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Total Synthesis of (±)-Cyclogalgravin and Its Dicarboxyl Analog Using $Sc(OTf)_3$-mediated Highly Diastereoselective Ring Expansion of 1-(Arylhydroxymethyl)cyclopropanecarboxylates

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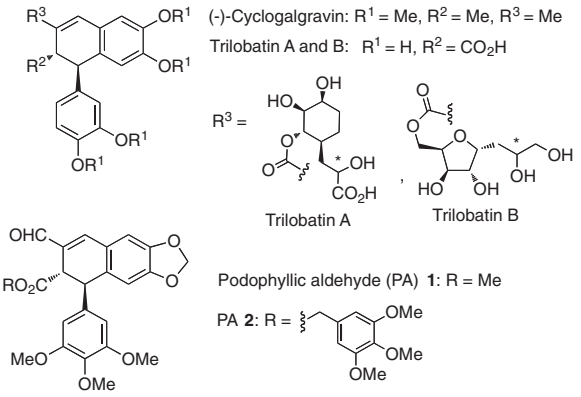
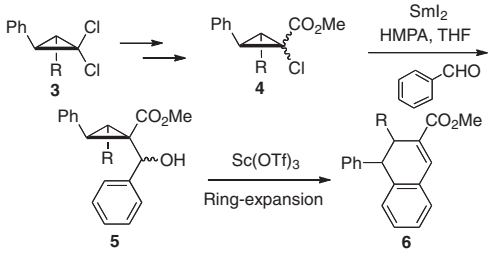
The total synthesis of (±)-cyclogalgravin and its dicarboxyl analog was achieved by using the SmI_2-promoted Reformatsky type reaction and $Sc(OTf)_3$-mediated diastereoselective ring expansion as key steps.

1-Aryl-1,2-dihydronaphthalene analogs are attracting considerable attention owing to their distribution in nature (i.e., cyclogalgravin, trilobatins A and B),[1] and significant biological activities of their analogs[2] (i.e., podophyllic aldehyde **1** and its derivative **2**), such as antineoplastic cytotoxicity and apoptosis-inducing activities[2d] (Scheme 1).

We have recently reported the highly stereoselective SmI_2-promoted Reformatsky type reaction of 1-chlorocyclopropanecarboxylate **4** derived from dichlorocyclopropane **3**, and the $Sc(OTf)_3$-mediated highly regioselective ring expansion of cyclopropylmethanol **5** to give 1-aryl-1,2-dihydronaphthalene **6** (R = H) (Scheme 2).[3–5] However, the diastereoselectivity of the ring expansion to afford 1-aryl-2-R-1,2-dihydronaphthalene **6** (R ≠ H) has not been investigated. Here, we report the diastereoselective ring expansion and its application for the total synthesis of (±)-cyclogalgravin and its dicarboxyl analog.

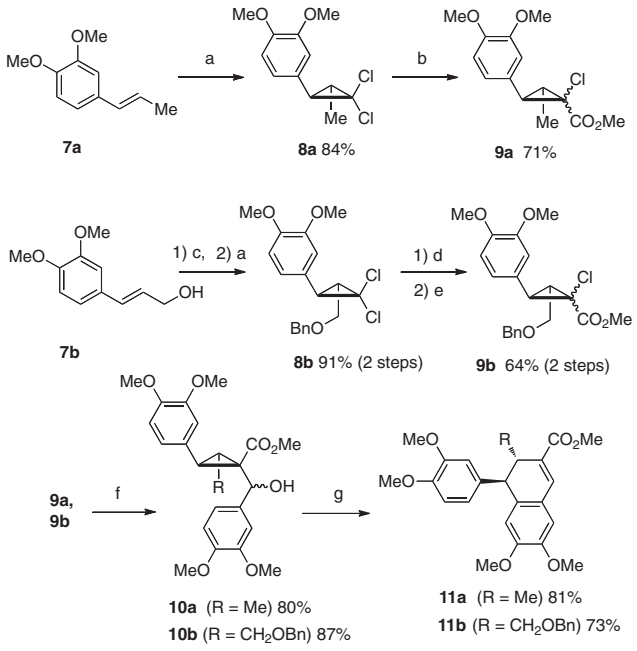


Scheme 1. 1-Aryl-1,2-dihydronaphthalene analogs.

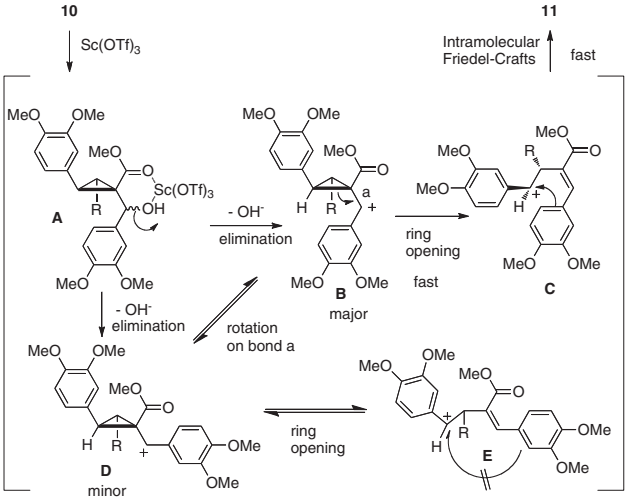


Scheme 2. Synthesis of 1-aryl-1,2-dihydronaphthalene from dichlorocyclopropane.

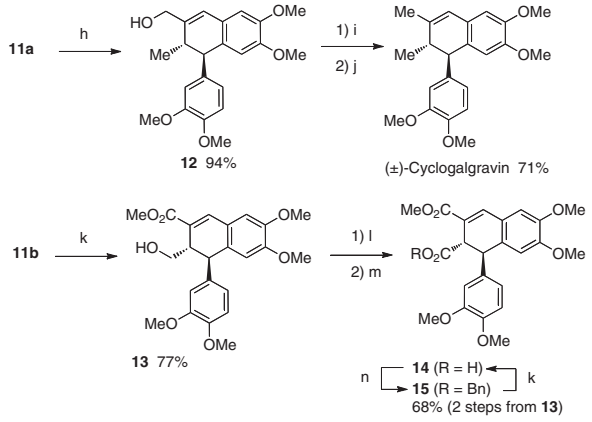
Scheme 3 outlines the diastereoselective synthesis of dihydronaphthalenes **11a** and **11b**. We synthesized **8a**–**11a** and **8b**–**11b** from **7a** and **7b**, respectively. Initially, alkene **7a** was converted to dichlorocyclopropane **8a** by a conventional method[6] using $CHCl_3$, 50%-NaOH, and a catalytic amount of benzyltriethylammonium chloride. After the benzyl protection of alcohol **7b**, dichlorocyclopropanation of the resulting benzyl ether with the same reagents afforded cyclopropane **8b**. Methoxycarbonylation of dichlorocyclopropane **8a** with *n*-BuLi and $ClCO_2Me$ gave methyl 1-chlorocyclopropanecarboxylate **9a** (3/2 mixture of diastereoisomers) with moderate diastereoselectivity. Carboxylation of dichlorocyclopropane **8b** with *t*-BuLi and CO_2, followed by treatment of the resulting carboxylic acid with K_2CO_3 and MeI afforded α-chloro ester **9b** (2/1 mixture of diastereoisomers).[3,4,7] The SmI_2-promoted Reformatsky type reaction[3a] of α-chloroester **9** to 3,4-dimethoxyphenyl aldehyde yielded alcohol **10** with excellent *trans*-stereoselectivity (*trans*-add/*cis*-add > 99/1) and poor *Re*-/*Si*-face selectivity (–OH: 1/1



Scheme 3. Reagents and conditions: (a) $CHCl_3$, 50%-NaOH, cat. benzyltriethylammonium chloride; (b) *n*-BuLi, $ClCO_2Me$, THF; (c) BnBr, NaH, DMF; (d) *t*-BuLi, CO_2, THF; (e) K_2CO_3, MeI, DMF; (f) SmI_2, HMPA, veratraldehyde, THF; (g) $Sc(OTf)_3$, CH_2Cl_2.



Scheme 4. Proposed mechanism of ring expansion.



Scheme 5. Reagents and conditions: (h) DIBAH, CH_2Cl_2; (i) 4-methylbenzoyl chloride, TMEDA, THF; (j) SmI_2, HMPA, tetrahydropyran (THP); (k) H_2, cat. $Pd(OH)_2$–C, AcOEt; (l) Dess–Martin periodinane, CH_2Cl_2; (m) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH; (n) K_2CO_3, BnBr, DMF.

mixture of diastereoisomers). Avoiding the notable steric repulsion of the aryl group of Sm-enolate, the Reformatsky type reaction of **9** took place only on the *trans*-face even though the R (Me or $BnOCH_2$) substituent was attached on the same face.[3a,8] The $Sc(OTf)_3$-mediated ring expansion[4] of alcohol **10** (1/1 mixture of diastereoisomers) afforded the desired dihydronaphthalene **11** as the sole product with excellent *trans*-selectivity (*trans*/*cis* > 99/1). We propose the plausible mechanism of the ring expansion as follows (Scheme 4).[9] $Sc(OTf)_3$ chelates with the OH and carbonyl of β-hydroxyester **10** to give intermediate **A**. Successive $Sc(OTf)_3$-promoted elimination of the OH group gives cationic intermediates **B** and **D** (the chelation of $Sc(OTf)_3$ would be advantageous to give the desired conformer **B**). The ring opening of intermediate **D** produces cation **E**, but the cyclization of intermediate **E** cannot proceed. Finally, the ring opening of **B** occurs to give cation **C**, and the Friedel–Crafts type cyclization sequentially occurs to give dihydronaphthalene **11** with excellent *trans*-selectivity.

Further functional transformations leading to target compounds were performed as follows (Scheme 5). The reduction of **11a** with DIBAH gave alcohol **12**. After the acylation of alcohol **12** with 4-methylbenzoyl chloride and TMEDA, treatment of the resulting 4-methylbenzoyl ester with SmI_2 resulted in reductive dehydroxylation to give (±)-cyclogalgravin.[10] The spectroscopic data of the synthesized (±)-cyclogalgravin were consistent with those of the natural cyclogalgravin.[1a,2a,2e] On the other hand, hydrogenation of **11b** with H_2 and $Pd(OH)_2$ afforded alcohol **13**. Monocarboxylic acid **14** (an analog of cyclogalgravin, trilobatin A, and trilobatin B) was obtained through the stepwise oxidation of alcohol **13** under mild conditions (the Dess–Martin oxidation followed by the Kraus oxidation).[11] The benzylation of carboxylic acid **14** with K_2CO_3 and BnBr yielded benzyl ester **15** (a synthetic segment for the total synthesis of trilobatins A and B). We confirmed that the deprotection of benzyl ester **15** with H_2 and $Pd(OH)_2$ proceeded to give carboxylic acid **14**.

In conclusion, we developed a highly stereoselective synthesis of *trans*-1-aryl-2-alkyl-1,2-dihydronaphthalene utilizing the $Sc(OTf)_3$-mediated ring expansion of cyclopropane **10**. The present method was also applied to the efficient total synthesis of (±)-cyclogalgravin and its dicarboxyl analog.

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References and Notes

1 a) S. F. Fonseca, L. T. Nielsen, E. A. Rúveda, *Phytochemistry* **1979**, *18*, 1703. b) M. Miyazawa, H. Kasahara, H. Kameoka, *Nat. Prod. Lett.* **1996**, *8*, 25. c) U. Martini, J. Zapp, H. Beker, *Phytochemistry* **1998**, *49*, 1139. d) F. Cullmann, H. Becker, *Phytochemistry* **1999**, *52*, 1651. e) J. M. Scher, J. Zapp, H. Becker, *Phytochemistry* **2003**, *62*, 769. f) T. da Silva, L. M. X. Lopes, *Phytochemistry* **2006**, *67*, 929.

2 a) B. L. Yvon, P. K. Datta, T. N. Le, J. L. Charlton, *Synthesis* **2001**, 1556. b) H. Yoda, Y. Nakaseko, K. Takabe, *Tetrahedron Lett.* **2004**, *45*, 4217. c) M. A. Castro, J. M. M. del Corral, M. Gordaliza, P. A. García, M. A. Gómez-Zurita, A. S. Feliciano, *Bioorg. Med. Chem.* **2007**, *15*, 1670. d) M. Á. Castro, J. M. M. del Corral, P. A. García, M. V. Rojo, J. de la Iglesia-Vicente, F. Mollinedo, C. Cuevas, A. S. Feliciano, *J. Med. Chem.* **2010**, *53*, 983. e) C. E. Rye, D. Barker, *J. Org. Chem.* **2011**, *76*, 6636.

3 a) T. Nagano, J. Motoyoshiya, A. Kakehi, Y. Nishii, *Org. Lett.* **2008**, *10*, 5453. b) E. Yoshida, T. Nagano, J. Motoyoshiya, Y. Nishii, *Chem. Lett.* **2009**, *38*, 1078.

4 E. Yoshida, K. Nishida, K. Toriyabe, R. Taguchi, J. Motoyoshiya, Y. Nishii, *Chem. Lett.* **2010**, *39*, 194.

5 Related benzannulation see: Y. Tanabe, S. Seko, Y. Nishii, T. Yoshida, N. Utsumi, G. Suzukamo, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2157.

6 See Supporting Information (SI). Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

7 V. Sander, P. Weyerstahl, *Chem. Ber.* **1978**, *111*, 3879. Based on the literature, major diastereoisomer would be *trans*-adduct. See SI.

8 For additional explanation, see SI pp. 10–11.

9 For detailed scheme and additional explanation, see SI p. 12.

10 K. Lam, I. E. Markó, *Org. Lett.* **2008**, *10*, 2773.

11 a) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175. b) B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091. The Jones oxidation of **15** gave a mixture of **16** and 1-arylnaphthalene.

