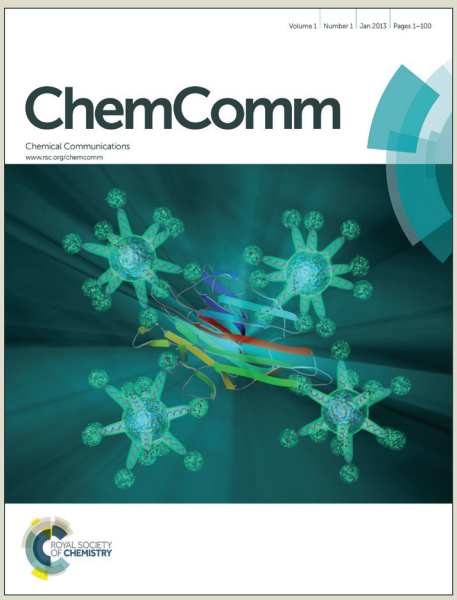
# ChemComm

Accepted Manuscript





ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

# Stereoselective synthesis of a highly oxygenated decahydrocyclopenta[g]chromene derivative: the common tricyclic framework of leucosceptrine and leucosesterterpenone

Cite this: DOI: 10.1039/x0xx00000x

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Hideki Abe, Yuri Horii, Megumi Hagiwara, Toyoharu Kobayashi, and Hisanaka Ito*

**Stereoselective construction of the highly oxygenated decahydrocyclopenta[g]chromene skeleton, which is the tricyclic core of leucosceptrine, which possesses prolylendopeptidase inhibitory activity, and leucosesterterpenone, which exhibits anti-angiogenic activity, from *Leucosceptrum canum*, was achieved.**

Many kinds of sesterterpenoids have recently been isolated from *Leucosceptrum*, a genus of flowering plant in the Lamiaceae family.[1] Leucosceptrine (**1**)[2] was isolated from *Leucosceptrum canum* as the first member of a new class of sesterterpenes. A structural feature of this sesterterpene is a tricyclic decahydrocyclopenta[g]chromene tethering a methyl furanone moiety by a butanone side chain. This highly oxygenated sesterterpene **1** exhibits inhibitory activity against prolylendopeptidase (PEP), catalyzing the degradation of proline-containing neuropeptides that are involved in the processes of learning and memory. The sesterterpene leucosesterterpenone (**2**) is similar to leucosceptrine (**1**) and was isolated from the same plant.[3] Sesterterpene **2** possesses anti-angiogenic activity,[4] in addition to its inhibition activity against PEP. These natural products **1** and **2** have a common tricyclic skeleton, while differing in the structure of the terminus of the side chain fragment. Twenty-six sesterterpenes,[3,5] e.g., leucosceptroids A (**3**)[5a], B (**4**)[5a] and D (**5**)[5b] as depicted in Figure 1, have been isolated from *Leucosceptrum canum*. These leucosceptroides have a tetrahydrofuran ring as part of the tricyclic skeleton instead of the dihydropyran ring. It was reported that these leucosceptroids showed potent antifeedant and antifungal activities. The structural complexity and potent biological activity of these sesterterpenes have attracted the interest of synthetic chemists,[6] and the first synthetic study of these sesterterpenes was reported by Horne and co-workers[7] in 2011 in the form of the asymmetric synthesis of the tricyclic core of leucosceptroids A–D (**3**–**5**). Liu and co-workers[8] reported the first asymmetric total synthesis of leucosceptroid B (**4**) in 2013. More recently, Magauer and co-workers[9] disclosed the total syntheses of norleucosceptroids A and B, and leucosceptroid K. In addition, Ma and co-workers[10] reported the total synthesis of

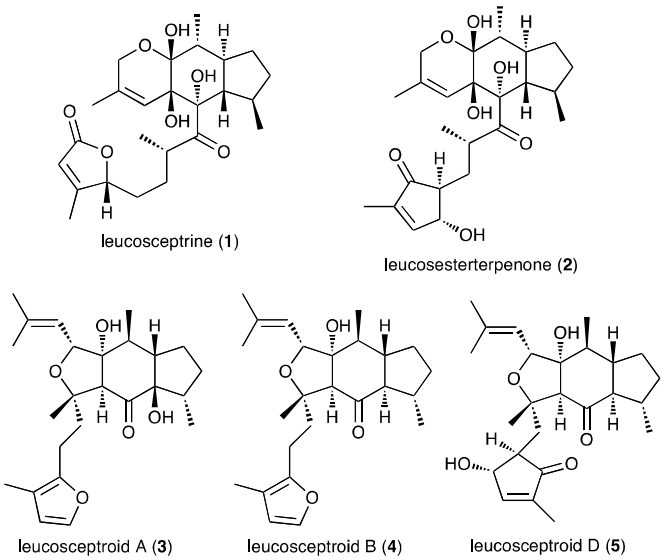
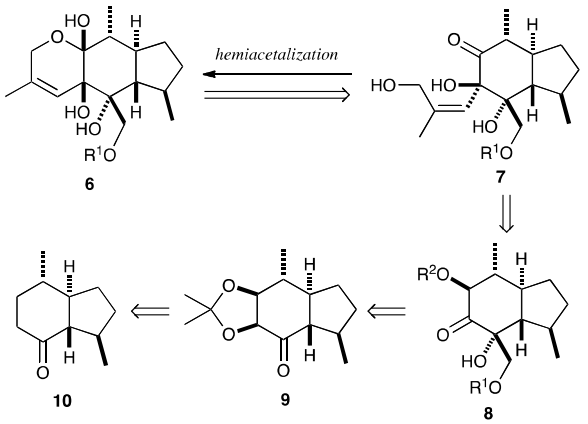



**Fig 1.** Structures of leucosceptrine (**1**) and related compounds **2**–**5**.

leucosceptride A (**3**) and B (**4**). However, there are yet no reported synthetic studies on leucosceptrine and leucosesterterpenone possessing the decahydrocyclopenta[g]chromene skeleton with hemiacetal functionality. We describe herein the stereoselective

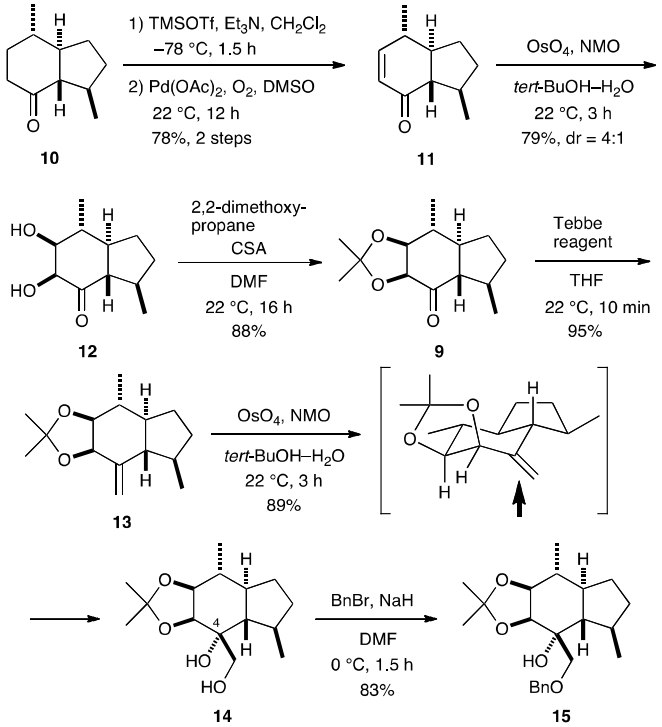
construction of the tricyclic decahydrocyclopenta[g]chromene core of leucosceptrine (**1**) and leucosesterterpenone (**2**) having a dihydropyran ring.




**Scheme 1.** Synthetic strategy for tricyclic model compound **6**.

Our synthetic strategy is outlined in Scheme 1. Construction of the dihydropyran with the hemiacetal functionality of tricyclic target molecule **6** would be achieved by hemiacetalization of **7** under acidic conditions at the final stage. The precursor **7** would be synthesized by stereoselective introduction of the alkenyl side chain to the ketone **8**. Ketone **8** would be derived from known bicyclic compound **10**[11] via repeated dihydroxylation steps.

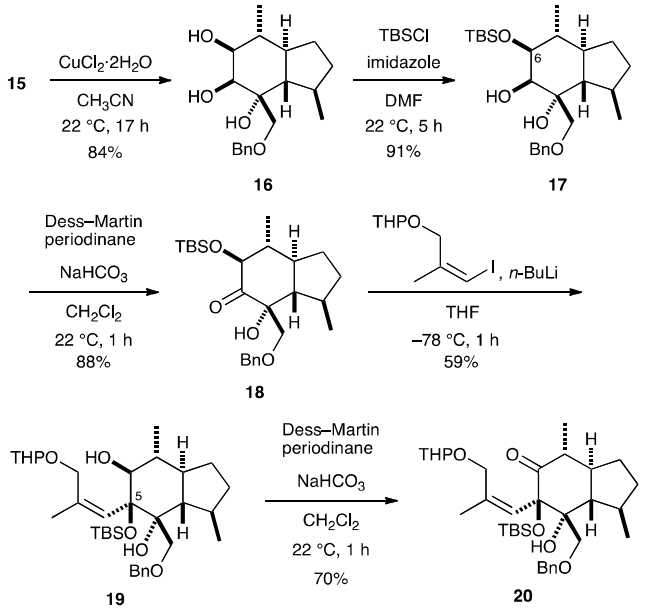
Our investigation started with the installation of four oxygen atoms to the bicyclic ketone **10**, prepared from 4-methylcyclohexane




**Scheme 2.** Synthesis of the alcohol **15**.

according to the reported procedure.[11] Oxidation of **10** by the Ito–Saegusa oxidation protocol[12] gave unsaturated ketone **11** in 78% yield over two steps (Scheme 2). Dihydroxylation of **11** with osmium tetraoxide afforded diol **12** as a separable mixture of diastereomers in a 4:1 ratio. After protection of the diol as its isopropyl acetal, methylenation of the resulting ketone **9** with Tebbe reagent[13] produced the alkene **13** in 95% yield. A second dihydroxylation of the resulting alkene **13** proceeded smoothly to furnish the diol **14** in 89% yield as a single diastereoisomer. This stereoselective dihydroxylation of **13** occurred from the opposite side of the 1,3-dioxolane ring fragment as depicted in Scheme 2. Selective protection of the resulting primary hydroxyl group of diol **14** with a benzyl group afforded **15** in 83% yield.

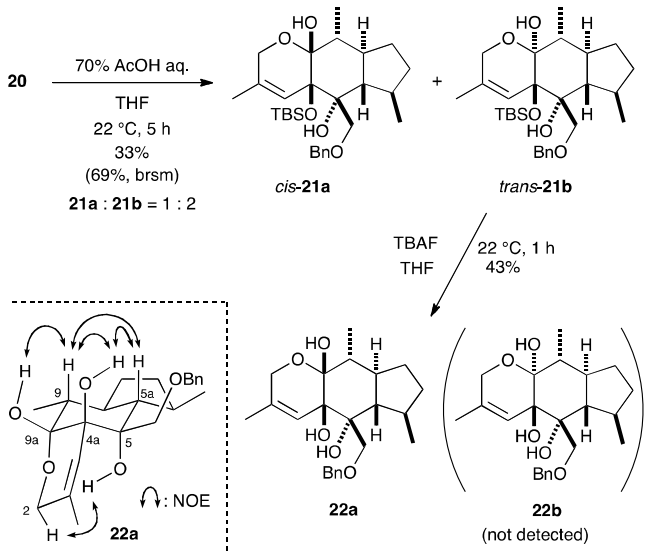
With the tetraoxygenated compound **15** in hand, we focused our efforts on the construction of the tricyclic decahydrocyclopenta[g]chromene fragment. As shown in Scheme 3, transformation of **15** to the ketone **18** was accomplished in a three-step operation as follows. Cleavage of the isopropylidene group of **15** using copper(II) chloride,[14] selective protection of the less hindered hydroxyl group at the C6 position of the resulting triol **16** with a TBS group, and oxidation of the secondary alcohol **17** afforded **18** in 67% yield over three steps. Stereoselective introduction of the alkenyl side chain to the ketone **18** was achieved using the vinyl lithium species generated from *n*-butyllithium and the known (*Z*)-iodoalkene[15] prepared from propargyl alcohol to give the unexpected TBS migration product **19** in 59% yield as a single isomer at the C5 position, followed by oxidation of the resulting **19** with Dess–Martin periodinane to afford the ketone **20** in 70% yield.




**Scheme 3.** Synthesis of the ketone **20**.

To complete the stereoselective construction of the tricyclic skeleton, hemiacetalization through cleavage of the THP group was carried out as shown in Scheme 4. As the result of many attempts, treatment of the ketone **20** with 70% acetic acid aqueous solution for 5 h at 22 °C gave the best result to produce the desired hemiacetalized product **21a** and its diastereomer **21b** in 33% yield in a 1:2 ratio along with the recovered ketone **20** (54%).[16] After separation of these tricyclic hemiacetals **21a** and **21b**, their stereochemistries were determined by NMR and X-ray crystallographic analysis of **21b**[17] as described in the Supporting Information. Since treatment of *trans*-**21b** with acetic acid at 22 °C for 1 h gave a mixture of **21a** and **21b** in a 1:3 ratio, these tricyclic

compounds exist as an equilibrium mixture under acidic condition. The *trans*-isomer **21b** is more stable than the desired *cis*-isomer **21a** at least as the TBS-protected molecules. Given that the ring junction of the perhydrochromene nucleus of the natural products leucosceptrine (**1**) and leucosesterterpenone (**2**) is the *cis* configuration, the *cis*-isomer without the TBS group is predicted to be more stable. Therefore, we expected that removal of the TBS group of tricyclic compounds **21** would afford the *cis*-fused compound predominantly. In fact, cleavage of the TBS group of **21b** having the *trans*-fused AB ring system with TBAF afforded the desired *cis*-fused product **22a** in 43% yield, and *trans*-isomer **22b** was not detected. The stereochemistry of the target molecule **22a** was confirmed by extensive spectroscopic analysis including NOESY experiments at 600 MHz. Selected NOESY correlations of **22a** are presented in Scheme 4. Clear NOE interactions between H9 and hydroxyl group at C4a, H5a, and hydroxyl group at C9a, and between H2 and the hydroxyl group at C5 were observed. These results indicate that the stereochemical relationship between the hydroxyl group at C9a and the methyl group at C9 was *anti*, and that the relationship of the two hydroxyl groups at C4a and C9a was *syn*. Moreover, removal of TBS group of the ketone **20**, followed by hemiacetalization through cleavage of THP group was carried out. Unfortunately this attempt gave the complex mixture in the removal stage of TBS group of **20**.




**Scheme 4.** Synthesis of the *cis*-fused target molecule **22a**.

## Conclusions

In conclusion, stereoselective construction of the common tricyclic core of leucosceptrine (**1**) and leucosesterterpenone (**2**) was demonstrated. Synthesis of the highly oxygenated decahydrocyclopenta[g]chromene derivative as a tricyclic model compound was accomplished. This synthetic route involves stereoselective dihydroxylation, stereoselective introduction of the alkenyl side chain to the ketone, hemiacetalization of the ketone through cleavage of the THP group under acidic conditions, and ring opening–re-cyclization of the hemiacetal ring with cleavage of the TBS group. This methodology will be useful for the synthesis of natural products leucosceptrine (**1**) and leucosesterterpenone (**2**), which is currently underway in our laboratory.

## Notes and references

[a] School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan.

† This work was supported by the Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1. Y. Liu, L. Wang, J. H. Jung, and S. Zhang, *Nat. Prod. Rep.*, 2007, **24**, 1401.
2. M. I. Choudhary, R. Ranjit, Atta-ur-Rahman, T. M. Shrestha, A. Yasin, and M. Parvez, *J. Org. Chem.*, 2004, **69**, 2906.
3. M. I. Choudhary, R. Ranjit, Atta-ur-Rahman, S. Hussain, K. P. Devkota, T. M. Shrestha, and M. Parvez, *Org. Lett.*, 2004, **6**, 4139.
4. S. Hussain, M. Slevin, S. Matou, N. Ahmed, M. I. Choudhary, R. Ranjit, D. West, J. Gaffney, *Angiogenesis*, 2008, **11**, 245.
5. (a) S.-H. Luo, Q. Luo, X.-M. Niu, M.-J. Xie, X. Zhao, B. Schneider, J. Gershenzon, and S.-H. Li, *Angew. Chem. Int. Ed.*, 2010, **49**, 4471; (b) S.-H. Luo, L.-H. Weng, M.-J. Xie, X.-N. Li, J. Hua, X. Zhao, and S.-H. Li, *Org. Lett.*, 2011, **13**, 1864; (c) S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, and S.-H. Li, *Org. Lett.*, 2012, **14**, 5768; (d) S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, and S.-H. Li, *Phytochemistry*, 2013, **86**, 29; (e) S.-H. Luo, J. Hua, C.-H. Li, Y. Liu, X.-N. Li, X. Zhao, and S.-H. Li, *Tetrahedron Lett.*, 2013, **54**, 235; (f) S.-H. Luo, C. L. Hugelshofer, J. Hua, S.-H. Jing, C.-H. Li, Y. Liu, X.-N. Li, X. Zhao, T. Magauer, S.-H. Li, *Org. Lett.* 2014, **16**, 6416.
6. D. T. Hog, R. Webster, and D. Trauner, *Nat. Prod. Rep.*, 2012, **29**, 752.
7. J. Xie, Y. Ma, and D. A. Horne, *J. Org. Chem.*, 2011, **76**, 6169.
8. X. Huang, L. Song, J. Xu, G. Zhu, and B. Liu, *Angew. Chem. Int. Ed.*, 2013, **52**, 952.
9. C. L. Hugelshofer, and T. Magauer, *Angew. Chem. Int. Ed.*, 2014, **53**, 11351.
10. S. Guo, J. Liu, D. Ma, *Angew. Chem. Int. Ed.*, 2015, **54**, 1298.
11. M. Tori, M. Ikawa, T. Sagawa, H. Furuta, M. Sono, and Y. Asakawa, *Tetrahedron*, 1996, **52**, 9999.
12. Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011.
13. In this methylenation of **9**, we firstly tried to Wittig reaction under any conditions. But Wittig methylenation was not effective procedure in this case.
14. P. Saravanan, M. Chandrasekhar, R. V. Anand, and V. K. Singh, *Tetrahedron Lett.*, 1998, **39**, 3091.
15. (a) J. G. Duboudin, and B. Jousseaume, *J. Organomet. Chem.*, 1979, **168**, 1; (b) J. G. Duboudin, and B. Jousseaume, *J. Organomet. Chem.*, 1979, **168**, 227; (c) C. M. Rayner, P. C. Astles, and L. A. Paquette, *J. Am. Chem. Soc.*, 1992, **114**, 3926.
16. When the reactions were carried out at 22 °C for 24 h or at 40 °C for 2 h, the starting material was disappeared. But yields of tricyclic compounds were very poor (11%, or 13%, respectively). The starting material could not be recovered under these conditions.

17. CCDC 1040519 contains the supplementary crystallographic data of **21b** for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.