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Total Synthesis of the Highly Potent Anti-HIV Natural Product Daurichromenic Acid along with Its Two Chromane Derivatives, Rhododaurichromanic Acids A and B

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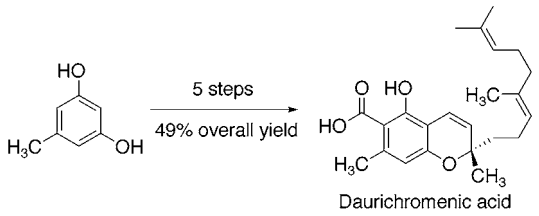
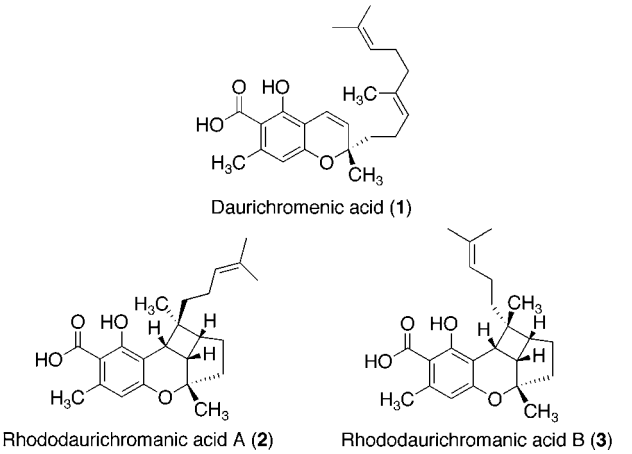
ABSTRACT



The highly potent anti-HIV natural product daurichromenic acid was successfully synthesized in only five steps with 49% overall yield. The key step in the synthetic strategy involves a microwave-assisted tandem condensation and intramolecular S_N2'-type cyclization to form the 2*H*-benzopyran core structure.

Two novel chromane derivatives rhododaurichromanic acids A (**2**) and B (**3**) were isolated from the leaves and twigs of *Rhododendron dauricum*, a plant that is distributed in the northern part of China, the eastern part of Siberia, and Hokkaido, Japan (Scheme 1).[1] A known natural product, daurichromenic acid (**1**), was also isolated from the same plant.[2] The absolute structures of these three compounds were determined on the basis of extensive spectroscopic examination and X-ray crystallographic analysis.[1] Daurichromenic acid (**1**) belongs to the family of chromene natural products and demonstrates highly potent anti-HIV activity in acutely infected H9 cells with an EC_{50} value of 5.67 ng/mL and therapeutic index (TI) of 3710. Rhododaurichromanic acids A (**2**) also showed relatively potent anti-HIV activity with an EC_{50} value of 0.37 mg/mL and a TI of 91.9. These two compounds represent a new class of anti-HIV agents and are attractive synthetic targets.[3]

Scheme 1



(1) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamasishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

(2) Jpn. Kokai Tokko Koho, JP 82-28,080, 1982.

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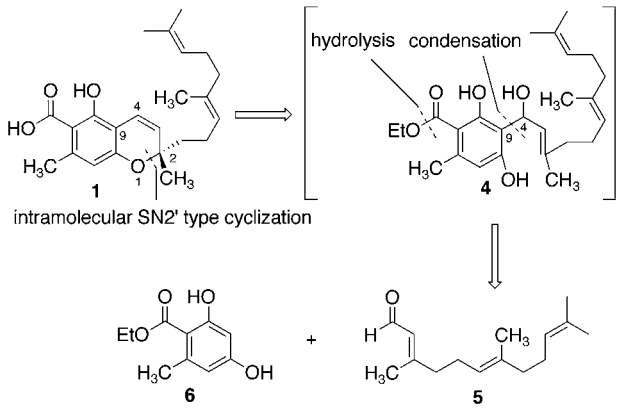
To supply sufficient quantities of the target material for pharmacological study, highly efficient syntheses of these complex molecules are required. Our careful analysis of the targets has led to a synthetic strategy that is characterized by the following important features: (1) convergency, (2) brevity, and (3) flexibility. Our retrosynthetic analysis of daurichromenic acid (**1**) is outlined in Scheme 2. Sequential

Scheme 2



disconnection at O1−C2 and C4−C9 reveal fragments **5** and **6** as two starting materials, with tandem condensation and intramolecular S_N2'-type cyclization playing crucial roles in the synthetic strategy.

Synthesis of 2*H*-benzopyrans (chrom-3-enes) has been the subject of many investigations.[4] The reaction developed by Shigemasa appeared to be quite promising for the synthesis of this class of natural products.[5] Unfortunately, we found that the reaction between **6** and **5**[6] was extremely slow under Shigemasa's conditions. The mixture gave only 15% yield of the desired product **7** after being heated at reflux for 4 days (Table 1, entry 1). The yield was improved to 32% when the mixture was heated at 90 °C in a sealed tube for 1 day (entry 2). However, the reaction stopped, and the yield could not be improved even with the addition of excess aldehyde **5** and longer heating time.

Because the intramolecular S_N2'-type cyclization is a fast reaction, the overall slow reaction is presumably due to the high activation energy in the condensation reaction. It is known that microwave irradiation can accelerate many reactions.[7] Thus, we decided to investigate the possibility of applying microwave irradiation to accelerate our tandem condensation and intramolecular S_N2'-type cyclization.

Table 1. Various Conditions for the Formation of 2*H*-Benzopyran, the Core Structure of Daurichromenic Acid

entry	conditions	yield
1	**5** (1.2 equiv), $Ca(OH)_2$ (0.83 equiv), MeOH, reflux, 4 days	15%
2	**5** (1.2 equiv), $Ca(OH)_2$ (0.83 equiv), MeOH, sealed tube, 90 °C, 1 day	32%
3	**5** (1.2 equiv), $Ca(OH)_2$ (0.83 equiv), MeOH, microwave irradiation, 3 × 1 min	23%
4	**5** (1.2 equiv), $CaCl_2{\cdot}2H_2O$ (0.83 equiv), NEt_3 (3.32 equiv), EtOH, microwave irradiation, 20 × 1 min	50%
5	**5** (1.2 equiv), $CaCl_2{\cdot}2H_2O$ (0.83 equiv), NEt_3 (3.32 equiv), EtOH, reflux, 2 days	<5%
6	(i) **5** (2.0 equiv), $CaCl_2{\cdot}2H_2O$ (0.83 equiv), NEt_3 (3.32 equiv), EtOH, microwave irradiation, 20 × 1 min; (ii) **5** (1.0 equiv), microwave irradiation, 20 × 1 min	70%
7	**5** (2.0 equiv), pyridine, microwave irradiation, 25 min	<5%

As expected, a much faster reaction was indeed observed when the reaction was irradiated in a microwave oven.[8] After only 3 min of irradiation, compound **7** was isolated in 23% yield (entry 3).[9] However, we were not able to improve the yield with longer irradiation time or with the addition of more aldehyde **5**. After screening a few different reaction conditions, we found that the reaction between **5** and **6** in the presence of $CaCl_2{\cdot}2H_2O$, NEt_3, and EtOH provided 50% yield of the desired product **7** and required only 20 min of microwave irradiation (entry 4). Without microwave irradiation, the yield of compound **7** was only 5% (entry 5). The optimized conditions were listed in entry 6 in which the mixture of compound **5** (2.0 equiv) and compound **6** (1.0 equiv) was irradiated for 20 min. Then, an additional 1.0 equiv of compound **5** was added and the mixture was irradiated again for 20 min. Using these optimized conditions allowed compound **7** to be isolated in 70% yield. It should be noted that in the absence of $CaCl_2{\cdot}2H_2O$, NEt_3, and EtOH, only a trace amount of compound **7** was isolated when the reaction was run in pyridine (entry 7).[10]

Unfortunately, the hydrolysis of the ester functionality of compound **7** to daurichromenic acid (**1**) proved to be extremely difficult. After examining many procedures,[11] we

(3) For the synthesis of rhododaurichromanic acids A and B and methyl daurichromenic ester, see: Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.

(4) (a) Dotz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689 and references therein. (b) Henry, G. E.; Jacobs, H. *Tetrahedron* **2001**, *57*, 5335. (c) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864. (d) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768. (e) North, J. T.; Kronenthal, D. R.; Pullockaran, A. J.; Real, S. D.; Chen, H. Y. *J. Org. Chem.* **1995**, *60*, 3397. (f) Gabbutt, C. D.; Hartley, D. J.; Hepworth, J. D.; Heron, B. M.; Kanjia, M.; Rahman, M. M. *Tetrahedron* **1994**, *50*, 2507. (g) Cruz-Almanza, R.; Perez-Flores, F.; Lemini, C. *Heterocycles* **1994**, *37*, 759. (h) Rao, U.; Balasubramanian, K. K. *Tetrahedron Lett.* **1983**, *24*, 5023. (i) Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem.* **1979**, *44*, 803.

(5) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768.

(6) Compound **5** was readily prepared via MnO_2-mediated oxidation of *trans*,*trans*-Farnesol (70%).

(7) For a recent review on microwave-assisted reactions, see: (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233.

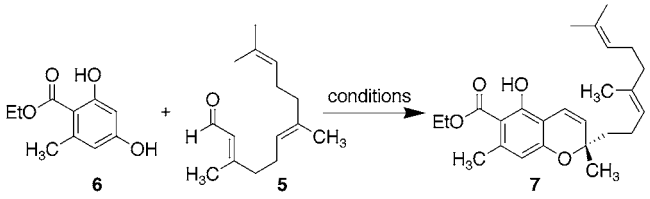
(8) We simply use a commerical household microwave to run the reaction. It is a Panasonic model NNS740 (1200 W).

(9) Reaction was carried out in a sealed 60 mL Teflon pressure vessel (purchased from Savillex Corp) filled with Argon.

(10) Subburaj, K.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 259.

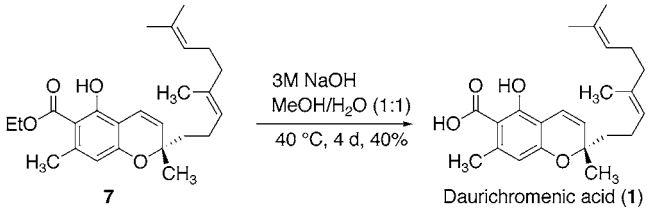
(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: New York, 1999.

Scheme 3



found that the best conditions (3 M NaOH in MeOH/H_2O at 40 °C for 4 days) provided daurichromenic acid (**1**) in only 40% yield. Although this two-step total synthesis is highly concise, the low yield in the hydrolysis step coupled with the expensive starting material **6** led us to investigate the possibility of conducting microwave-assisted reaction using carboxylic acid as the substrate.

Scheme 4



The revised approach is outlined in Scheme 5. Formylation of orcinol **8** with $POCl_3$ and DMF gave aldehyde **9** (98%),[12] which was oxidized to the corresponding carboxylic acid **10** ($NaClO_2$, 99%).[13] However, microwave irradiation of the mixture of compounds **10** and **5** failed to provide any desired product **1**. Therefore, we decided to synthesize β-trimethylsilyl ethyl ester **11** that can be easily converted to carboxylic acid in the end. Reaction of **10** with 2-(trimethylsilyl)ethanol under Mitsunobu conditions afforded ester **11** in 90% yield.[14] A mixture of compound **11**, aldehyde **5** (2 equiv), $CaCl_2 \cdot H_2O$, NEt_3, and EtOH was sealed in a Teflon pressure vessel and irradiated in a microwave oven 20 times for 1 min intervals. The desired product **12** was isolated in 60% yield.[15] Treatment of compound **12** with TBAF gave daurichromenic acid in 95% yield.[16] Compound **1** was irradiated with a low-pressure mercury lamp for about 5 days to afford a mixture of rhododaurichromanic acids A (40%) and B (20%).[17] The physical data of synthetic daurichromenic acid are identical to those reported by Kashiwada,[1] whereas the physical data of rhododaurichromanic acids A and B are identical to those reported by Hsung et al.[18]

In conclusion, we have successfully developed highly efficient total syntheses of daurichromenic acid and rhododaurichromanic acids A and B. We have demonstrated the versatility of microwave technology in the synthesis of 2*H*-benzo[*b*]pyrans (chrom-3-enes). The synthetic application of microwave technology in the synthesis of designed analogues and in the solid-phase combinatorial synthesis is currently underway in our laboratories and will be reported in due course. Furthermore, the highly potent anti-HIV activity of these molecules suggests an exciting adventure into the realms of investigations of molecular design, chemical synthesis, and biological activity.

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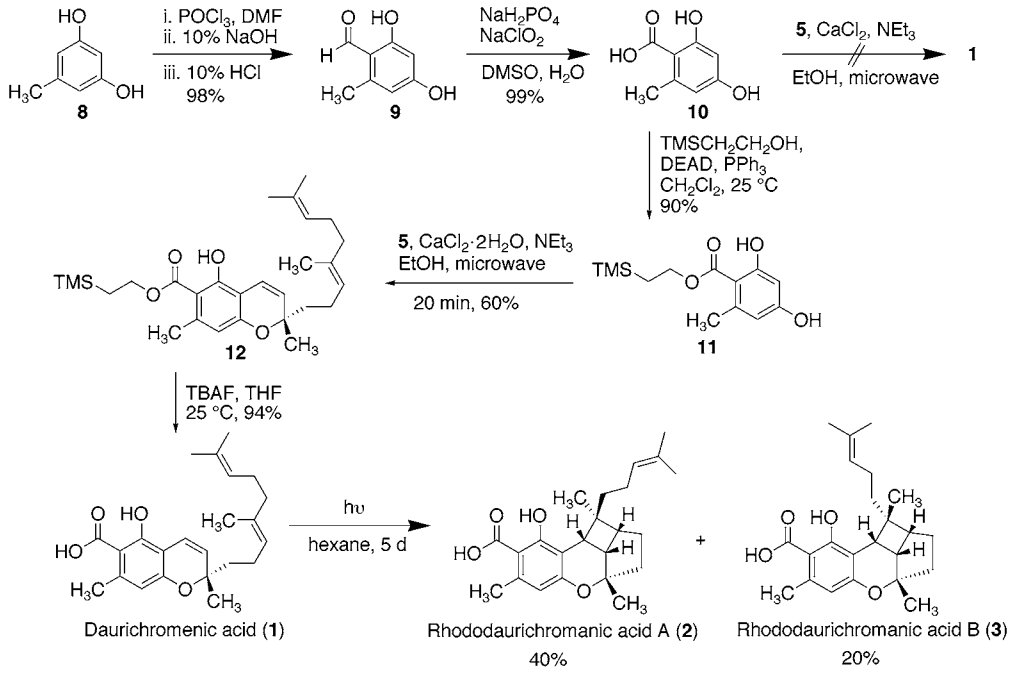
Scheme 5



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Supporting Information Available: Complete spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030109M

(12) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 664.

(13) Nicolaou, K. C.; Rodríguez, R. M.; Mitchell, H. J.; Suzuki, H.; Fylaktakidou, K. C.; Baudoin, O.; van Delft, F. L. *Chem. Eur. J.* **2000**, *6*, 3095.

(14) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331.

(15) Control reactions (heating in either reflux or in a sealed tube) appeared to be extremely slow without microwave irradiation.

(16) All compounds have been fully characterized.

(17) Based on recovered starting material.

(18) Hsung noted that there were three critical typos in the ^{13}C NMR of rhododaurichromanic acids A and B reported by Kashiwada. See Supporting Information of Hsung's paper: Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3938.