



CrossMark
click for updates

Cite this: *Chem. Sci.*, 2016, 7, 4372

Expeditious synthesis of the fused hexacycle of puberuline C via a radical-based cyclization/translocation/cyclization process†

Koichi Hagiwara, Toshiki Tabuchi, Daisuke Urabe and Masayuki Inoue*

The fused 6/7/5/6/6/6-hexacyclic ring system of puberuline C was assembled in 18 steps from 2-(ethoxycarbonyl)cyclohexanone. After the azabicyclo[3.3.1]nonane derivative was sequentially coupled with propargyl magnesium bromide, 2-iodo cyclopentenone and allyl bromide, the pentacycle was constructed in a single step via a radical-based cyclization/translocation/cyclization process. The C11-bridgehead radical generated via C–Br homolysis participated in a 7-endo cyclization, and the 1,5-hydrogen translocation of the resultant radical was followed by transannular 6-exo cyclization to simultaneously realize the construction of the two rings and the introduction of the five contiguous stereocenters. The last 6-exo cyclization was induced by the Mukaiyama aldol reaction, and the C16-ketone was stereoselectively reduced by the action of $\text{SmI}_2/t\text{-BuOH}$, leading for the first time to the synthesis of the entire hexacycle of puberuline C.

Received 13th February 2016
Accepted 11th March 2016

DOI: 10.1039/c6sc00671j

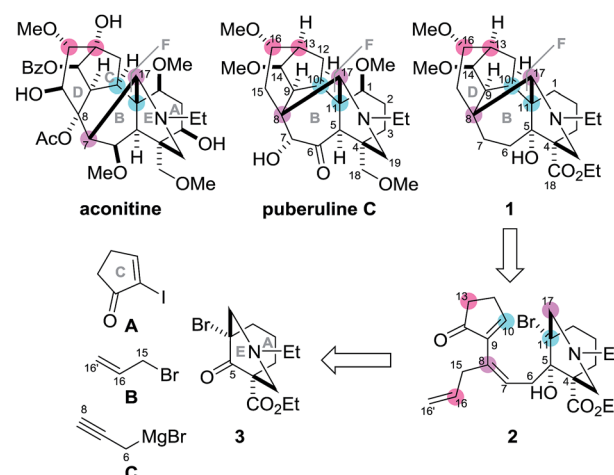
www.rsc.org/chemicalscience

Plants of the genera *Aconitum* and *Delphinium* have been used for centuries in traditional oriental medicines for their anti-inflammatory, analgesic, and anti-rheumatic activities.¹ Efforts to identify the pharmacologically important compounds in these plant families have resulted in the determination of over 600 structurally complex C19-diterpenoid alkaloids, of which aconitine is a representative example (Scheme 1).² In 2009, puberuline C was isolated from a traditional Chinese medical plant, *Aconitum barbatum* var. *puberulum*,³ and was found to belong to the C19-diterpenoid alkaloid family. Its architecturally complex hexacyclic system is composed of fused 6/7/5/6/6/6-membered (A/B/C/D/E/F) rings containing one nitrogen group and six oxygen-based polar functionalities. These structural features significantly increase the challenge of chemically synthesizing puberuline C.⁴

Puberuline C differs structurally from the majority of C19-diterpenoid alkaloids in its C17-bond connection. Specifically, the C8–17 bond of puberuline C constitutes the six-membered F-ring, while the C7–17 bond of aconitine forms a five-membered counterpart. To date, considerable synthetic effort has been focused on the aconitine-type alkaloids,^{5,6} culminating in the historic total syntheses of talatisamine, chasmanine and 13-desoxydelphonine by Wiesner's group,⁷ neofinaconitine by Gin's group,⁸ and weisaconitine D and liljestrandinine by

Sarpong's group.⁹ In sharp contrast, the molecular framework of puberuline C has not been chemically assembled.¹⁰ In this manuscript, we describe the efficient synthesis of the unique hexacyclic ring system of puberuline C by utilizing a radical-based cyclization/translocation/cyclization process and the Mukaiyama aldol reaction as the two key transformations.

To devise a novel strategy for the total synthesis of puberuline C, we designed a simplified puberuline C (**1**) as a model target compound (Scheme 1). Although the oxidation states at the C1, 5, 6, 7 and 18 positions of **1** are different from those of puberuline C, **1** retains its entire hexacyclic framework and nine



Scheme 1 Structures of aconitine and puberuline C, and a retrosynthetic plan of the model target compound **1**.

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: inoue@mol.f.u-tokyo.ac.jp; Fax: +81-3-5841-0568

† Electronic supplementary information (ESI) available. CCDC 1452192. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc00671j

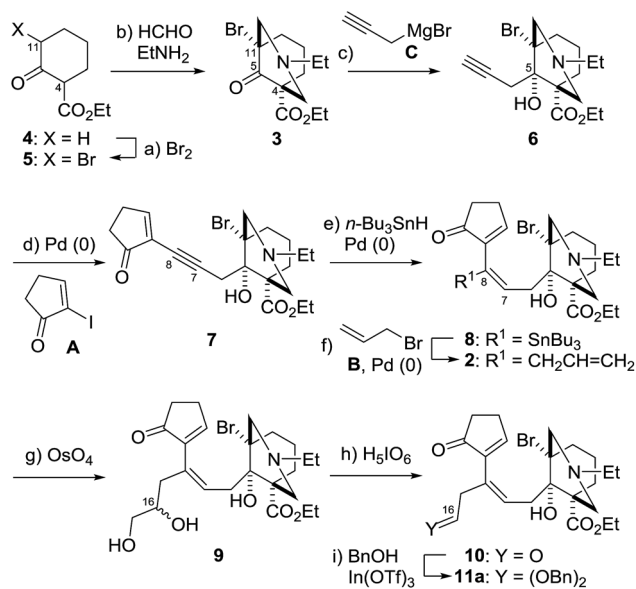


stereocenters (C4, 8, 9, 10, 11, 13, 14, 16, 17). In our retrosynthesis, the three ring structures of **1** were disconnected at the C10–11, C13–16 and C8–17 bonds to identify **2** as a pivotal intermediate. Compound **2** was proposed as the precursor of the bridgehead radical at C11. We presumed that the bridgehead radical would enable stereoselective construction of the sterically hindered C10–11 bond because of its potent reactivity, stereochemically predestined nature, and high orthogonality to diverse polar functional groups.¹¹ In the synthetic direction, the C11-bridgehead radical generated through C–Br homolysis of triene **2** would chemoselectively react with the C9–10 double bond of the C-ring enone, leading to the formation of the seven-membered B-ring. After radical cyclization, the remaining C16–16' and C7–8 double bonds were to be utilized to connect the C13/16 and C8/17 atoms to transannulate the six-membered D- and F-rings of **1**, respectively, thereby establishing the stereochemistry of these four positions. As the radical precursor **2** has only three stereocenters (C4, 5, 11), the route to **2** would be greatly simplified. Highly unsaturated **2** would be prepared through a series of carbon chain extensions by step-wise attachment of three achiral units (five-membered C-ring **A**, **B** and **C**) to the chiral 6/6-fused AE-ring **3**.

The synthesis of **1** commenced by preparing the known material **3**¹² (Scheme 2). 2-(Ethoxycarbonyl)cyclohexanone (**4**) was first brominated to **5**, which was then treated with ethylamine and formaldehyde to induce a double Mannich reaction, giving rise to **3** equipped with the C11-bromo group. Propargyl

magnesium bromide **C**, which was prepared from 3-bromopropyne, magnesium turnings, and catalytic ZnBr₂,¹³ then attacked the C5-ketone of **3** to afford the three carbon extended **6** as the major product (dr = 3.2 : 1). In this reaction, the tertiary amine of **3** would assist the stereoselective delivery of the organomagnesium reagent from the β-face of the molecule through chelation. Next, three Pd-catalyzed reactions from **6** completed the synthesis of the key intermediate **2**. The five-membered C-ring **A** was attached to the terminal alkyne of **6** through a Sonogashira coupling¹⁴ [PdCl₂(PPh₃)₂ and CuI], providing tricyclic compound **7**. Upon treatment of **7** with PdCl₂(PPh₃)₂ and *n*-Bu₃SnH,¹⁵ the C8 position of the internal triple bond was regioselectively functionalized with the *n*-Bu₃Sn group to form **8**, presumably because the C8 position was less sterically shielded by the bulky azabicyclic AE-ring. Additionally, stereoselective hydrostannylation defined the syn-relationship of the AE- and C-rings, which later served as an important structural factor to facilitate 7-*endo* cyclization. The thus introduced C8-stannyl moiety of **8** was changed to the allyl group by π-allyl Stille coupling. Namely, Pd₂(dba)₃·CHCl₃ and Ph₃As^{16,17} effected the coupling between **8** and allyl bromide **B** to furnish triene **2**. Therefore, only six steps were required for the conversion of monocycle **4** to tricycle **2**, which possesses all the requisite carbons for the synthesis of the skeleton of **1**. To prepare for the key radical cyclization, substrates **9** and **11a** were derivatized from **2** via chemoselective manipulations of the C8-allyl group. Dihydroxylation of the least sterically shielded olefin of triene **2** afforded triol **9** as a 1 : 1 C16-diastereomixture. Alternatively, dibenzyl acetal **11a** was formed by oxidative glycol-cleavage with H₃IO₆, followed by In(OTf)₃-catalyzed acetalization with benzyl alcohol.¹⁸

Remarkably, the single radical reaction of **2** promoted cyclization not only of the requisite seven-membered B-ring, but also of the six-membered F-ring (entry 1, Table 1). Treatment of



Scheme 2 Synthesis of the three substrates for the radical reaction. Reagents and conditions: (a) Br₂, Et₂O, 0 °C to RT; (b) aq. HCHO, aq. EtNH₂, MeOH, 0 °C to RT; (c) **C**, ZnBr₂ (5 mol%), CH₂Cl₂, –78 °C, 49% (dr at C5 = 3.2 : 1); recrystallization 29% for **6** (3 steps); (d) **A**, PdCl₂(PPh₃)₂ (5 mol%), CuI (10 mol%), *i*-Pr₂NEt, CH₃CN, 0 °C, 65%; (e) *n*-Bu₃SnH, PdCl₂(PPh₃)₂ (5 mol%), THF; (f) **B**, Pd₂(dba)₃·CHCl₃ (4 mol%), Ph₃As (16 mol%), THF, 60 °C, 59% (2 steps); (g) OsO₄ (10 mol%), NMO, THF, H₂O, 81% (dr = 1 : 1); (h) H₃IO₆, THF, 0 °C, 72%; (i) BnOH, In(OTf)₃, CH₂Cl₂, 0 °C, 79%. Bn = benzyl, dba = dibenzylideneacetone, NMO = *N*-methylmorpholine-*N*-oxide, THF = tetrahydrofuran.

Table 1 Radical-based cyclization/translocation/cyclization process^a

Entry	Substrate	R ²	Product	Yield
1	2		12	29%
2	9^b		13^c	55%
3	11a		14a	54%

^a Conditions: substrate (1.0 equiv.), *n*-Bu₃SnH (5 equiv.), V-40 (0.4 equiv.), toluene (0.02 M), reflux. *n*-Bu₃SnH and V-40 (0.2 equiv.) in toluene were added by syringe pump over 3 h. Reactions were performed on a 0.10 mmol scale. ^b **9** was used as a 1 : 1 C16-diastereomixture. ^c Product **13** was obtained as the hemiacetal forms (**13α** : **13β** = 1 : 1.5). V-40 = 1,1'-azobis(cyclohexanecarbonitrile).



tricyclic **2** with *n*-Bu₃SnH and V-40 in refluxing toluene provided pentacyclic **12**, with the formation of two C–C bonds (C10–11, C8–17) and five stereocenters (C8, 9, 10, 11, 17). The low yield (29%) of **12** from **2** was attributed to involvement of the C16-olefin in undesired radical pathways. Consequently, compounds **9** and **11a** with no C16 radical acceptor were next submitted to the same reaction conditions (entries 2 and 3): the yields of the corresponding pentacyclic products **13** and **14a** from **9** and **11a**, respectively, almost doubled (55% for **13** and 54% for **14a**).^{19,20} After the reaction in entry 2, **13** was obtained as C16-epimeric hemiacetals (**13α** : **13β** = 1 : 1.5) due to addition of the C16-secondary hydroxy group to the C14-ketone. The structure of crystalline C16-β-alcohol **13β** was unambiguously determined by X-ray crystallographic analysis (Fig. 1), which revealed its unusually complicated shape. On the other hand, the newly formed ring systems of **12** and **14a** were established by judicious NMR analyses and chemical derivatizations.²¹

The present cascade pathway involves three essential radical reactions: 7-*endo* cyclization at C10 and C11, 1,5-radical translocation from C7 to C17, and 6-*exo* cyclization at C17 and C8. This intricate reaction course is illustrated in Scheme 3A using the transformation of **11a** to **14a** as an example. The bridgehead radical **Int-1a** is first generated from **11a** by the action of the stannyl radical. To maximize the SOMO/LUMO interaction, the electron rich C11-radical of **Int-1a** selectively reacts with the electron deficient sp²-carbon atom at C10, thereby forming the C10–11 bond of **Int-2Aa** through a 7-*endo* cyclization. The C10-stereochemistry is controlled at this stage, while the configuration of the fixed C11-bridgehead position is retained. The vinylogous ketone moiety of **Int-2Aa** bestows an electron deficient character to the C7-radical, which preferentially reacts with the electron rich *N*- α -C–H bond at the proximal C17 position *via* facile 1,5-hydrogen abstraction.²² Next, a transannular 6-*exo* cyclization of the translocated nucleophilic C17-radical of **Int-3a** with the electrophilic C8–9 double bond produces **Int-4a**. This intramolecular radical addition occurs within the fused

rings to introduce the correct C8,17-stereogenic centers. Finally, the radical process is terminated by the hydrogenation of **Int-4a** from the convex face of the BC-ring to generate the C9-stereocenter of **14a**.

The multiple radical reactions proposed above were evaluated by DFT calculations of the energy diagram at the UM06-2X/6-31G(d) level of theory (Scheme 3B).²³ To facilitate the calculations, we used the structurally abbreviated radical intermediates, in which R² and R³ were changed from CH(OBn)₂ and Et to H and Me, respectively (see **11a** and **11b**). The calculated activation energy from **Int-1b** to **Int-2Ab** is smaller than that from the same **Int-1b** to the C10-epimeric **Int-2Bb** ($\Delta G^\ddagger = +8.2$ kcal mol⁻¹ for **TS-1A**, +9.4 kcal mol⁻¹ for **TS-1B**), supporting the observed C10-stereoselectivity of the 7-*endo* cyclization. The higher energy of **TS-1B** than **TS-1A** would originate from the close C14O–C15H contact in **TS-1B** (2.42 Å, Scheme 3C) within the sum of the van der Waals radii (2.72 Å) in comparison with that in **TS-1A** (2.68 Å). After formation of the stable delocalized radical **Int-2Ab** through the endothermic reaction (–23.2 kcal mol⁻¹), 1,5-hydrogen abstraction (**Int-2Ab** → **Int-3b**) requires a relatively large activation energy (+19.5 kcal mol⁻¹) and gives a less stable intermediate (+5.8 kcal mol⁻¹). However, **TS-3** is lower in energy than **TS-2** by –6.6 kcal mol⁻¹. Thus, the forward reaction from **Int-3b** to **Int-4b** is favored over the reverse reaction to **Int-2Ab**. Furthermore, 6-*exo* cyclization gives the thermodynamically preferred radical **Int-4b**, rather than **Int-3b** (–15.1 kcal mol⁻¹). The gain in energy of the overall process from the starting radical **Int-1b** to the end radical **Int-4b** is –32.5 kcal mol⁻¹, corroborating the high efficiency of the present cyclization/translocation/cyclization process.

Having constructed the five fused ring system with the seven stereocenters, the remaining tasks for the synthesis of the target **1** were the construction of the six-membered D-ring and the introduction of the C13,14 and 16 stereogenic centers (Scheme 4). We anticipated that an intramolecular aldol reaction between the C14-ketone and C16-aldehyde of **15a** would stereoselectively form the C13–16 bond. The aldol substrate **15a** was readily prepared from hemiacetal **13β** through oxidative cleavage by H₅IO₆. However, treatment of **15a** under acidic or basic conditions (*e.g.*, aq. HCl/dioxane or DBU/benzene) resulted in either decomposition or recovery of **15a**. These negative results were rationalized by DFT calculations of **15b** and **16b**, in which Et (R³) was replaced with Me. Although the reacting C13 and C16 atoms of **15b** are in close proximity, C13–16 bond formation significantly increases the potential energy of **16b** (+17.6 kcal mol⁻¹). The bond angle ($\theta = 101.3^\circ$) between C14–13 and C13–16 of **16b** deviates significantly from the ideal value, indicating its unusually strained character. Accordingly, the retro-aldol reaction from **16a** to **15a** would readily occur, even when **16a** was produced.

The above data and considerations led us to employ an irreversible Mukaiyama aldol reaction for cyclization of the strained D-ring (Scheme 5).^{24,25} To realize the transformation, an alternative aldol substrate **17** was designed to have the silyl enol ether as the nucleophile and the dibenzyl acetal as the activatable electrophile. The requisite TBS enol ether structure

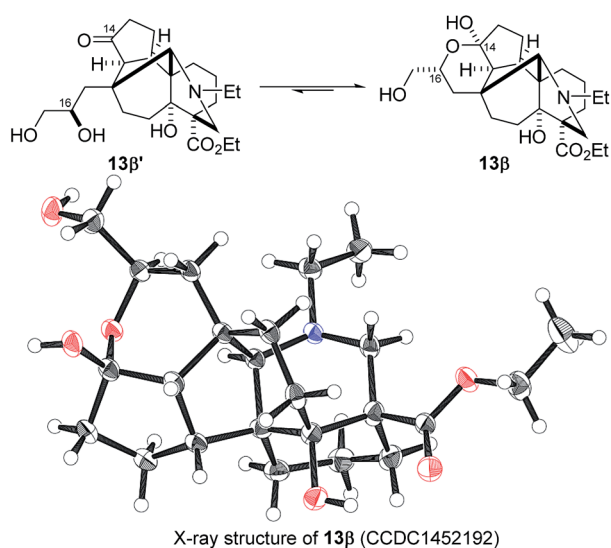
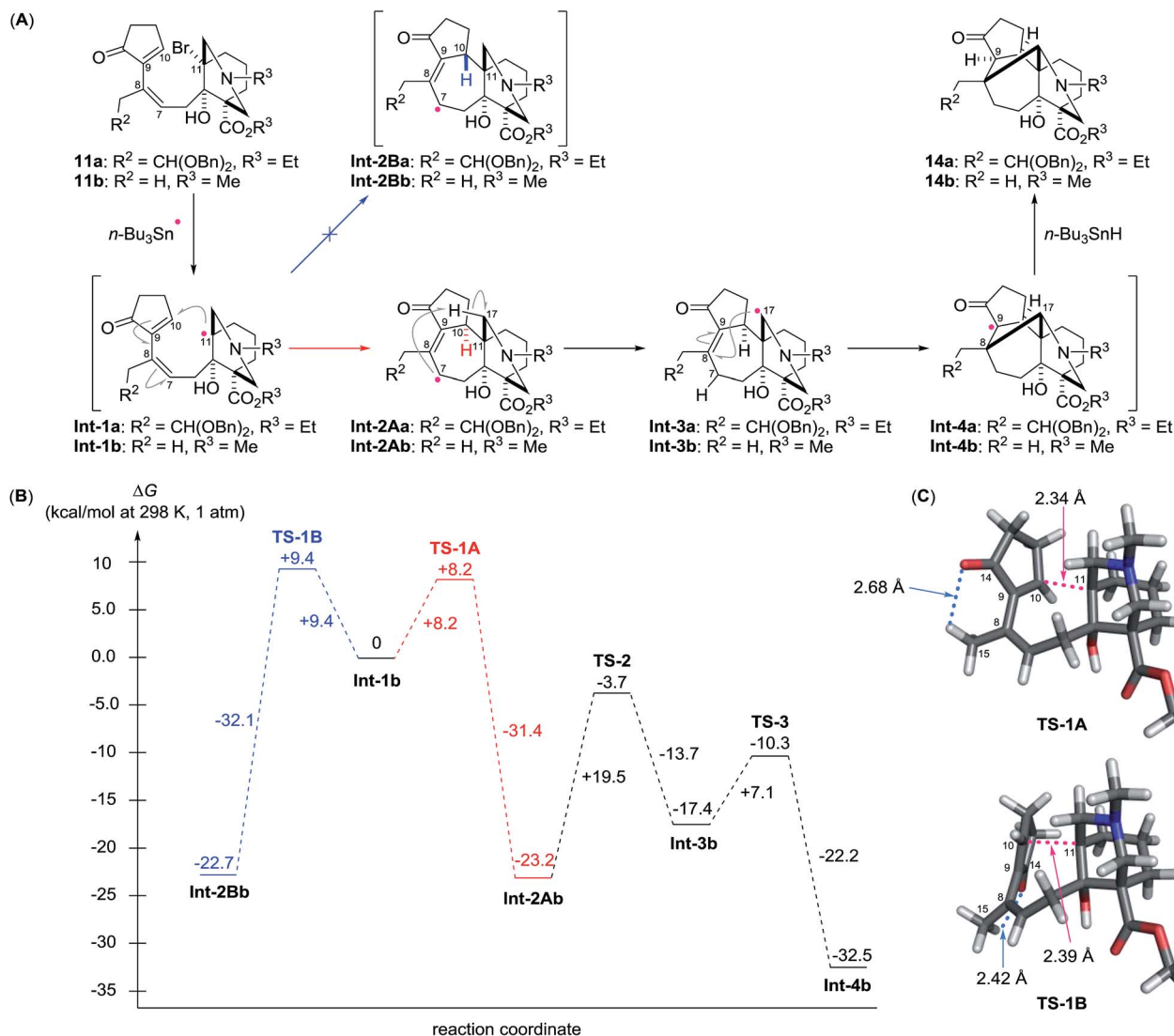


Fig. 1 X-ray structure of C16-β-alcohol **13β**.



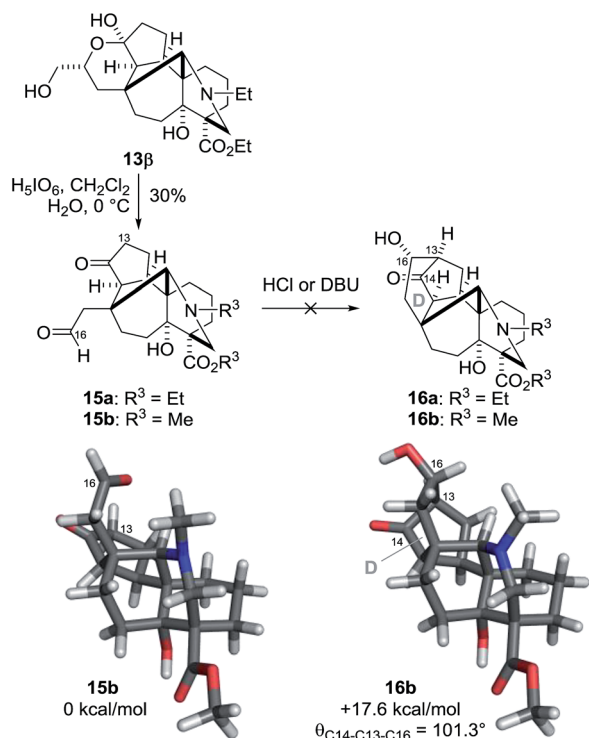


Scheme 3 (A) Plausible reaction pathway for the radical cascade reaction. (B) Calculated energy diagram for the cascade reaction. The changes in Gibbs free energy from Int-1b were calculated at the UM06-2X/6-31G(d) level and are shown in kcal mol^{-1} (298 K, 1 atm, gas phase). (C) The pink dotted line represents the C10–11 bond being formed, and the cyan dotted line represents the C14O–C15H interaction in the TS-1A and TS-1B structures.

of **17** was regioselectively constructed by applying TBSOTf and Et_3N to C14-ketone **14a**. A number of Lewis acids (*e.g.*, SnCl_2 , $\text{Sn}(\text{OTf})_2$, ZnBr_2 , $\text{BF}_3 \cdot \text{OEt}_2$, AlCl_3 and TiCl_4) activated the acetal moiety, yet failed to give the requisite product because the C14-oxygen atom instead of the C13 atom reacted with the C16-cation. Eventually, it was found that SnCl_4 attained the requisite C13–16 bond formation. Treatment of **17** with SnCl_4 in CH_2Cl_2 at -78 to 0°C permitted effective construction of hexacycle **19**, with installation of the C13 and 16-stereocenters. Therefore, capping the C16-hydroxy group with the benzyl group indeed inhibited the retro-aldol type reaction of adduct **19** under the reaction conditions. As illustrated by **18**, the newly generated C16-stereochemistry of **19** would originate from nucleophilic attack of the silyl enol ether from the Si-face of the oxocarbenium ion, which would be fixed by the binding of SnCl_4 between the oxygen and nitrogen atoms.

The synthesis of **1** was finalized by functional group manipulations at the C14 and C16 positions (Scheme 5). The C14-ketone of **19** was stereoselectively reduced from the convex face to provide the hydroxy group of **20**. Alcohol **20** was in turn converted to methyl ether **21** using MeI and *t*-BuOK. Then, the C16-configuration was inverted by an oxidation/reduction sequence. After removal of the benzyl group from **21**, the resultant hydroxy group of **22** was chemoselectively oxidized to the ketone within **23** in the presence of tertiary amine using the reagent combination AZADO/ $\text{CuCl}/2,2'$ -bipyridine/DMAP under air.²⁶ However, the NaBH_4 reduction of **23** only afforded its precursor **22**: hydride selectively attacked from the convex face to generate the undesired β -oriented C16-alcohol. Conversely, SmI_2 , a one-electron reducing agent, produced the correct C16-epimer.^{27,28} When **23** was treated with SmI_2 in THF/HMPA in the presence of *t*-BuOH, the α -oriented C16-alcohol **24** was obtained

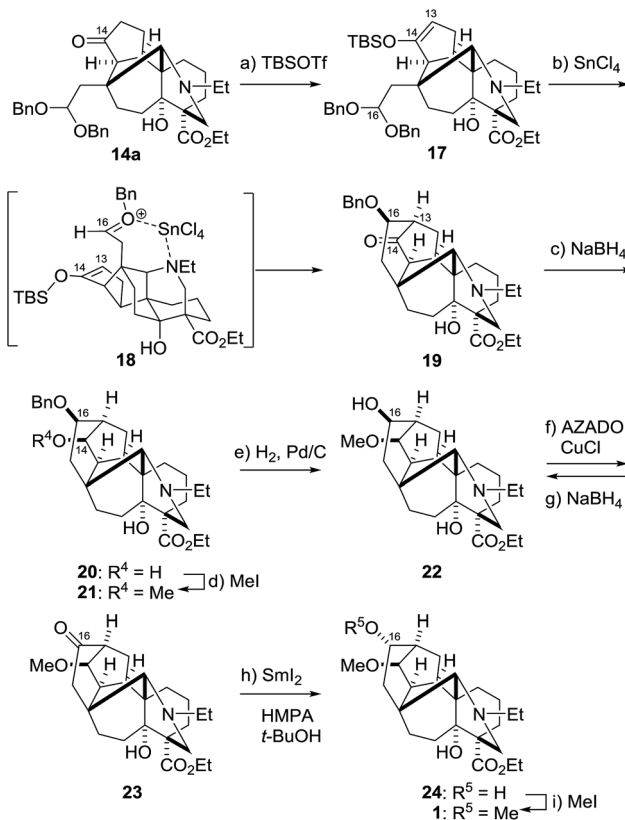




Scheme 4 Attempted D-ring formation by the aldol reaction. The relative Gibbs free energy values were calculated at the UM06-2X/6-31G(d) level (298 K, 1 atm, gas phase).

as the major product (**22** : **24** = 1 : 8). It is noteworthy that the use of H₂O or MeOH instead of *t*-BuOH decreased the stereoselectivity for **24** (**22** : **24** = 1.5 : 1),²⁹ indicating that the slower protonation of the C16-carbanion intermediate had a beneficial effect for generating **24**. Lastly, methylation of the C16-hydroxy group of **24** provided the targeted puberuline C skeleton **1** with its ten contiguous stereocenters.²¹

In summary, we have accomplished the expeditious synthesis of the entire 6/7/5/6/6/6-membered ring system **1** of the C₁₉-diterpenoid alkaloid puberuline C [18 steps from 2-(ethoxycarbonyl)cyclohexanone (**4**)]. The six ABCDEF rings and the ten stereogenic centers were constructed by a series of powerful transformations. First, the double Mannich reaction cyclized the AE-ring **3**, with implementation of the two tetra-substituted carbons (C4, 11). Second, carbon elongation from **3** to **2** was realized by nucleophilic addition of C and palladium-catalyzed couplings of A and B, introducing the C5-stereocenter and the C-ring structure. Third, the C11-bridgehead radical reaction of the highly unsaturated substrate **11a** underwent a 7-*endo* cyclization/1,5-radical translocation/6-*exo* cyclization process to form the B- and F-rings, establishing the stereochemistries of the two quaternary (C8, 11) and three tertiary carbons (C9, 10, 17) in a single step. Fourth, the Mukaiyama aldol reaction, followed by hydride and one-electron reductions, constructed the D-ring and the C13,14,16-stereocenters. Importantly, detailed DFT-calculations fully validated the reaction course and the stereoselective outcome of the salient radical cascade reaction. Further synthetic studies of



Scheme 5 Synthesis of the hexacyclic ring system of puberuline C. Reagents and conditions: (a) TBSOTf, Et₃N, CH₂Cl₂, 0 °C, 90%; (b) SnCl₄, CH₂Cl₂, -78 to 0 °C, 46%; (c) NaBH₄, MeOH, 0 °C, 96%; (d) MeI, *t*-BuOK, THF, 0 °C, 93%; (e) H₂, Pd/C, aq. HCl, MeOH, 95%; (f) AZADO (15 mol%), CuCl (15 mol%), 2,2'-bipyridine (15 mol%), DMAP (30 mol%), CH₃CN, air, 82%; (g) NaBH₄, MeOH, 0 °C, 50%; (h) Sml₂, *t*-BuOH, HMPA, THF, **22** : **24** = 1 : 8, 75% for **24**; (i) MeI, *t*-BuOK, THF, 0 °C, 93%. AZADO = 2-azaadamantane *N*-oxyl, HMPA = hexamethylphosphoric triamide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

puberuline C based on the newly developed strategy are underway in our laboratory.

Acknowledgements

This research was financially supported by the Funding Program a Grant-in-Aid for Scientific Research (A) to M.I. (JSPS) and (C) (JSPS) and on Innovative Areas (MEXT) to D.U. A fellowship from JSPS to K.H. is gratefully acknowledged. We thank Dr Kenji Yoza (Bruker AXS) for X-ray crystallographic analysis.

Notes and references

- F.-P. Wang and Q.-H. Chen, The C₁₉-Diterpene Alkaloids, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Elsevier Science, New York, 2010, vol. 69, p. 1.
- K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Lett.*, 1959, **1**, 15.



- 3 (a) L.-M. Sun, H.-L. Huang, W.-H. Li, Z.-D. Nan, G.-X. Zhao and C.-S. Yuan, *Helv. Chim. Acta*, 2009, **92**, 1126. Khairitdinova reported the isolation of the same compound from *Aconitum septentrionale* K., and designated it as septontrionine. In this paper, we used puberuline C as the compound name; (b) E. D. Khairitdinova, E. M. Tsyrlina, L. V. Spirikhin, A. A. Balandina, S. K. Latypov and M. S. Yunusov, *Russ. J. Org. Chem.*, 2008, **44**, 536.
- 4 For selected reviews on total synthesis of terpenoids, see: (a) K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 44; (b) R. M. Wilson and S. J. Danishefsky, *J. Org. Chem.*, 2007, **72**, 4293; (c) T. J. Maimone and P. S. Baran, *Nat. Chem. Biol.*, 2007, **3**, 396; (d) D. Urabe, T. Asaba and M. Inoue, *Chem. Rev.*, 2015, **115**, 9207.
- 5 For representative synthetic studies on aconitine-type alkaloids, see: (a) J. L. van der Baan, J. W. F. K. Barnick, G. van Beek and F. Bickelhaupt, *Tetrahedron*, 1992, **48**, 2773; (b) G. A. Kraus and S. Kesavan, *Tetrahedron Lett.*, 2005, **46**, 1111; (c) D. F. Taber, J.-L. Liang, B. Chen and L. Cai, *J. Org. Chem.*, 2005, **70**, 8739; (d) R. M. Conrad and J. Du Bois, *Org. Lett.*, 2007, **9**, 5465; (e) H. Cheng, F.-H. Zeng, D. Ma, M.-L. Jiang, L. Xu and F.-P. Wang, *Org. Lett.*, 2014, **16**, 2299.
- 6 For reviews on synthetic studies of the related diterpenoid alkaloids, see: (a) K. J. Goodall, D. Barker and M. A. Brimble, *Synlett*, 2005, 1809; (b) E. C. Cherney and P. S. Baran, *Isr. J. Chem.*, 2011, **51**, 391; (c) A. M. Hamlin, J. K. Kisunzu and R. Sarpong, *Org. Biomol. Chem.*, 2014, **12**, 1846; (d) X.-Y. Liu and Y. Qin, *Asian J. Org. Chem.*, 2015, **4**, 1010; (e) G. Zhu, R. Liu and B. Liu, *Synthesis*, 2015, **47**, 2691.
- 7 Total synthesis of aconitine-type alkaloids from Wiesner's group. Talatisamine: (a) K. Wiesner, T. Y. R. Tsai, K. Huber, S. E. Bolton and R. Vlahov, *J. Am. Chem. Soc.*, 1974, **96**, 4990; (b) K. Wiesner, *Pure Appl. Chem.*, 1975, **41**, 93. Chasmanine: (c) S.-F. Lee, G. M. Sathe, W. W. Sy, P.-T. Ho and K. Wiesner, *Can. J. Chem.*, 1976, **54**, 1039; (d) T. Y. R. Tsai, C. S. J. Tsai, W. W. Sy, M. N. Shanbhag, W. C. Liu, S. F. Lee and K. Wiesner, *Heterocycles*, 1977, **7**, 217; (e) K. Wiesner, T. Y. R. Tsai and K. P. Nambiar, *Can. J. Chem.*, 1978, **56**, 1451. 13-Desoxydelphonine: (f) K. Wiesner, *Pure Appl. Chem.*, 1979, **51**, 689.
- 8 Y. Shi, J. T. Wilmot, L. U. Nordström, D. S. Tan and D. Y. Gin, *J. Am. Chem. Soc.*, 2013, **135**, 14313.
- 9 C. J. Marth, G. M. Gallego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. M. Kou, J. Qin, R. Lilien and R. Sarpong, *Nature*, 2015, **528**, 493.
- 10 For conversion of the naturally occurring aconitine-type alkaloids to the puberuline frameworks, see: (a) T. Amiya and T. Shima, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 1957; (b) O. E. Edwards, *Can. J. Chem.*, 1981, **59**, 3039; (c) P. Tang, L. Wang, Q.-F. Chen, Q.-H. Chen, X.-X. Jian and F.-P. Wang, *Tetrahedron*, 2012, **68**, 5031.
- 11 α -Alkoxy bridgehead radicals were utilized for the intra- and intermolecular reactions in our laboratory: (a) D. Urabe, H. Yamaguchi and M. Inoue, *Org. Lett.*, 2011, **13**, 4778; (b) D. Urabe, M. Nagatomo, K. Hagiwara, K. Masuda and M. Inoue, *Chem. Sci.*, 2013, **4**, 1615; (c) K. Murai, S. Katoh, D. Urabe and M. Inoue, *Chem. Sci.*, 2013, **4**, 2364; (d) D. Kamimura, D. Urabe, M. Nagatomo and M. Inoue, *Org. Lett.*, 2013, **15**, 5122; (e) M. Nagatomo, M. Koshimizu, K. Masuda, T. Tabuchi, D. Urabe and M. Inoue, *J. Am. Chem. Soc.*, 2014, **136**, 5916; (f) T. Asaba, Y. Katoh, D. Urabe and M. Inoue, *Angew. Chem., Int. Ed.*, 2015, **54**, 14457; (g) M. Nagatomo, K. Hagiwara, K. Masuda, M. Koshimizu, T. Kawamata, Y. Matsui, D. Urabe and M. Inoue, *Chem.-Eur. J.*, 2016, **22**, 222.
- 12 G. A. Kraus and J. Shi, *J. Org. Chem.*, 1991, **56**, 4147.
- 13 H. P. Acharya, K. Miyoshi and Y. Kobayashi, *Org. Lett.*, 2007, **9**, 3535.
- 14 For a review, see: J. A. Marsden and M. M. Haley, Cross-Coupling Reactions to sp Carbon Atoms, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, vol. 1, p. 317.
- 15 J.-F. Betzer, F. Delalogue, B. Muller, A. Pancrazi and J. Prunet, *J. Org. Chem.*, 1997, **62**, 7768.
- 16 For a review, see: V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1.
- 17 V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585.
- 18 B. M. Smith and A. E. Graham, *Tetrahedron Lett.*, 2006, **47**, 9317.
- 19 For recent reviews on radical cascade reactions, see: (a) A. Baralle, A. Baroudi, M. Daniel, L. Fensterbank, J.-P. Goddard, E. Lacôte, M.-H. Larrauffie, G. Maestri, M. Malacria and C. Ollivier, *Radical Cascade Reactions*, in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, ed. C. Chatgililoglu and A. Studer, John Wiley & Sons Ltd, Chichester, 2012, vol. 2, p. 729; (b) U. Wille, *Chem. Rev.*, 2013, **113**, 813; (c) J.-R. Chen, X.-Y. Yu and W.-J. Xiao, *Synthesis*, 2015, **47**, 604.
- 20 For recent reviews on cascade reactions in natural product synthesis, see: (a) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (b) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442.
- 21 For the structural determinations, see ESI.†
- 22 For selected reports on the radical translocation/cyclization process, see: (a) D. C. Lathbury, P. J. Parsons and I. Pinto, *J. Chem. Soc., Chem. Commun.*, 1988, 81; (b) D. P. Curran, D. Kim, H. T. Liu and W. Shen, *J. Am. Chem. Soc.*, 1988, **110**, 5900; (c) V. Snieckus, J. C. Cuevas, C. P. Sloan, H. Liu and D. P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 896; (d) J. Robertson, M. A. Peplow and J. Pillai, *Tetrahedron Lett.*, 1996, **37**, 5825; (e) F. Beaufils, F. Dénès, B. Becattini, P. Renaud and K. Schenk, *Adv. Synth. Catal.*, 2005, **347**, 1587; (f) M. Fujitani, M. Tsuchiya, K. Okano, K. Takasu, M. Ihara and H. Tokuyama, *Synlett*, 2010, 822; (g) J. K. Vellucci and C. M. Beaudry, *Org. Lett.*, 2015, **17**, 4558. For reviews, see: (h) J. Robertson, J. Pillai and R. K. Lush, *Chem. Soc. Rev.*, 2001, **30**, 94; (i) F. Dénès, F. Beaufils and P. Renaud, *Synlett*, 2008, 2389.
- 23 (a) Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215; (b) Y. Zhao and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 157.



- 24 T. Mukaiyama, T. Izawa and K. Saigo, *Chem. Lett.*, 1974, 323.
- 25 For a review on Mukaiyama aldol reaction in natural product synthesis, see: S. B. J. Kan, K. K.-H. Ng and I. Paterson, *Angew. Chem., Int. Ed.*, 2013, **52**, 9097.
- 26 Y. Sasano, S. Nagasawa, M. Yamazaki, M. Shibuya, J. Park and Y. Iwabuchi, *Angew. Chem., Int. Ed.*, 2014, **53**, 3236.
- 27 P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693.
- 28 For a book, see: *Organic Synthesis using Samarium Diodide A Practical Guide*, ed. D. J. Procter, R. A. Flowers II and T. Skrydstrup, RSC publishing, Cambridge, 2010.
- 29 For the effects of proton source on stereoselective reduction of ketones, see: (a) S. K. Upadhyay and S. Hoz, *J. Org. Chem.*, 2011, **76**, 1355; (b) P. R. Chopade, E. Prasad and R. A. Flowers II, *J. Am. Chem. Soc.*, 2004, **126**, 44.

