scalable stereodivergent synthesis of both enantiomers of arundic acid by employing proline catalysed asymmetric α-aminooxylation and Wittig olefination-Claisen rearrangement protocol as key steps (**Fig. 2**).

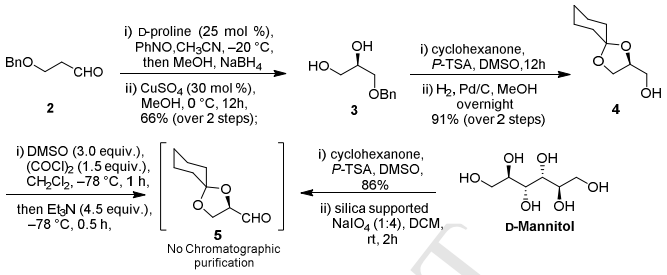
Our retrosynthetic strategy towards the synthesis of (*R*)-(-)-arundic acid and (*S*)-(+)-arundic acid is outlined in Scheme 1. The carboxylic acids **1** and *ent*-**1** could be accessible via hydrogenation of alkenes following oxidative cleavage of diol. While alkenes **11** and **9** would be the product of a Wittig olefination reaction on aldehyde, which in turns conceived to derive by performing Wittig olefination-Claisen rearrangement protocol on aldehyde **5**. Intermediate (*R*)-2,3-*O*-cyclohexylidene D-glyceraldehyde **5** could be obtained either by performing proline catalysed asymmetric α-aminooxylation of nonchiral aldehyde **2** or from D-mannitol.[15a]



Scheme 1 Retrosynthesis of (*R*)-(-) and (*S*)-(+)-arundic acid

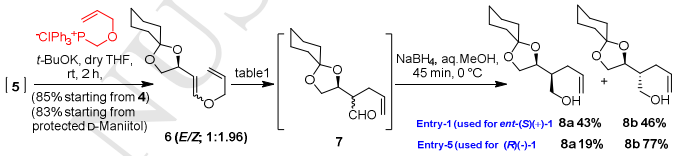
2. Result and discussion

Scheme 2 summarizes synthetic sequence for the enantioselective synthesis of (*R*)-**5** from chiral and nonchiral materials. Our synthesis commenced with aminooxylation of aldehyde **2**[15b] using nitroso benzene as oxygen source and D-proline as a catalyst furnished crude α-aminooxy aldehyde, which on subsequent reduction with $NaBH_4$ provided crude aminooxy alcohol. Treatment of the crude aminooxy alcohol with 30 mol % $CuSO_4.5H_2O$ in methanol furnished (*R*)-3-(benzyloxy) propane-1,2-diol **3** in 66% yield over two steps with 95% *ee*.[15b] The absolute and relative configuration of diol **3** is based on L/D-proline used in the reaction and analogous to those as reported in our earlier studies.[15b] Later on, cyclohexedene protection of the diol **3** followed by deprotetion of benzyl ether over (H_2, Pd/C, MeOH) afforded (*S*)-(1,4-dioxaspiro [4.5] decan-2-yl) methanol **4** in 91% yield over two steps. Oxidation of alcohol **4** under Swern oxidation condition afforded crude (*R*)-2,3-*O*-cyclohexylidene D-glyceraldehyde **5**. (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde **5**[15a] also obtained *via* cyclohexedene protection of D-mannitol and C–C bond scissoring using silica supported $NaIO_4$ (see experimental section).



Scheme 2 Synthesis of Wittig precursor glyceraldehyde **5**

Wittig olefination of crude (*R*)-2,3-*O*-cyclohexylidene D-glyceraldehyde **5** with allyoxy methylene triphenyl phosphine using *t*-BuOK as base provided the allyl vinyl ether **6** as an inseparable mixture of *E/Z* isomers in 1:1.96 ratio. The thermal and microwave induced [3,3] sigmatropic Claisen rearrangement reaction of allyl vinyl ether **6** was investigated in detail to obtain better diastereoselectivity and yield (Scheme 3).



Scheme 3 Synthesis of alcohols **8a** and **8b**

Table 1. Diastereoselective Claisen rearrangement of 6

Entry	Conditions	dr[a] of **7**	Yield %[b] **8a+8b**
1	**neat, 180 °C, 10 min**	**1:1.05**	**89% (43+46)**
2	neat, mw, 150 °C, 10 min	1:1.40	91% (36+55)
3	xylene, 140-140 °C, 8 h	1:2.27	94% (29+65)
4	xylene, mw, 120 °C, 25 min	1:1.65	92% (35+57)
5	toluene 110-115 °C, 18 h	1:3.05	94 % (22+72)
6	**benzene, 80-85 °C, 24 h**	**1:4.16**	**96% (19+77)**
7	benzene/mw, 85 °C, 1 h	1:3.51	92% (20+72)
8	neat/mw, 80-85 ℃, 48 h		No reaction
9	CH_2Cl_2, 40-45 °C, 48 h		No reaction
10	CH_2ClCH_2Cl, 2 equiv., MAD,[c] rt, 48 h		No reaction

[a]dr ratio of the **7** was determined by ^{1}H NMR.
[b]yields of product are referred to isolated yields of alcohol **8a** and **8b** obtained after claisen followed by reduction.
[c]MAD = methyl aluminium bis(2,6-di-*tert*-butyl-4-methylphenolate).

The allyl vinyl ether **6** on heating at 180 °C provided aldehyde **7** as inseparable mixture of diastereomers in 1:1.05 ratio, which on subsequent reduction provided chromatographically separable diastereomeric alcohols **8a** and **8b** in 43% and 46%, respectively (Table 1, entry1). The absolute configuration of new stereogenic centres of **8a** and **8b** were analogous with earlier studies as reported by our group.[13] The same transformation could also be induced through microwave irradiation in a much shorter time, with improved diastereoselectivity for **8a** and **8b** (Table 1; entries 2, 4 and 7). The diastereoselectivity in Claisen rearrangement gradually increased with lower boiling solvents (entries 3–6). When reaction performed in benzene, aldehyde **7**

obtained as diastereomeric mixture in 1:4.16 ratio, which on reduction provided **8b** as major diastereomer exclusively in 77% and **8a** in 19% yield, respectively. The neat and microwave induced Claisen rearrangement reaction at 80-85 °C as well as in CH_2Cl_2 at 40-45 °C was failed to delivered desired product (Table 1; entries 8 and 9). The Lewis acid catalysed rearrangement also attempted, but to our disappointment we could not get desired results.

The probable explanation for increase in diastereoselectivity of Claisen rearrangement is provided in figure 3. Consider the s-cis chair like transition states of allyl vinyl ether **6**, transition states I and II would be derived from **6**-(2*S*,*Z*) and **6**-(2*S*,*E*), respectively. The transition state II is more stable and favourable as compared to transition state I, as it encounters less steric hindrance due to minimum number of bonding interactions. The diastereoselective Claisen rearrangement in benzene at lower temperature might be proceeding through kinetically favoured transition state II, which delivers aldehyde **7b** as a major diastereomer, shown in figure 2. The increase in diastereomeric excess in benzene is might be attributed to a partial stabilization of dipolar transition state of Claisen rearrangement of allyl vinyl ether in the benzene at 80-85 °C.[16]

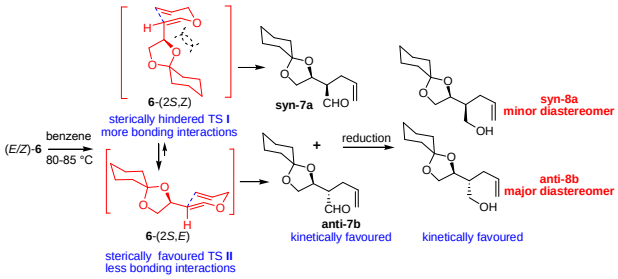
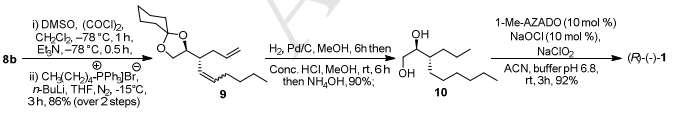


Figure 3 Probable mechanistic explanation for observed diastereoselectivity in Claisen rearrangement

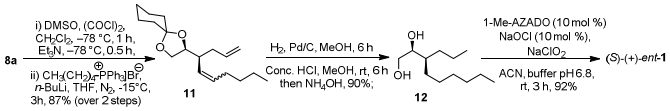
With stereo chemically assigned alcohols **8a** and **8b** in hand, we proceeded for completion of the synthesis of the anti Alzheimer therapeutic agent (*R*)-(-)-arundic acid **1** and *ent*-**1**. The synthesis of (*R*)-(-)-arundic acid **1** is shown in Scheme 4. Accordingly, the synthetic sequence commenced with the synthesis of alcohol **8b** using conditions in Table 1; entry 6. Further, oxidation of alcohol **8b** under swern oxidation condition gave aldehyde, which without any further chromatographic purification subjected for next reaction. Wittig olefination of crude aldehyde with pentyl-triphenyl-phosphonium bromide salt at -15 °C using *n*-BuLi as base gave dialkene **9** as an inseparable mixture of *E/Z* isomers in 86% yield over two steps. From ^{1}H NMR spectra of **9**, ratio of the *E/Z* isomers found to be 1:1.10.



Scheme 4 Synthesis of (*R*)-(-)-arundic acid **1**

The palladium catalysed hydrogenation of **9** followed by acid catalyzed deketalization of the spiroketal provided diol **10** in 90% yield. The organocatalytic one-pot oxidative cleavage[17] of terminal 1,2-diol **10** by combination of 1-Me-AZADO (*cat.*), NaOCl (*cat.*), and $NaClO_2$ under mild conditions gave one-carbon-unit-shorter (*R*)-(-)-arundic acid **1** in 92% yield. $[\alpha]_D^{25}$= -5.8 (*c* =2.00, EtOH); lit[7c] $[\alpha]_D^{20}$ = -6.1 (*c* =2.00, EtOH).

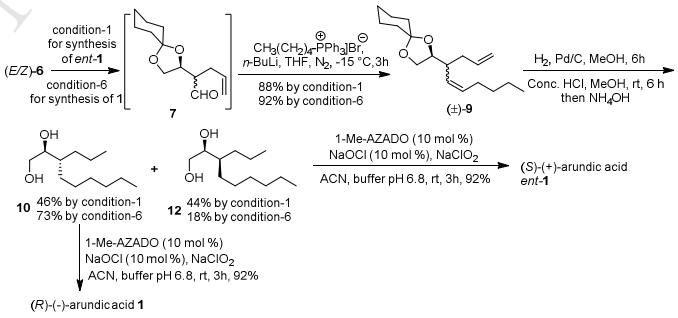
The synthesis of (*S*)-(+)-arundic *ent*-**1** is outlined in scheme 5. Synthetic commenced with the preparation of alcohol **8a** using conditions in entry 1 (Table 1).



Scheme 5 Synthesis of (*S*)-(+)-arundic acid*ent*-**1**

Swern oxidation of alcohol **8a** gave aldehyde, which on subsequent Wittig olefination with pentyl-triphenyl-phosphonium bromide salt gave dialkene **11** as 1:1.65 mixtures of *E/Z* isomers in 87% yield over two steps. The Palladium catalysed hydrogenation of dialkene **11** in methanol and subsequent acid catalyzed deketalization provided diol **12** in 90% yield. The treatment of diol **12** with 1-Me-AZADO (*cat.*), NaOCl(*cat.*), and $NaClO_2$ caused smooth one-pot oxidative cleavage provided one carbon unit shorter (*S*)-(+)-arundic acid *ent*-**1** in 92% yield, $[\alpha]_D^{25}$= +6.3 (*c* =0.50, EtOH); lit[10] $[\alpha]_D^{25}$= +6.6 (*c* =0.54, EtOH).

After confirming possibility of chromatography separation of diastereomeric diols **10** and **12**, we developed a more facile enantioselective route to anti-Alzheimer agent **1** in which reduction/oxidation sequence is avoided (Scheme 6). For the synthesis of **1**, the Claisen rearrangement of allyl vinyl ether **6** was carried out in benzene to give aldehyde **7**, after evaporation of solvent **7** was subsequently subjected to Wittig olefination with pentyl-triphenyl-phosphonium bromide salt gave dialkene **9** as an inseparable mixture of diastereomers in 92% yield over two steps.



Scheme 6 Synthesis of (*R*)-(-)-arundic acid **1**

Further, palladium catalysed hydrogenation followed by acid catalyzed deketalization afforded separable diastereomeric diols **10** and **12** in 73% and 18% yields, respectively. The organocatalytic one-pot oxidative cleavage[17]of terminal 1,2-diols in **10** afforded (*R*)-(-)-**1** in 92% yield.

The synthesis of (*S*)-(+)-arundic *ent*-**1** commenced from aldehyde **7** obtained by employing condition in entry-1(Table 1). The olefination of crude aldehyde **7** with pentyl-triphenyl-phosphonium bromide salt at -15 °C using *n*-BuLi as base gave dialkene (±)-**9** as an inseparable mixture of *E/Z* isomers in 88% yield. Later on, palladium catalysed hydrogenation followed by acid catalyzed deketalization provided separable diastereomeric diols **10** and **12** in 46% and 44% yields, respectively. Oxidative cleavage[17] of terminal 1,2-diol of **12** under previously employed condition afforded (*S*)-(+)-*ent*-**1** in 92% yield.

3. Conclusion

In conclusion, short and efficient synthesis of anti-Alzheimer agent (*R*)-(-)-arundic **1** as well as (*S*)-(-)-arundic acid *ent*-**1** has been developed using proline catalysed asymmetric α-aminooxylation and Wittig olefination-Claisen rearrangement protocol. Following are some highlighted features of the synthesis strategy, (i) shorter route for the synthesis of the (*R*)-(-)-arundic **1** (4 steps, 51%) and (*S*)-(+)-arundic *ent*-**1** (4 steps, 28%) from chiral D-glyceraldehyde **5** starting material (ii) synthesis of the (*R*)-(-)-arundic **1** in 32% and (*S*)-(+)-arundic *ent*-**1** in 17% overall yield from nonchiral starting aldehyde **2** in 9 steps. (iii) The key intermediate 4-pentenal obtained through performing [3,3] Claisen rearrangement can be useful for the synthesis of other related analogues by changing the Wittig reagent. Further study towards the improvement of the diastereoselectivity in the [3,3] sigmatropic Claisen rearrangement of allyl vinyl ether **6** and application of this strategy for the synthesis of bioactive molecules is under progress**.**

4. Experimental section

General Experimental Details

All reagents were obtained from commercial suppliers unless otherwise stated and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. All moisture sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were magnetically stirred and monitored by analytical thin-layer chromatography (TLC) E. Merck 0.25 mm silica gel 60 F_{254}. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of potassium permanganate ($KMnO_4$), an acidic solution of anisaldehyde or a solution of PMA followed by heating with a heat gun. Chromatography was performed using silica gel (100-200 mesh) with solvents distilled prior to use. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material. All spectra were recorded at 25 °C. ^{1}H NMR spectra were recorded on 500 MHz and 400 MHz spectrometers and ^{13}C NMR spectra were obtained at 500 NMR (126 MHz) and 400 (101 MHz) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Chemical shifts were recorded in ppm, and coupling constants (*J*) were in Hz. HRESIMS were taken on Bruker Impact HD quadrupole plus ion trap at CIF Savitribai Phule Pune University. Infrared spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet dd: doublet of doublet for proton spectra. Optical rotations were measured on a digital polarimeter

Experimental section:

*4.1 (R)-3-(Benzyloxy) propane-1,2-diol (**3**)*

To a stirred solution of aldehyde **2** (2 g, 12.2 mmol) and nitrosobenzene (1 g, 9.34 mmol) in CH_3CN (25 mL) was added D-proline (0.270 g, 2.43 mmol) at -20 °C. The reaction mixture was stirred for 24 h at the same temperature, then diluted with MeOH (15 mL) and to this solution was added $NaBH_4$ (1.06 g, 28 mmol). After 30 min, the reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The $CuSO_4.5H_2O$ (0.7 g, 2.8 mmol) was added at 0 °C to the solution of crude product in MeOH (20 mL) and stirred for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 50 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography using ethyl acetate/hexane (1:5) to give diol **3** (0.727 g, 66%) as a viscous liquid.

[Spectral data of **3**]**:** R_f = 0.3 (EtOAc/ hexane, 1:5);
$[\alpha]_D^{25}$= +5.56 (*c* 1.0, $CHCl_3$);
IR: 3417, 2920, 2880, 1085 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.23 (5H, m), 4.55 (2H, s), 3.93 – 3.86 (1H, m), 3.68 (1H, dd, *J* = 3.6, 11.2 Hz,), 3.63 – 3.49 (3H, m), 3.25 (2H, s);
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 128.5, 127.9, 127.8, 73.5, 71.6, 70.8, 64.0;
HRMS (ESI^+)$[M+Na]^+$: found 205.0837. $C_{10}H_{14}NaO_3$ requires 205.0841.

*4.2 (S)-(1,4 Dioxaspiro [4.5]decan-2-yl)methanol (**4**)*

[Spectral data of **4**]: R_f = 0.5 (EtOAc/ hexane, 1:4);
$[\alpha]_D^{25}$= -4.2 (*c* 1.0, $CHCl_3$);
IR (neat): 3520, 1450, 1090, 937 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.15 (1H, m), 4.15 – 3.90 (2H, m), 3.83 – 3.64 (2H, m), 3.67 – 3.51 (1H, m, OH), 1.65 – 1.37 (10H, m);
^{13}C NMR (101 MHz, $CDCl_3$) δ 109.9, 75.7, 65.3, 63.1, 34.7, 34.7, 25.1, 24.0, 23.7;
HRMS (ESI^+)$[M+ Na]^+$: found 199.0995. $C_{10}H_{16}NaO_3$ requires 199.0997.

*4.3(S)-2-(2-(Allyloxy)-vinyl)-1,4-dioxospiro[4.5]-decane(**6**)*

Oxalyl chloride (2.24 mL, 0.0261 mol, 1.5 equiv.) was gradually added to a solution of DMSO (3.71 mL, 0.052 mol, 3 equiv.) in CH_2Cl_2 (50 mL) at -78 °C over a period of 5 min. After stirring for 10 min, a solution of alcohol **4** (3 g, 0.0174 mol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 1 h. Then NEt_3 (10.9 mL, 0.078 mol, 4.5 equiv.) was added, and the mixture was stirred for 30 min. The mixture was gradually warmed to room temperature, and then it was diluted with CH_2Cl_2 (20 mL). Water (20 mL) was added, and then the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated to give the crude ketone (0.187 g), which was used directly in the next reaction. To a suspension of crude 2,3-*O*-*C*yclohexylidene-D-glyceraldehyde **5** and allyloxy methylene triphenyl-phosphonium chloride (9.61 g, 0.0261 mol, 1.5 equiv) in dry THF (150 mL), potassium *t*-butoxide (2.92 g, 0.0261 mol, 1.5 equiv) was added portion wise over the period of 10 min. The reaction was stirred for 1 h at the same temperature. After completion of reaction (TLC check), THF was removed under reduced pressure. Residue was suspended in water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using petroleum ether as eluent, gave pure allyl vinyl ether **6**as colourless thick liquid. The product in hand was the inseparable mixture of *E*- and *Z*- isomers (1:1.96) 3.32 g (85%) over two steps.

From protected D-mannitol- To a magnetically stirred solution of cyclohexedene protected diol (3 g, 0.0087 mmol) in CH_2Cl_2 (20 mL) silica supported $NaIO_4$ (4:1) was added and stirring was continued for 2 h at rt. The mixture was then filtered through a cotton plug, and the residue was washed with CH_2Cl_2 (3 x 25 mL). The filtrate was concentrated to give the crude aldehyde **5** which without any purification subjected to Wittig olefination with allyoxy methylene triphenyl phosphine using same procedure above to give allyl-vinyl ether **6** (1.63 g, 83%) yield.

#Preparation of silica gel supported $NaIO_4$ (4:1): 1 g, 4.69 mmol) of sodium periodate are suspended in 2 mL of water. Under magnetic stirring the mixture is heated to 70°C in a 50 mL flask. To this slightly cloudy solution is added silica (4 g 230–400 mesh) in one go (at 70 °C). The flask is removed from the heating bath fitted with a stopper and swirled until a fine homogenous powder has developed.

[Spectral data of **6**]: R_f = 0.6 (EtOAc/ hexane, 1:4);
IR (neat): 2940, 1690, 1105, 930 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (1H, d, *J* = 12.9 Hz, *E*-isomer), 5.97 (1H, d, *J* = 7.0 Hz, *Z*-isomer), 5.95 – 5.85 (1H, m), 5.31 (1H, m), 5.27 – 5.19 (2H, m), 4.45 – 4.39 (1H, m), 4.29 (1H, d, *J* = 5.4 Hz), 4.23 – 4.17 (2H, m), 4.05 (1H, dd, *J* = 8.0, 6.6 Hz), 3.96 (1H, dd, *J* = 8.1, 6.5 Hz), 3.70 (1H, t, *J* = 8.0 Hz, *E*-isomer), 3.63 (1H, t, *J* = 8.0 Hz, *Z*-isomer), 1.70 – 1.62 (8H, m), 1.41 – 1.32 (2H, m);
^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 143.2, 133.8, 133.7, 117.5, 117.5, 110.9, 109.2, 101.8, 101.5, 72.8, 72.7, 71.4, 67.0, 66.5, 35.9, 35.1, 30.3, 25.3, 23.9;
HRMS (ESI^+)[M+ $Na]^+$: found 247.1312. $C_{13}H_{20}NaO_3$ requires 247.1310.

*4.4 (S)/(R)-2-(1,4-Dioxaspiro[4.5]-decan-2-yl)-pent-4-enal (**7**)*

The isomeric mixture of allyl vinyl ether **6** (0.5g, 2.46 mmol) was dissolved in benzene (5 mL) (Entry 6) and the solution was refluxed for 24 h. After completion of the reaction (TLC check), the benzene was removed under reduced pressure to afford pure 4-pentenal as colourless oil. The product in hand was the mixture of two inseparable diastereoisomers in a ratio of 1:4.10.

[Spectral data of **6**]: R_f = 0.7 (EtOAc/ hexane, 1:4);
IR (neat): 2930, 1725, 1650, 1101, 915 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, d, *J* = 2.7 Hz, minor isomer), 9.77 (1H, d, *J* = 1.3 Hz, major isomer), 5.89 – 5.71 (m, 1H), 5.13 (2H, tdt, *J* = 17.5, 6.3, 1.4 Hz), 4.35 – 4.29 (1H, m), (1H, m), 4.17 – 4.11 (1H, m), 3.75 (1H, dd, *J* = 7.9, 6.2 Hz, minor isomer), 3.67 (1H, dd, *J* = 8.5, 6.6 Hz, major isomer), 2.72 – 2.64 (1H, m), 2.63 – 2.44 (2H, m), 1.70 – 1.52 (8H, m), 1.42 (2H, bs);
^{13}C NMR: (75 MHz, $CDCl_3$): δ 203.0, 202.9, 134.4, 134.2, 117.6, 109.9, 109.4, 74.7, 73.6, 67.2, 67.1, 54.4, 36.1, 36.0, 34.7, 34.5, 30.5, 30.0, 25.0, 23.9, 23.8 and 23.6;
HRMS (ESI^+)[M+ $Na]^+$: found 247.1312. $C_{13}H_{20}NaO_3$ requires 247.1310.

*4.5(S)-2-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)pent-4-en-1-ol (**8a**)/(R)-2-((S)-1,4-dioxaspiro[4.5]decan-2-yl)pent-4-en-1-ol (**8b**)*

To the solution of crude mixture of aldehyde **7** in 5% aqueous methanol (5 mL), sodium borohydride (1.5 equiv.) was added portion wise over a period of 10 min at 0 °C. The reaction mixture was stirred at same temperature for 30-35 min. After completion of reaction (TLC check), the methanol was removed under reduced pressure, residue was diluted with water and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using petroleum ether: ethyl acetate (97: 3) to give the alcohol **8a** (0.095 g, 19%) and **8b** (0.388 g, 77%) as colourless liquids.

[Spectral data of **8a**]: R_f = 0.3 (EtOAc/ hexane, 1:4);
$[\alpha]_D^{25}$= -0.5 (*c* =2.00, $CHCl_3$);
IR (neat): 3463, 2930, 1623, 1454, 1098, 937 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 17.2, 10.0, 7.2 Hz), 5.10 – 5.02 (2H, m), 4.11 (1H, dd, *J* = 7.9, 6.2 Hz), 4.05 (1H, dd, *J* = 8.2.1, 6.5 Hz), 3.76 (1H, dd, *J* =8.3, 6.4 Hz), 3.72 – 3.65 (2H, m), 2.05 – 1.99 (2H, m), 1.82 – 1.76 (1H, m), 1.62 – 1.56 (8H, m), 1.40 (2H, bs);
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 117.0, 109.7, 79.0, 68.4, 64.6, 43.82, 36.2, 35.0, 32.9, 25.0, 24.0, 23.8;
HRMS (ESI^+)[M+ $Na]^+$: found 249.1467. $C_{13}H_{22}NaO_3$ requires 249.1462.

[Spectral data of **8b**]: R_f = 0.3 (EtOAc/ hexane, 1:4);
$[\alpha]_D^{25}$= +0.7 (*c* =3.00, $CHCl_3$);
IR (neat): 3467, 2943, 1637, 1447, 1109, 925 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (1H, ddt, *J* = 17.3, 10.0, 7.1 Hz), 5.11 – 5.02 (2H, m), 4.23 (1H, dd, *J* = 8.4, 6.2 Hz), 4.02 (1H, dd, *J* = 8.1, 6.4 Hz), 3.75 (1H, t, *J* = 8.0 Hz), 3.72 – 3.62 (2H, m), 2.18 – 2.10 (2H, m), 1.99 – 1.93 (1H, m), 1.65 – 1.57 (8H, m), 1.40 (2H, bs);
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 116.7, 109.2, 79.9, 66.2, 63.0, 42.4, 36.1, 34.7, 31.8, 25.1, 24.0, 23.8;
HRMS (ESI^+)[M+ $Na]^+$: found 249.1467. $C_{13}H_{22}NaO_3$ requires 249.1462.

4.6(S)-2-((R)-Deca-1,5-dien-4-yl)-1,4-dioxaspiro[4.5]decane (*9*)

Oxalyl chloride (0.28 mL, 3.33 mmol, 1.5 equiv.) was gradually added to a solution of DMSO (0.47 mL, 6.66 mmol, 3 equiv.) in CH_2Cl_2 (25 mL) at –78 °C over a period of 5 min. After stirring for 10 min, a solution of **8b** (0.500 g, 2.22 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 1.5 h. Et_3N (1.42 mL, 9.99 mmol, 4.5 equiv.) was added, and the mixture was stirred for 30 min. The mixture was gradually warmed to room temperature, and then it was diluted with CH_2Cl_2 (20 mL). Water (20 mL) was added, and then the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde (0.488 g), which was used directly in the next reaction. *n*-BuLi (1.6 m in hexane; 1.63 mL, 2.61 mmol, 1.2 equiv.) was added to a suspension of pentyltriphenylphosphonium bromide (1.08 g, 2.61 mmol, 1.2 equiv.) in dry THF (15 mL) at -15 °C. After stirring at -15 °C for 30 min, a solution of the crude aldehyde in dry THF (5 mL) was added, and the resulting mixture was stirred at 0°C for 3 h. The reaction was then quenched with a few drops of water, and the organic phase was filtered through a cotton plug. The residue was washed with Et_2O (5 mL). The filtrate was concentrated and extracted with Et_2O (3 x 15 mL). Organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography to afford title compound **9** (0.535 g) in 87% yield over two steps.

[Spectral data of **9**]: R_f = 0.6 (EtOAc/ hexane, 1:5);
$[\alpha]_D^{20}$= +12.10 (*c* =0.42, MeOH);
IR (neat): 1680, 1665, 1109, 925cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 – 5.71 (1H, m), 5.50 (1H, dtd, *J* = 11.1, 7.3, 0.6 Hz,), 5.08 – 5.01 (2H, ddt, *J* = 5.6, 2.7, 1.7 Hz,), 5.01 – 4.95 (1H, m), 3.95 – 3.88 (2H, m), 3.57 (1H, t, *J* = 6.6 Hz,), 2.62 – 2.55 (1H, m), 2.54 – 2.46 (1H, m), 2.09 – 2.00 (3H, m), 1.69 – 1.56 (10H, m), 1.43 – 1.32 (6H, m), 0.91 (3H, t, *J* = 7.1 Hz);
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 132.7, 128.2, 115.9, 109.5, 78.2, 67.8, 41.9, 36.7, 36.6, 35.2, 31.8, 27.7, 25.2, 24.0, 23.9, 22.4, 14.0;
HRMS (ESI^+)[M+Na]$^+$: found 301.2141. $C_{18}H_{30}NaO_2$ requires 301.2143.

*4.7(2S,3R)-3-Propylnonane-1,2-diol (**10**):*

To a solution of **9** (0.500 g, 10 mmol) in MeOH (20 mL), 10% palladium on charcoal (0.190 g, 10 mol %) was added and the mixture was kept under hydrogen (1 atm). The reaction mixture

was stirred at room temperature for 1 h and then the suspension was filtered through a pad of Celite, washed with ethyl acetate (2 x 50 mL) and the solvent was evaporated to yield the crude product, which without any chromatographic purification directly subjected in the next reaction. Solution of the above crude 1,4-dioxaspiro compound in methanol add 0.5 mL of conc. HCl was stirred at rt for 6 h. After completion of reaction, the reaction mixture was diluted with ethyl acetate (50 mL) and washed repeatedly with saturated aqueous NH_4OH solution (3 x 15 mL) till it was alkaline. The organic layer was dried and concentrated. Column chromatography of the residual mass [ethyl acetate/petroleum ether (1:1)] afforded the corresponding diol **10** (0.328 g) in 90% yield over two steps.

[Spectral data of **10**]: R_f = 0.2 (EtOAc/ hexane, 4:6);
$[\alpha]_D^{20}$= +7.54 (*c* =0.21, MeOH);
IR (neat): 3567, 3540, 925 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 – 3.65 (4H, m), 3.56 (2H, dd, *J* = 10.8, 8.6 Hz), 2.40 (3H, s), 1.47 – 1.18 (15H, m), 0.91 (3H, t, *J* = 7.3 Hz), 0.87 (3H, t, *J* = 7.0 Hz,);
^{13}C NMR (126 MHz, $CDCl_3$) δ, 74.3, 65.0, 40.7, 31.8, 31.6, 29.8, 29.7, 27.1, 22.6, 20.2, 14.5, 14.1;
HRMS (ESI^+)[M+ Na]$^+$: found 255.1832. $C_{12}H_{26}NaO_2$ requires 255.1830.

*4.8(R)-(-)-Arundic acid (**1**):*

To A mixture of 4-phenyl-1,2-butanediol **28** (80 mg, 0.395 mmol) and 1-Me-AZADO (5.90 mg, 0.0395 mmol) in MeCN (1.5 mL) and Phosphate buffer (0.7 mL, pH = 6.8) was stirred at room temperature. Then $NaClO_2$ (96.3 mg, 80%, 1.186 mmol in 0.3 mL H_2O) and dilute bleach (0.247 mL, 0.0395 mmol) were added simultaneously over 30 seconds. The mixture was stirred at room temperature for 3 h. It was quenched with phosphate buffer (3 mL, pH = 2.3), added NaCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials was purified by flash column chromatography to give *(R)-(-)-Arundic acid* **27** (67.7 mg, 92%).

[Spectral data of (*R*)-(-)-arundic acid **1**]-$[\alpha]_D^{25}$= -5.8 (*c* =2.00, EtOH); lit[7c]$[\alpha]_D^{20}$= -6.1 (*c* =2.00, EtOH);
IR: 1700 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.46 (1H, s), 2.29–2.21 (1H, m), 1.57–1.33 (14H, m), 1.01 (3H, t, *J* = 7.2 Hz), 0.99 (3H, t, *J* = 7.5 Hz);
^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 45.7, 34.8, 32.4, 31.53, 29.7, 27.8, 23.0, 20.4, 14.1, 14.0;
HRMS (ESI^+)[M+ H]$^+$: found 187.1696. $C_{11}H_{23}NaO_2$ requires 187.1698.

4.9(R)-2-((R)-Deca-1,5-dien-4-yl)-1,4dioxaspiro[4.5]decane(11):

The title compound was prepared from **8a** (0.250 g, 1.11 mmol) according to a procedure similar to that described for the conversion **8b** to **9** to give **11**(0.268 g 87%) as colourless oil.

[Spectral data of **11**]: R_f = 0.6 (EtOAc/ hexane, 1:5);
$[\alpha]_D^{20}$= +17.06 (*c* =0.58, MeOH);
IR (neat):1680, 1665, 1109, 925 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 – 5.72 (1H, m), 5.56 (1H, dtd, *J* = 11.3, 7.5, 0.8 Hz), 5.28 – 5.18 (1H, m), 5.07 – 4.97 (2H, m), 4.08 (1H, dd, *J* = 7.7, 6.3 Hz), 3.99 (1H, dd, *J* = 7.9, 6.3 Hz), 3.64 (1H, t, *J* = 7.7 Hz) 2.64 – 2.58 (1H, m), 2.32 – 2.22 (1H, m), 2.10 – 2.02 (3H, m), 1.66 – 1.58 (10H, m), 1.38 – 1.31 (6H, m), 0.94 (3H, t, *J* = 7.5);
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 132.4, 128.6, 115.9, 109.1, 77.6, 66.8, 40.0, 36.1, 35.9, 35.0, 31.8, 27.5, 25.23, 23.9, 23.8, 22.4, 14.0;
HRMS (ESI^+)[M+ Na]$^+$: found 301.2141. $C_{18}H_{30}NaO_2$ requires 301.2143.

*4.10 (2S,3S)-3-Propylnonane-1,2-diol) (**12**):*

The title compound was prepared from **11** (0.200 g, 0.718 mmol) according to a procedure similar to that described for the conversion **9** to **10** to give **12**(0.131 g 90%) as colourless thick oil.

[Spectral data of **12**]: R_f = 0.2 (EtOAc/ hexane, 4:6);
$[\alpha]_D^{20}$= +5.14 (c= 0.21, MeOH);
IR (neat): 3570, 3554 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 – 3.66 (2H, m), 3.55 (1H, dd, *J* = 10.8, 8.6 Hz,), 2.42 (2H, bs, exchangeable with D_2O), 1.46 – 1.16 (15H, m), 0.91 (3H, t, *J* = 7.1 Hz,), 0.87 (3H, t, *J* = 7.4 Hz,);
^{13}C NMR (126 MHz, $CDCl_3$) δ 74.2, 65.0, 40.7, 32.1, 31.8, 29.7, 29.3, 27.1, 22.6, 20.3, 14.4, 14.1;
HRMS (ESI^+)[M+ Na]$^+$: found 255.1832. $C_{12}H_{26}NaO_2$ requires 255.1830.

*4.11 (S)-(-)-Arundic acid (**1**)*

The title compound was prepared from **12** (0.040 g, 0.198 mmol) according to a procedure similar to that described for the conversion of **10** to **1** to give ***ent*-1** (0.034 g, 84%) as colourless oil.

[Spectral data of (*S*)-(-)-arundic acid *ent*-**1**]: $[\alpha]_D^{25}$= +6.3 (*c* =0.50, EtOH); lit[10]$[\alpha]_D^{25}$= +6.6 (*c* =0.54, EtOH);
IR (neat): 1700 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$) 11.27 (1H, s), 2.29–2.20 (1H, m), 1.56–1.19 (14H, m), 0.92 (3H, t, *J* = 7.4 Hz), 0.90 (3H, t, *J* = 7.6 Hz);
^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 45.7, 34.5, 32.4, 31.6, 29.3, 27.0, 22.5, 20.3, 14.3, 14.1;
HRMS (ESI^+)[M+ H]$^+$: found 187.1696. $C_{11}H_{23}NaO_2$ requires 187.1698.

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Supplementary Material