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One Pot Synthesis and Optical Resolution of Synthetic Mimic of Abscisic Acid Affecting Plant's Physiology

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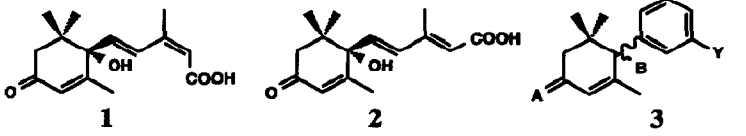
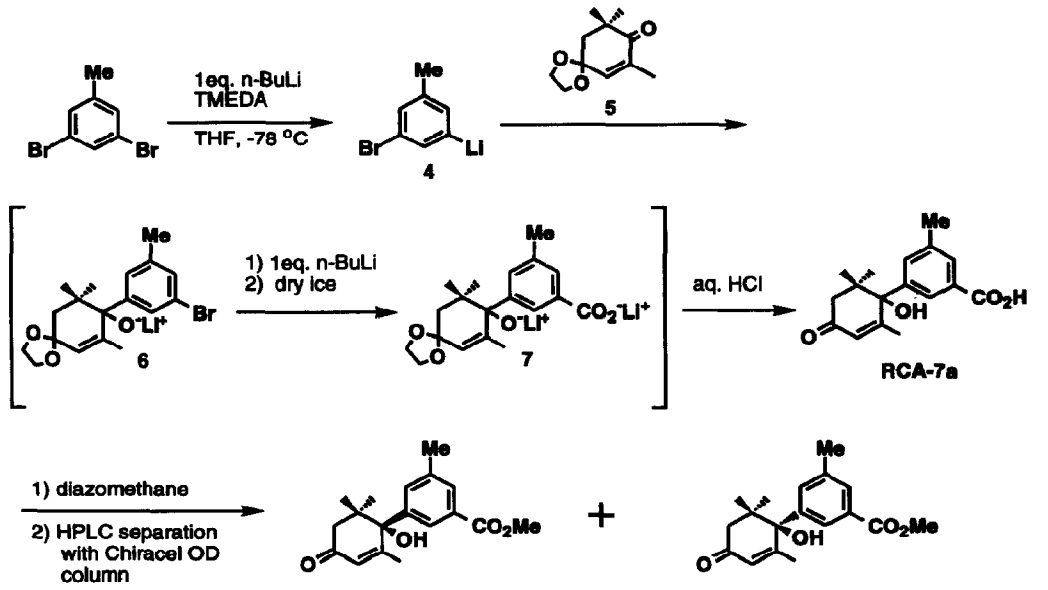
Abstract: When conjugated dienic side chain of abscisic acid is substituted with 3-carboxyl-5-methylphenyl group, the product shows abscisic acid-like activity. We developed one pot synthetic pathway of it, which was optically resolved with chiral HPLC column.

Abscisic acid (ABA, **1**) is a plant hormone regulating many physiological processes in plants. However, it has a serious drawback for its application as a plant growth regulator, because 1) its side chain (2-*Z*-4-*E*-3-methyl-2,4-pentadienoic acid moiety) is readily isomerized to a biologically inactive 2-*E* isomer (**2**) by light and 2) it is readily metabolized into an inactive form. Creating highly active ABA analogues, whcih have a solid structure in its side chain and show a resistance against metabolism, may provide new compounds as useful plant growth regulators, and may provide an understanding of the mechanism of functions of ABA. Despite of intensive works, previously synthesized chemicals did not have enough ABA-like activity[1]. Recently, we reported that replacement of the side chain of ABA with a phenyl group substituted with the proper functional groups resulted in light-stable racemic ABA analogues (**3**). Some of these newly synthesized compounds exhibited biological activities equivalent to 1/3 to 1/10 that of ABA[2] in the bioassay tests for ABA. While, these compounds showed a greater duration of germination inhibitory activity[3] than ABA and killed grass in *in vivo* test[4]. Through the structure-activity relationships studies on **3**, we found that the combination of the functional groups of A=O, B=OH, X=Me and Y= COOH was the best for activity exhibition (we called this compound as RCA-7a). The previous synthesis of RCA-7a required more than 15 steps , therefore, a simpler synthetic method has been required. In this paper, we report the one-pot synthesis and optical resolution of RCA-7a.



RCA-7a was prepared as shown in the scheme. We used the previously reported ketoketal **5**[5] and commercially available 3, 5-dibromotoluene as starting materials. Ketoketal **5** was prepared from ketoisophorone in high yield. The key steps in the scheme are coupling reaction of **5** and 3, 5-dibromotoluene and carboxylation reaction of **6** with dry ice. In this reaction, 3, 5-dibromotoluene was firstly treated with one equivalent of *n*-buthyllithium to afford mono-lithiated intermediate, which reacted with **5** to give **6**. Coupled intermediate **6** was again treated with one equivalent of *n*-buthyllithium to give dilithiated intermediate. After 10 min, excess amount of dry ice was added and a key intermediate **7** was thus yielded in an one pot reaction. After carboxylation with dry ice, racemic RCA-7a was readily available by treating the reaction mixture with aqueous hydrochloric acid, followed by separation by silica gel column and recrystallization. Total yield from starting material was more than 40 %, that was remarkably improved when compared with that of the previously reported method[2a]. ^{1}H-NMR data of RCA-7a thus obtained[6] were in good agreement with those of the compound listed in the previous paper[2a]. Racemate was converted to methyl ester with diazomethane and methyl ester of RCA-7a was optically resolved with chiral HPLC column (Chiracel OD, Daicel Chemical Industries, Ltd.) eluted with the solvent of MeOH: H_2O=90: 10. Successive demethylation with KOH in

refluxing EtOH and acidification with aq.HCl gave each enantiomer of (+)-RCA-7a ($[\alpha]_D$ +165.3°) and (-)-RCA-7a ($[\alpha]_D$ -178.6°).



Synthetic procedure of RCA-7a

n-Butyl lithium (22 mmol) in *n*-hexane was added dropwise to a stirred solution of 5.0 g (20 mmol) of 3,5-dibromotoluene and 2.32 g (20 mmol) of tetramethylethylenediamine in 50 ml of dry THF at -78 °C under N_2 flow and stirred for 10min. Then, 3.92 g of ketoketal **5** (20 mmol) in 20 ml of dry THF was added dropwise to the solution. After 30 min, *n*-butyl lithium (22 mmol) in *n*-hexane was again added dropwise to the stirred solution at -78 °C and stirred for 10 min. Excess amount of dry ice was added to the solution and then dry ice bath was removed and the solution was allowed to warm to room temperature. The reaction mixture was poured into 300 ml of 0.5N hydrochloric acid and extracted three times with ethyl acetate. After drying the organic phase with anhydrous sodium sulfate, the solvent was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel (*n*-hexane: EtOAc= 4: 1) to give crude RCA-7a. Recrystallization (MeOH-H_2O) gave 2.73 g (44 %) of RCA-7a.

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6. ^{1}H-NMR: 0.75(3H, s), 1.20(3H, s), 1.84(3H, s), 2.15(1H, d, J=17Hz), 2.36(1H, d, J=17Hz), 2.41(3H, s), 6.18(1H, s), 7.43(1H, s), 7.82(1H, s), 7.94(1H, s).

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