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New approach for two chromene carboxylic acids having a fully substituted benzene ring

Seiji Yamaguchi,* Mikiko Maekawa, Yohei Murayama, Masahiro Miyazawa and Yoshiro Hirai

Department of Chemistry, Faculty of Science, Toyama University, Toyama 930-8555, Japan

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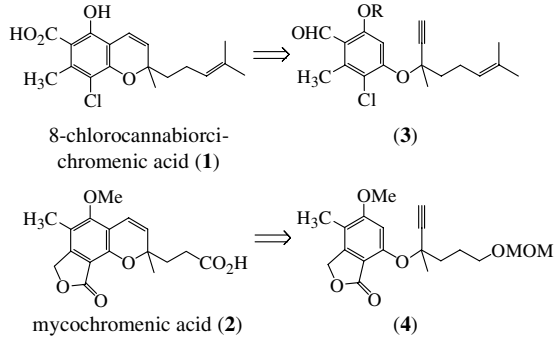
Abstract—Two chromene carboxylic acids having a fully substituted benzene ring, 8-chlorocannabiorcichromenic acid (**1**) and mycochromenic acid (**2**), were synthesized via thermal cyclization of the corresponding four substituted phenyl propargyl ethers.

Many 2*H*-chromenes, having a long side-chain at position 2, have been isolated from various plants.[1] In our previous paper, we reported a new approach for natural cannabichromene using condensation of a salicyl aldehyde with isopropylidenemalonate giving 2*H*-chromene-2-acetate and following side-chain conversion.[2] We also reported another approach for teretifolione B using regioselective thermal cyclization of the corresponding phenyl propargyl ether.[3] Now, in this paper, the syntheses of two 2*H*-chromene carboxylic acids having a fully substituted benzene ring, 8-chlorocannabiorcichromenic acid (**1**), isolated from *Cylindrocapron olidum*,[4] and mycochromenic acid (**2**), isolated from *Penicillium brevicompactum*,[5] are described (Scheme 1).



Scheme 1. Strategy for 8-chlorocannabiorcichromenic acid (**1**) and mycochromenic acid (**2**) via thermal cyclization.

Once, respective approaches to natural 8-chlorocannabiorcichromenic acid (**1**) and mycochromenic acid (**2**) used the condensation method, but the results were unsuccessful.[6] For respective approaches of natural **1** and **2** using the thermal cyclization method, both efficient preparation of the corresponding propargyl ethers **3** and **4** and effective cyclization might be needed. Some papers described that some propargyl ethers having an electron-withdrawing carbonyl group showed low yields in cyclization, but we showed these were ambiguous, in our previous paper.[3] In the paper, we also described the regioselectivity in thermal cyclization. These two chromene carboxylic acids show a fully substituted benzene ring. And we might expect more effective cyclization of **3** and **4**, because they have the only site for cyclization.

The substrate **3** might be prepared by coupling of 3-chloro-4-hydroxy-2-methyl-6-(protected)oxybenzaldehyde **5** with 3,7-dimethyl-oct-6-en-1-yn-3-yl methyl carbonate **6b** and the substrate **4** might be prepared by coupling of 7-hydroxy-4-methyl-5-(protected)oxyphthalide **9** with 3-methyl-6-(protected)oxy-oct-1-yn-3-yl methyl carbonate **6c**.

As the starting material for **1**, 3-chloro-4,6-dihydroxy-2-methylbenzaldehyde **5c**, was prepared from 3,5-dimethoxytoluene in three steps: (1) Vilsmeier formylation with DMF–$POCl_3$ (90%), (2) chlorination with NCS–DMF (75%), (3) deprotection with BBr_3 (95%), and then converted to its 6-methoxy derivative **5a** in three steps: (1) MOM protection with MOMCl–diisopropylamine (99%), (2) methylation with Me_2SO_4–K_2CO_3 (92%), (3)

* Corresponding author. Tel.: +81-76-445-6617; fax: +81-76-445-6549; e-mail: seiji@sci.toyama-u.ac.jp

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deprotection with MeOH–concd. HCl (57%) and to its 6-MOMoxy derivative **5b** in three steps: (1) acetylation with Ac_2O–pyridine (81%), (2) MOM protection with MOMCl–diisopropylamine (99%), (3) deprotection with aq NaOH–EtOH (63%) (Scheme 2).

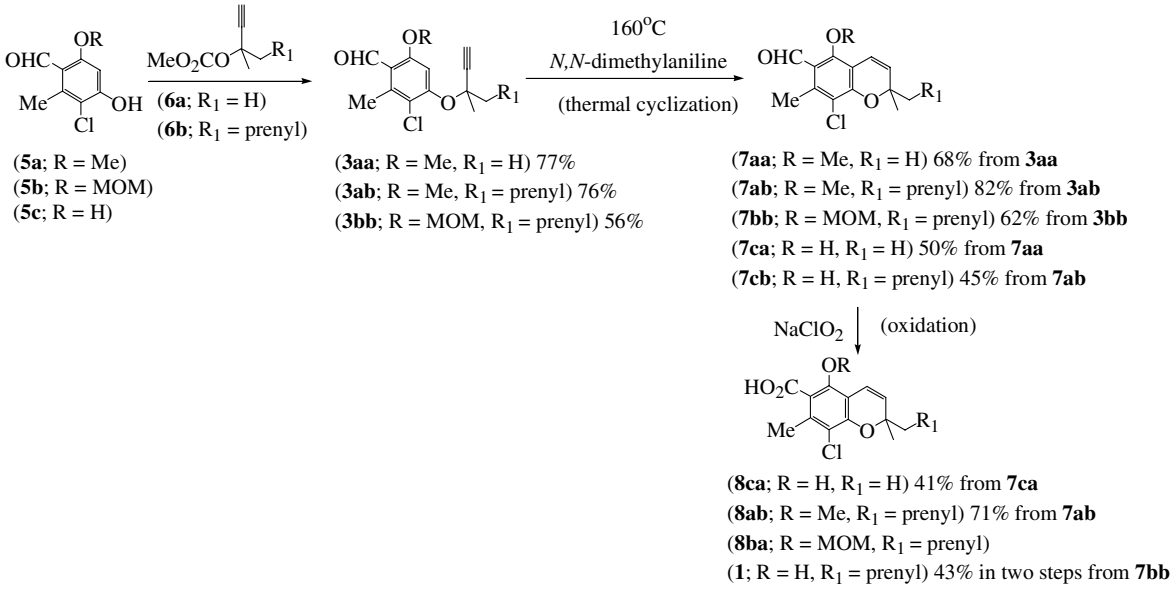
As the stating material for **2**, 7-hydroxy-5-methoxy-4-methylphthalide **9**, was prepared from 3,5-dimethoxybenyl methyl ether in six steps: (1) Vilsmeier formylation with DMF–$POCl_3$ (93%), (2) Wolf-Kishner reduction with NH_2NH_2–KOH (89%), (3) Vilsmeier formylation with DMF–$POCl_3$ (75%), (4) oxidation with $NaClO_2$ (61%), (5) lactonization with NaOH (64%), (6) selective demethylation with MgI_2–OEt_2 (72%).

Coupling and thermal cyclization of **5a** were prestudied with a dimethyl analog; coupling of **5a** with methyl 2-methylbut-3-yn-2-yl carbonate **6a** using $CuCl_2$–DBU gave the corresponding propargyl ether **3aa** (77%), and the following thermal cyclization gave 2,2-dimethyl-2*H*-chromene **7aa** (68%). And, **7aa** was converted to 5-hydroxy-6-carboxylic acid **8ca** by demethylation with MgI_2–OEt_2 (50%) followed by oxidation with $NaClO_2$ (41%).

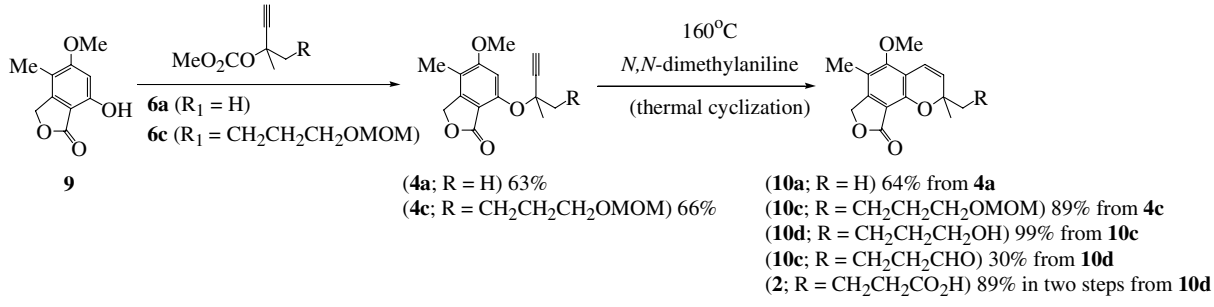
Similar coupling of **5a** with 3,7-dimethyl-oct-6-en-1-yn-3-yl methyl carbonate **6b** gave propargyl ether **3ab** (76%), and the following thermal cyclization gave the corresponding 2*H*-chromene **7ab** (82%). Demethylation of **7ab** with MgI_2–OEt_2 gave 5-hydroxy-6-carbaldehyde **7cb** (45%), and oxidation of **7ab** gave 5-methoxy-6-carboxylic acid **8ab** (71%). But, for both conversions to **1**, oxidation of **7cb** and demethylation of **8ab** (50%) were unsuccessful. So, MOM-protected **5b** was prepared and subjected to a similar conversion.

Similar coupling of **5b** with 3,7-dimethyl-oct-6-en-1-yn-3-yl methyl carbonate **6b** gave propargyl ether **3bb** (56%), and the following thermal cyclization gave the corresponding 2*H*-chromene **7bb** (62%). And, **7bb** was converted to 5-hydroxy-6-carboxylic acid **1** by oxidation with $NaClO_2$ followed by deprotection (43% in two steps) (Scheme 3).

Coupling and thermal cyclization of 7-hydroxyphthalide **9** were also prestudied with a dimethyl analog; coupling of **9** with methyl 2-methylbut-3-yn-2-yl carbonate **6a** using $CuCl_2$–DBU gave the correspond-



Scheme 2. Approach for 8-chlorocannabiorcichromenic acid (**1**) via thermal cyclization.



Scheme 3. Approach for mycochromenic acid (**2**) via thermal cyclization.

ing propargyl ether **4a** (63%), and the following thermal cyclization gave 2,2-dimethyl-2*H*-chromene **10a** (64%).

Similar coupling of **9** with 6-MOMoxy-3-methylhex-1-yn-3-yl methyl carbonate **6c** gave propargyl ether **4c** (66%), and the following thermal cyclization gave the corresponding 2*H*-chromene **10c** (89%). And, **10c** was converted to mycochromenic acid **2** (49%) in three steps: (1) deprotection with MeOH–concd. HCl giving **10d**, (2) oxidation with PDC giving **10e**, (3) oxidation with Ag_2O giving mycochromenic acid **2**.

Both chromene carboxylic acid **1** and **2** were identical with natural 8-chlorocannabiorcichromenic acid and mycochromenic acid in all reported spectral data.[4,5]

References and notes

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6. These details will be reported soon in a full paper.