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A diethyltartrate-based synthesis of both (−)- and (+)-arundic acid

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ABSTRACT

A diethyltartrate-based synthesis of both enantiomers of the acute ischemic stroke therapeutic agent, arundic acid is presented. Separable diastereomers were obtained through the Johnson–Claisen rearrangement of the chiral vicinal diol based on the diethyltartrate skeleton and were converted separately into the two enantiomers of arundic acid.

Stroke is a major cause of death worldwide and is caused due to oxygen deprivation leading to rapid nerve cell death and dysfunction of the body part controlled by the affected nerve cells. Stroke is responsible for serious long-term disability, for example, paralysis, cognitive deficits, dementia, dizziness, vertigo, impaired vision, language deficits, emotional difficulties and pain. Research towards synthesis of new therapeutic agents and analogues of inhibitors to prevent and treat stroke is a priority. One novel agent that emerged is (*R*)-(−)-arundic acid **1** (Ono-2506,[1] Fig. 1), which has shown efficacy in preventing expansion of cerebral infarction by improving astrocyte function. Arundic acid is undergoing phase II development for the treatment of acute ischemic stroke, as well as clinical development in other neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.[2]

Arundic acid has been a synthetic target in recent years and a few enantioselective syntheses are reported in the literature.[3–9] The strategies employed so far are based on resolution of recemates,[3,7] asymmetric alkylation of chiral enolates,[4] chiral auxiliaries,[5,9] diastereoselective photodeconjugation[6] and metal-mediated crotylation.[8] In continuation of our research efforts in asymmetric synthesis of natural products[10] we have recently demonstrated that chiral vicinal diols are good platforms for separable diastereomers in the Johnson–Claisen rearrangement.[10e] We envisioned a similar strategy to synthesize both the enantiomers of arundic acid based on (*R*,*R*)-diethyltartrate as a chiral pool. Our retrosynthetic plan is shown in Scheme 1. Separation of C-4 diastereomers of **2**, acetonide deprotection, cleavage of 1,2-diol to acid and diene reduction was expected to give either enantiomers of arundic acid. The Johnson–Claisen rearrangement of allyl alcohol **4** with trimethylorthoacetate would give the diastereomer mixture **3** and further chain elongation would result in **2**. Compound **4** can easily be derived from (*R*,*R*)-diethyltartrate **5**.

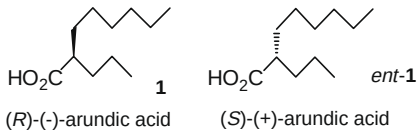
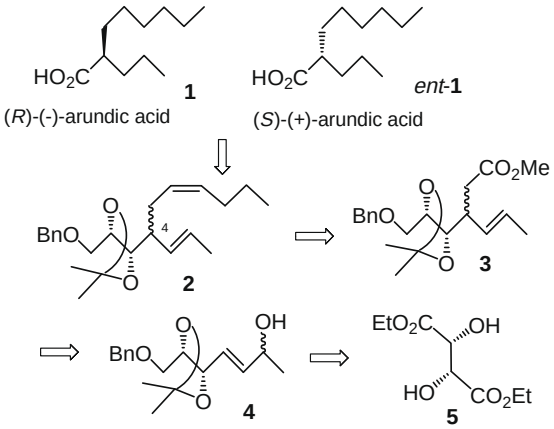


Figure 1. Arundic acids.



Scheme 1. Retrosynthetic analysis of (−)- and (+)-arundic acid.

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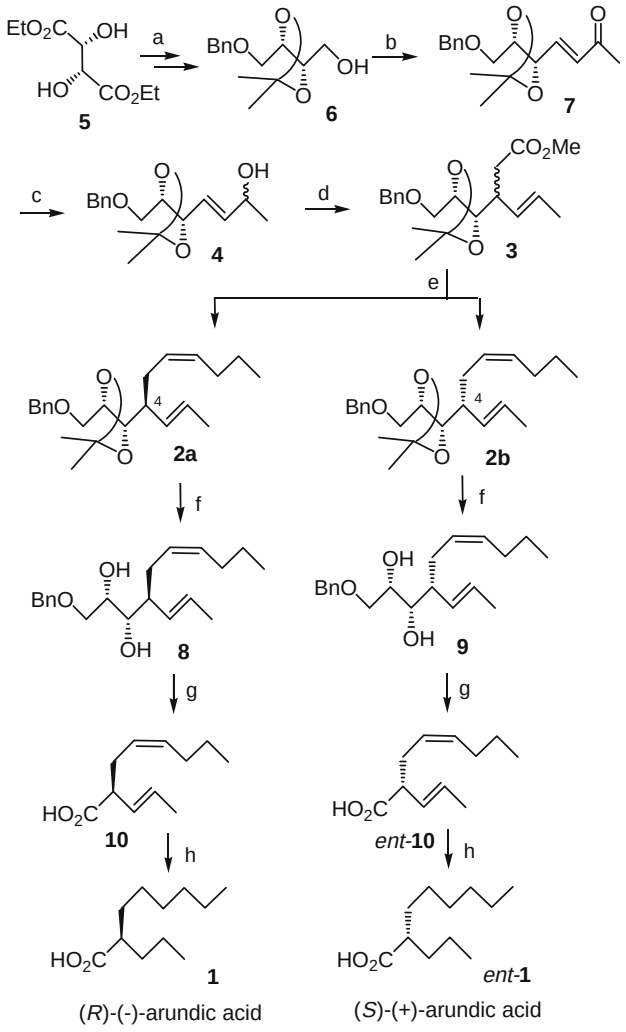

Scheme 2. Reagents and conditions: (a) Ref. 10a; (b) (i) $(COCl)_2$ (1.2 equiv), DMSO (1.5 equiv), −78 °C, 20 min, **6**, 1 h, Et_3N (4.0 equiv), −60 °C, 30 min, to rt, 1 h; (ii) $Ph_3P{=}CHCOCH_3$ (1.2 equiv), THF, rt, 12 h, 82% (two steps); (c) DIBAL-H (1.5 equiv), 0 °C, CH_2Cl_2, 2 h, 95%; (d) $MeC(OMe)_3$ (10.0 equiv), $EtCO_2H$ (cat), toluene, reflux, 12 h, 85%; (e) (i) DIBAL-H (1.1 equiv), −80 °C, CH_2Cl_2, 2 h; (ii) $Ph_3P^+CH_2CH_2CH_2$-CH_3Br^- (1.3 equiv), *n*-BuLi (1.4 equiv), THF, −80 °C, 15 min, aldehyde from **3**, warmed to rt, 8 h, **2a** (41%), **2b** (40%); (f) 3 N HCl, MeOH, rt, 6 h, 90%; (g) (i) $NaIO_4$ (2.0 equiv), $NaHCO_3$, CH_2Cl_2, rt, 6 h; (ii) $NaClO_2$ (10 equiv), $NaH_2PO_4{\cdot}H_2O$ (7.0 equiv), cyclohexene (5.0 equiv), *t*-BuOH, rt, 12 h, 66% (two steps); (h) H_2 (4 atm), Pd–C, MeOH, 2 h, 96%.

The synthesis of both enantiomers of arundic acid by a common strategy is depicted in Scheme 2. (*R*,*R*)-Diethyl tartrate **5** was converted into the known alcohol **6**.[10a] Oxidation of the alcohol **6** and subsequent Wittig olefination provided the α,β-unsaturated methyl ketone **7** in good yields of 82%. DIBAL-H reduction of the ketone led to the allyl alcohol **4** (95%) which on Johnson–Claisen rearrangement[11] (with trimethylorthoacetate and catalytic propionic acid) provided calcd[12] 1:1, C-3 diastereomeric mixture **3** in 85% yield. The reduction of methyl ester with DIBAL-H and subsequent Wittig olefination of the corresponding aldehyde at −80 °C provided the C-4 diastereomers **2a** and **2b** which were efficiently separated by flash column chromatography in 41% and 40% yields, respectively.[13,14] Deprotection of the acetonide functionality in **2a** and **2b** led to the diols **8** and **9**, respectively (90% for each). The $NaIO_4$-mediated cleavage of the diol **8** followed by further oxidation of the corresponding aldehyde furnished the acid **10** in 66% yield. Reduction of the diene functionality by hydrogenation provided the (*R*)-(−)-arundic acid **1**,[15] in 96% yield, $[\alpha]_D^{25}$ −6.8 (*c* 0.82, EtOH), lit.[7] $[\alpha]_D^{25}$ −6.1 (*c* 2, EtOH). A similar sequence of reactions with **2b** gave the acid *ent*-**10** which on hydrogenation led to (*S*)-(+)-arundic acid *ent*-**1**,[15] $[\alpha]_D^{25}$ +6.6 (*c* 0.54, EtOH).

In summary, we have developed an efficient strategy to both enantiomers of arundic acid. The highlights of the synthesis are (i) the use of (*R*,*R*)-diethyltartrate as a chiral pool to generate the separable diastereomers in the Johnson–Claisen rearrangement, (ii) a stereodivergent approach targeting both enantiomers of arundic acid in seven steps from the known compound **6** and in 21% overall yield and (iii) the versatility of the intermediates (e.g., **3**) for the synthesis of analogues by changing the chain length of the Wittig reagent to get different alkyl groups attached. Further application of this strategy to the synthesis of other related natural products is in progress.

Acknowledgements

The authors are indebted to IRCC, IIT-Bombay for financial support. A.B.I. is grateful to CSIR New Delhi for a research fellowship.

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12. Diastereomeric ratio was determined by ^1H NMR.
13. The relative configuration for the C-4 centre in **2a** and **2b** was assigned after converting them separately into the known enantiomers of arundic acid and working backward. In flash column chromatography the compound **2b** was eluted first followed by **2a** (petroleum ether/EtOAc, 95:5).
14. *Data for* **2a**: Colourless oil. $[\alpha]_D^{25}$ −20.2 (*c* 1.1, $CHCl_3$). IR ($CHCl_3$): ν = 3012, 2983, 2932, 2863, 1600, 1495, 1455, 1379, 1251, 1215, 1169, 1087, 971, 905, 856, 758, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.89 (t, *J* = 7.3 Hz, 3H), 1.21–1.35 (m, 2H), 1.39 (s, 6H), 1.67 (d, *J* = 5.2 Hz, 3H), 1.96–2.06 (m, 2H), 2.07–2.12 (m, 2H), 2.13–2.28 (m, 1H), 3.53 (d, *J* = 4.9 Hz, 2H), 3.88 (dd, *J* = 8.4, 2.3 Hz, 1H), 3.97–4.01 (m, 1H), 4.59 (d, *J* = 7.0 Hz, 2H), 5.22–5.3 (m, 1H), 5.31–5.42 (m, 3H), 7.27–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.7, 26.8, 26.9, 27.0, 27.1, 29.3, 44.3, 70.5, 70.7, 73.3, 79.9, 108.7, 126.8, 127.1, 127.4, 127.5, 127.6, 128.2, 128.3, 129.0, 130.8, 138.0. HRMS (ESI-TOF) (*m*/*z*) [M$^+$] calcd for $C_{23}H_{34}O_3$: 358.2509, found 358.2514.
Data for **2b**: Colourless oil. $[\alpha]_D^{25}$ −17.2 (*c* 3.2, $CHCl_3$). IR ($CHCl_3$): ν = 3019, 2868, 1602, 1451, 1380, 1372, 1216, 1163, 1084, 1040, 971, 916, 858, 757, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.88 (t, *J* = 7.3 Hz, 3H), 1.31–1.38 (m, 2H), 1.41 (s, 3H), 1.42 (s, 3H), 1.55 (dd, *J* = 6.4, 1.5 Hz, 3H), 1.95–2.0 (m, 2H), 2.0–2.1 (m, 1H), 2.15–2.2 (m, 1H), 2.38–2.41 (m, 1H), 3.41–3.43 (m, 1H), 3.57 (dd, *J* = 10.5, 2.6 Hz, 1H), 3.65 (t, *J* = 8.1 Hz, 1H), 3.94–3.98 (m, 1H), 4.58 (d, *J* = 6.4 Hz, 2H), 4.99–5.04 (m, 1H), 5.25–5.5 (m, 3H), 7.31–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.7, 27.0, 27.1, 27.2, 27.9, 29.8, 48.2, 70.8,

73.2, 79.3, 79.7, 108.8, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 129.1, 129.8, 130.6, 138.1. HRMS (ESI-TOF) (*m*/*z*) [M^+] calcd for $C_{23}H_{34}O_3$: 358.2509, found 358.2511.

15. The spectroscopic and analytical data including optical rotation of **1** and **2** were in full agreement with those reported.[7,9] The sign of optical rotation values reported in Ref. 9 is just reverse for each enantiomer.