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Simple Methods for the Preparation of Enantiomerically Pure Abscisic Acid (ABA) Analogues from (S)-(+)-ABA

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SIMPLE METHODS FOR THE PREPARATION OF ENANTIOMERICALLY PURE ABSCISIC ACID (ABA) ANALOGUES FROM (*S*)-(+)-ABA

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ABSTRACT: (1'*S*, 2*Z*, 4*E*)-3-Methyl-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexenyl)-2,4-pentadienoic acid (abscisic acid, ABA) is efficiently converted into the corresponding aldehyde, primary alcohol, and triol derivatives using readily available reagents (oxalyl chloride, $NaBH_4$, MnO_2) and simple reaction conditions.

Abscisic acid (ABA, **1**), a widely distributed plant hormone, is implicated in the regulation of a variety of biological processes including inhibition of germination, reduction of transpiration, and induction of cold tolerance.[1,2] Despite the large number of ABA structure-activity studies that have been carried out, few definitive conclusions can be drawn due, in part, to the frequent use of racemic materials.[1,2] Several syntheses of ABA have been reported.[3,4] Synthetic (±)-ABA and the natural (*S*)-(+)-ABA (**1**) are available commercially[5] and both the resolution[6] and HPLC separation[7] of the racemate have been reported. However, because of its high cost, the use of ABA as a starting material for analogue synthesis has been impractical. Until now, most ABA analogues have been

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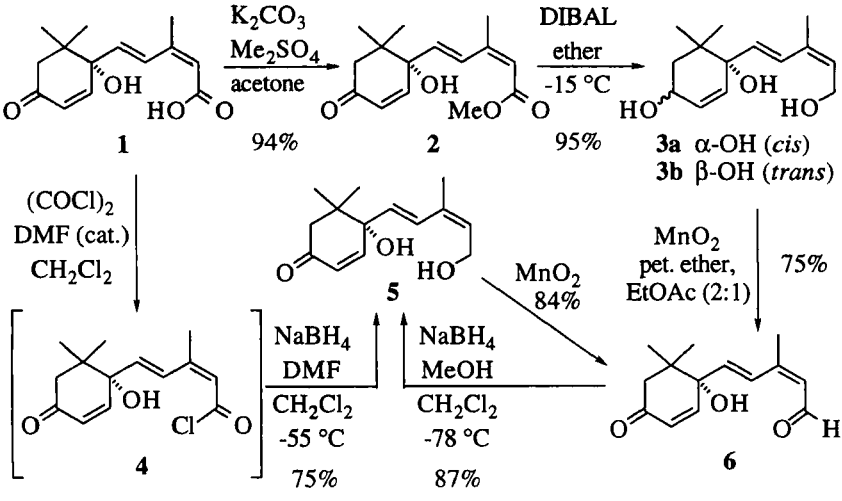
prepared by total synthesis,[8] usually in racemic form, and typically by adaptation of the route of Mayer *et al.*[3e] Thus, obtaining enantiomerically pure analogues has normally required resolution or separation of the racemates.[9] (*S*)-(+)-ABA can be obtained by fermentation[10] and, recently, has become available in large quantities.[11] Consequently, the use of (*S*)-(+)-ABA as a starting material for analogue synthesis is now a viable option and herein we report the efficient conversion of (*S*)-(+)-ABA into the enantiomerically pure analogues **3a**, **3b**, (*S*)-(+)-ABA-CH_2OH (**5**), and (*S*)-(+)-ABA-CHO (**6**) (Scheme 1).

Scheme 1



Both (±)-ABA-CH_2OH (**5**) and (±)-ABA-CHO (**6**) have been reported to have greater inhibitory activity in seed germination assays than (±)- or (+)-ABA (**1**).[12] We set out to prepare the enantiomerically pure analogues (+)-**5** and (+)-**6** by reduction of (*S*)-(+)-ABA (**1**). The methyl ester **2** has been prepared numerous times by reaction of **1** with CH_2N_2;[7] we obtained **2** in near quantitative yield by treatment **1** with K_2CO_3 and $(CH_3)_2SO_4$. Reduction of **2** with DIBAL gave the triols **3** as a separable 1.4:1 mixture of the *trans*- and *cis*-isomers, **3b** and **3a**

respectively. Both **3b** and *ent*-**3a** have been prepared by total synthesis and their MnO_2 oxidation to the aldehydes **6** (80%) and *ent*-**6** (65%), respectively, has been reported.[4e] In our hands, MnO_2 oxidation[13] of **3** in CH_2Cl_2[4e] or THF[3e] resulted in poor yields of aldehyde **6** (40-50%); however, conducting the oxidation in a 2:1 mixture of petroleum ether and EtOAc gave (+)-ABA-CHO (**6**) in 75% yield (71% from ABA). Chemoselective reduction of the aldehyde group in **6** with $NaBH_4$ using our previously developed protocol[14] gave (+)-ABA-CH_2OH (**5**) (87%; 61% from ABA).

We also investigated the direct conversion of **1** to **5** and **6**. Numerous methods for the selective reduction of a carboxylic acid group to an aldehyde or primary alcohol have been reported.[15] Considering the chemoselectivity required for the desired transformations, we initially examined the reaction of **1** with $BH_3{\cdot}SMe_2$ alone[16] and in the presence of $B(OMe)_3$.[17] In both cases, a mixture of several products was obtained, some of which appeared to be dihydroxy acids thereby indicating poor chemoselectivity. Alternatively, ABA (**1**) was converted into the unstable acid chloride **4**. Attempted reduction of **4** with $NaBH_4$ in CH_2Cl_2/HOAc[18] or in EtOH/CH_2Cl_2,[14] conditions that can chemoselectively reduce an enal in the presence of a enone, failed to give **5** in the former case, and in the latter, gave the desired (+)-ABA-CH_2OH (**5**) along with the ethyl ester resulting from reaction of **4** with EtOH. Similarly, reduction of **4** with Bu_4NBH_4 in CH_2Cl_2 gave **5** in poor yield.[19] Finally, reaction of of **4** with $NaBH_4$ in DMF/THF[20] gave (+)-ABA-CH_2OH (**5**) in 75% yield in one operation from **1**. We were unable to obtain the aldehyde **6** in good yield by a similar reduction in the presence of pyridine.[20] Oxidation of **5** using MnO_2 in petroleum ether and EtOAc (2:1) gave (+)-ABA-CHO (**6**) in 84% yield (63% from ABA).[21]

In summary, we have converted (*S*)-(+)-ABA (**1**) into several enantiomerically pure derivatives (**2**, **3a**, **3b**, **5**, **6**) in good yields using readily

available reagents and simple reaction conditions that do not require any special equipment or techniques. These and other compounds similarly derived from **1** will be of interest to researchers studying ABA structure-activity relationships.

Experimental[22]

Methyl (1'*S*, 2*Z*, 4*E*)-3-Methyl-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexenyl)-2,4-pentadienoate (2). A stirred suspension of (*S*)-(+)-ABA (**1**)[11] (1.0 g, 3.8 mmol), dimethyl sulfate (0.93 mL, 9.84 mmol), and K_2CO_3 (2.62 g, 18.9 mmol) in acetone (50 mL) was heated under refluxed for 1 h. The cooled (rt) mixture was extracted with ethyl acetate (×3), and the combined organic layer was washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a solid (990 mg, 94%): m.p. 103-104 °C (ether, hexane); $[\alpha]_D$ +360 (*c* 1.0, C_2H_5OH); IR ν_{max} 3486, 3031, 2960, 1714, 1661, 1601, 1435, 1236, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 16 Hz), 6.15 (1H, d, *J* = 16 Hz), 5.93 (1H, s), 5.74 (1H, s), 3.69 (3H, s), 2.46 (1H, d, *J* = 17 Hz), 2.27 (1H, d, *J* = 17 Hz), 2.00 (3H, s), 1.91 (3H, s), 1.10 (3H, s), 1.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8 (s), 166.4 (s), 162.5 (s), 149.4 (s), 136.3 (d), 128.1 (d), 127.1 (d), 118.2 (d), 79.7 (s), 51.2 (q), 49.8 (t), 41.5 (s), 24.3 (q), 23.1 (q), 21.2 (q), 18.9 (q); LRMS (CI, NH_3), *m/z* (relative intensity): 279 ($[M+1]^+$, 99), 261 (100), 247 (15), 190 (90), 162 (24). HRMS *m/z* calcd. for $C_{16}H_{22}O_4$: 279.1596 (M+H); found: 279.1597. Elemental analysis calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97; found: C, 69.18; H, 8.08.

(1'*S*, 2*Z*, 4*E*, 4'*RS*)-5-(1,4-Dihydroxy-2,6,6-trimethyl-2-cyclohexen-1-yl)-3-methyl-2,4-pentadien-1-ol (3). DIBAL (1.5 M in toluene; 7.6 mL, 11.4 mmol) was added dropwise via syringe to a solution of ester **2** (740 mg, 2.66 mmol) in ether (10 ml) at -10 to -20 °C under argon. The mixture was stirred for 30 min at -10 to -20 °C and then quenched by addition of methanol

(2 mL). The ice bath was removed and the mixture was stirred at rt for ca. 1 h (a white precipitate comes out). The mixture was diluted with ether and washed with sat. NaCl, dried over Na_2SO_4, and concentrated to give **3** as a 1.4:1 mixture of *trans*- and *cis*-isomers (675 mg, quantitative) which was used without further purification. Fractionation of the product from a similar experiment (**2**, 100 mg) by medium pressure chromatography (MPC)[23] (10% methanol in CH_2Cl_2) gave the *cis*-triol **3a** (35 mg, 39%) and the *trans*-triol **3b** (48 mg, 53%).

(1'*S*, 2*Z*, 4*E*, 4'*R*)-5-(1,4-Dihydroxy-2,6,6-trimethyl-2-cyclohexen-1-yl)-3-methyl-2,4-pentadien-1-ol (3a). $[\alpha]_D$ +107 (*c* 1.7, C_2H_5OH); IR ν_{max} 3342, 2939, 1445, 1436, 1019, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 15.5 Hz), 5.67 (1H, d, *J* = 15.5 Hz), 5.57 (2H, m), 4.28 (3H, m), 2.58 (3H, br s), 1.85 (3H, s), 1.73 (2H, m), 1.64 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.4 (s), 134.7 (s), 132.3 (d), 127.9 (d), 127.6 (d), 126.3 (d), 77.4 (s), 65.3 (d), 58.1 (t), 42.2 (t), 38.4 (s), 24.5 (q), 24.3 (q), 20.7 (q), 19.5 (q); LRMS (FAB, glycerol/LiBr), *m/z* (relative intensity): 259 ($[M+Li]^+$, 15), 191 (17), 100 (100). HRMS *m/z* calcd. for $C_{15}H_{24}O_3$: 259.1885 (M+Li); found: 259.1873. Elemental analysis calcd. for $C_{15}H_{24}O_3$: C, 70.81; H, 9.94; found: C, 70.38; H, 9.50.

(1'S, 2Z, 4E, 4'S)-5-(1,4-Dihydroxy-2,6,6-trimethyl-2-cyclohexen-1-yl)-3-methyl-2,4-pentadien-1-ol (3b). $[\alpha]_D$ +221 (*c* 2.4, C_2H_5OH) (lit.[4e] +216; 1% in C_2H_5OH); IR ν_{max} 3366, 2969, 1449, 1436, 1103, 1018, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (1H, d, *J* = 15.5 Hz), 5.74 (1H, d, *J* = 15.5 Hz), 5.56 (2H, m), 4.20 (3H, m), 2.75 (3H, br s), 1.83 (3H, s), 1.70 (1H, dd, *J* = 6,13 Hz), 1.62 (3H, s), 1.51 (1H, dd, *J* = 10,13 Hz), 0.98 (3H, s), 0.87 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (s), 135.0 (s), 133.5 (d), 128.0 (d), 127.4 (d), 126.3 (d), 79.5 (s), 65.4 (d), 43.7 (t), 39.8 (s), 24.8

(q), 22.3 (q), 20.5 (q), 17.9 (q); LRMS (FAB, glycerol/LiBr), *m/z* (relative intensity): 259 ([M+Li]$^+$, 14), 191 (11), 100 (100). HRMS *m/z* calcd. for $C_{15}H_{24}O_3$: 259.1885 (M+Li); found: 259.1878. Elemental analysis calcd. for $C_{15}H_{24}O_3$: C, 70.81; H, 9.94; found: C, 70.45; H, 9.68.

(1'*S*, 2*Z*, 4*E*)-3-methyl-5-(1-hydroxy-4-oxo-2,6,6-trimethyl-cyclohex-2-en-1-yl)-2,4-pentadien-1-ol (5). Method A:[14] $NaBH_4$ (0.285 g, 7.5 mmol) was added to a solution of **6** (0.186 g, 0.75 mmol) in 38% (v/v) methanol in CH_2Cl_2 (30 mL) at -78 °C. The reaction mixture was stirred for 2.5-3 h at -78 °C and then acetaldehyde (1 mL) was added. The mixture was allowed to warm to rt and then was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated, and fractionated by flash column chromatography (FCC)[24] (5% methanol in CH_2Cl_2) to give **3** (10 mg, 2.6%) and **5** (0.164 g, 87%).

Method B:[20] Oxalyl chloride (0.050 mL, 0.57 mmol) was dropwise added to a solution of (*S*)-(+)-ABA (**1**) (0.10 g, 0.38 mmol) and dry DMF (0.015 mL, 0.19 mmol) in dry CH_2Cl_2 (5 mL) at 10-15 °C. After 30 min, the reaction mixture had turned yellow and the solvent was removed on a rotary evaporator. The yellow residue was dissolved in dry THF (7.5 mL) and $NaBH_4$ (4 M in DMF; 0.68 mL, 2.7 mmol) was added at -55 °C to the stirred solution. After 2.5 h at -55 °C, the reaction was quenched by addition of acetic acid (0.5 mL) and then the mixture was diluted with ethyl acetate, washed with sat. $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was fractionated by FCC (5% methanol in CH_2Cl_2) to give **5** (71 mg, 75%): m.p. 104-105 °C (ethyl acetate, hexane); $[\alpha]_D$ +335 (*c* 1.0, C_2H_5OH); IR ν_{max} 3589, 3027, 2968, 1657, 1650, 1373 cm^{-1}; ^{1}H NMR[25] (300 MHz, $CDCl_3$) δ 6.75 (1H, d, *J* = 15.5 Hz), 5.90 (1H, s), 5.80 (1H, d, *J* = 15.5 Hz), 5.62 (1H, br t, *J* = 6.5 Hz), 4.29 (2H, ap d, *J* = 6.5 Hz), 2.45 (1H, d, *J* = 17 Hz), 2.26 (1H, d, *J* = 17 Hz), 1.89 (3H, s), 1.85 (3H, s), 1.08 (3H, s), 0.99 (3H,

s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3 (s), 163.3 (s), 134.2 (s), 130.7 (d), 129.4 (d), 127.0 (d), 126.7 (d), 79.6 (s), 58.2 (t), 49.7 (t), 41.4 (s), 24.3 (q), 23.0 (q), 20.6 (q), 19.0 (q); LRMS (FAB, glycerol/LiBr), *m/z* (relative intensity): 257 ($[M+Li]^+$, 67), 191 (10), 105 (42), 100 (100). HRMS *m/z* calcd. for $C_{15}H_{22}O_3$: 257.1729 (M+Li); found: 257.1741. Elemental analysis calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; found: C, 71.89; H, 8.80.

(1'*S*, 2*Z*, 4*E*)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-2,4-pentadienal (6). Method A. Manganese dioxide (7 g) was added to a solution of **3** (a 1.4:1 mixture of **3b**:**3a**; 0.35 g, 1.4 mmol) in ethyl acetate (20 mL) and petroleum ether (40-60°C; 40 mL) and the mixture was stirred for 1 h at rt and then filtered. The combined filtrate and ethyl acetate washings was concentrated to give **6** as a solid (0.255 g, 74%).

Method B. Oxidation of **5** (0.120 g, 0.48 mmol) with manganese dioxide (1.2 g) as described above gave **6** as a solid (0.100 g, 84%): m.p. 124-125°C (CH_2Cl_2, hexane) (lit.[4e] 127-128 °C); $[\alpha]_D$ +417 (*c* 1.0, C_2H_5OH) (lit.[4e] +450; 1% in C_2H_5OH); IR ν_{max} 3475, 3028, 2965, 2873, 2760, 1684, 1650, 1631, 1587, 1133 cm^{-1}; ^1H NMR[25] (300 MHz, $CDCl_3$) δ 10.18 (1H, d, *J* = 8 Hz), 7.49 (1H, d, *J* = 15.5 Hz), 6.21 (1H, d, *J* = 15.5 Hz), 5.93 (1H, s), 5.92 (1H, d, *J* = 8 Hz), 2.77 (1H, br s), 2.47 (1H, d, *J* = 17 Hz), 2.33 (1H, d, *J* = 17 Hz), 2.08 (3H, s), 1.91 (3H, s), 1.11 (3H, s), 1.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6 (s), 190.3 (d), 162.1 (s), 153.3 (s), 137.8 (d), 129.2 (d), 127.2 (d), 126.0 (d), 79.6 (s), 49.7 (t), 41.5 (s), 24.4 (q), 23.1 (q), 21.5 (q), 18.9 (q); LRMS (CI, NH_3), *m/z* (relative intensity): 266 ($[M+18]^+$, 21), 249 ($[M+1]^+$, 100), 233 (23), 231 (36), 192 (21), 95 (41). HRMS *m/z* calcd. for $C_{15}H_{20}O_3$: 249.1490 (M+H); found: 249.1499. Elemental analysis calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; found: C, 72.33; H, 8.13.

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