

HETEROCYCLES, Vol. 77, No. 2, 2009, pp. 855 - 863. © The Japan Institute of Heterocyclic Chemistry  
Received, 9th October, 2008, Accepted, 10th November, 2008, Published online, 11th November, 2008  
DOI: 10.3987/COM-08-S(F)120

## FLEXIBLE ACCESS TO MONOTERPENOID INDOLE ALKALOIDS USING A CYCLOPENTANOID CHIRAL BUILDING BLOCK

Masato Hayashi, Keiichi Motosawa, Atsushi Satoh, Masatoshi Shibuya,  
Kunio Ogasawara, and Yoshiharu Iwabuchi\*

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aobayama,  
Sendai 980-8578, Japan

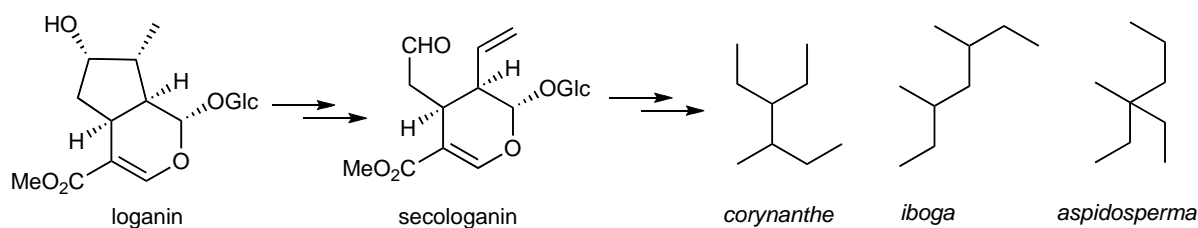
E-mail: iwabuchi@mail.pharm.tohoku.ac.jp

**Abstract** – Expedient, diastereocontrolled transformations of **1** to the key synthetic intermediate of *corynanthe*, *iboga*, and *aspidosperma*-class of monoterpene indole alkaloids which led up to a formal synthesis of (+)-20*R*-dihydrocleavamine, (–)-eburnamonine, and a total synthesis of (+)-aspidospermidine (**2**) have been demonstrated.

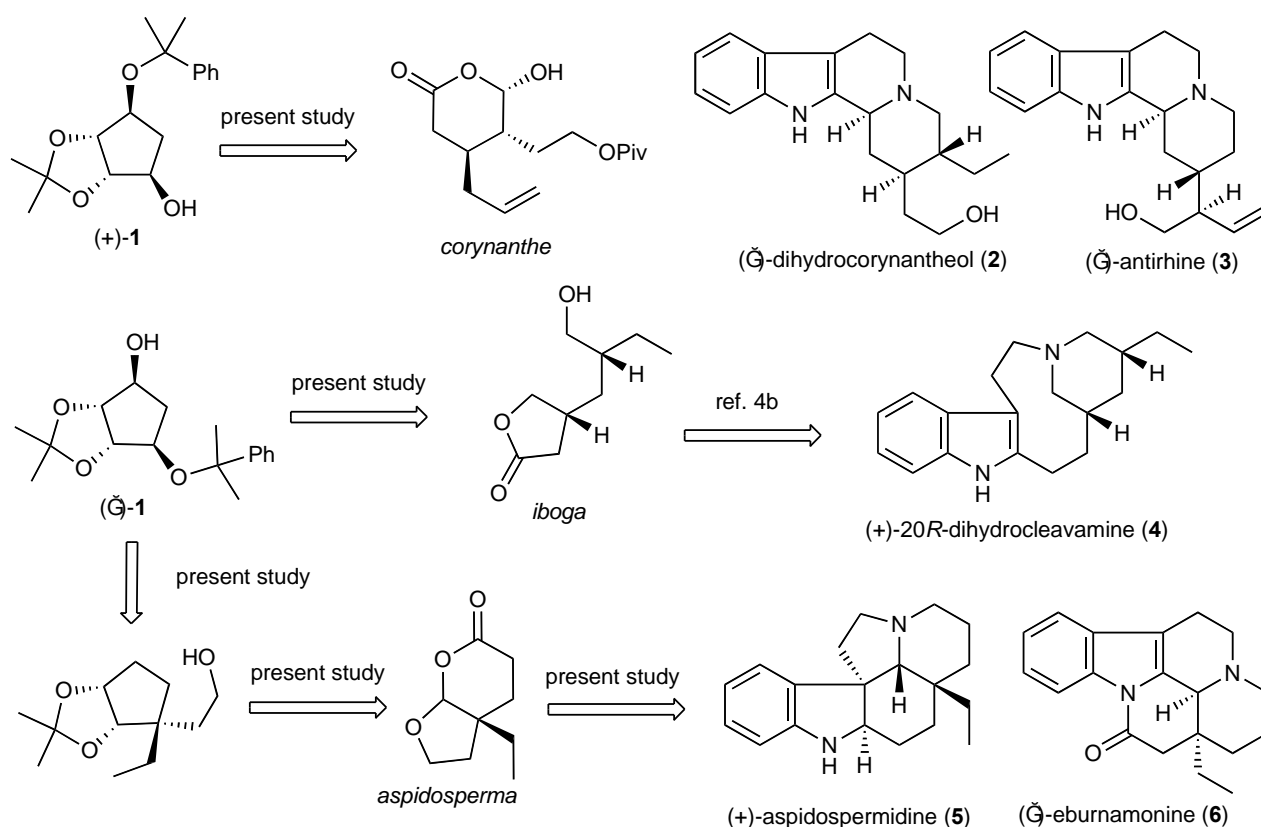
Molecules capable of dictating regio- and diastereoselective modifications thereof offer versatile use in organic synthesis. We previously reported an efficient chemoenzymatic preparation of the 2,3,4-trioxycyclopentanol **1** having a dioxabicyclo[3.3.0]octane framework in both enantiomeric forms<sup>1</sup> and demonstrated its use in the efficient stereocontrolled synthesis of  $\alpha$ -cuparenone,<sup>2a</sup> (+)-estrone,<sup>2b</sup> Calabar bean alkaloids,<sup>2c</sup> and *Scelletium* alkaloids.<sup>2d</sup> Highlighting its flexible features, we have now explored its potential as a chiral building block for the representative class of monoterpene indole alkaloids derived from secologanin:<sup>3</sup> the facts that the overwhelming structural diversity of monoterpene indole alkaloids is originated from the common intermediate, secologanin via the adoption of multiple set of biochemical transformations and that secologanin is produced by the oxidative scission of the cyclopentane-ring of loganin (Scheme 1) stimulated our challenge to exploit the further versatility of **1**. We report here the diastereocontrolled transformation of **1** to the key intermediates for the synthesis of *corynanthe*, *iboga*, and *aspidosperma*-class of monoterpene indole alkaloids which led up to a formal synthesis of (+)-20*R*-dihydrocleavamine (**4**),<sup>4</sup> (–)-eburnamonine (**6**),<sup>5</sup> and a total synthesis of (+)-aspidospermidine (**5**).<sup>3b,6,7,8</sup> (Scheme 2).

---

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



Scheme 1

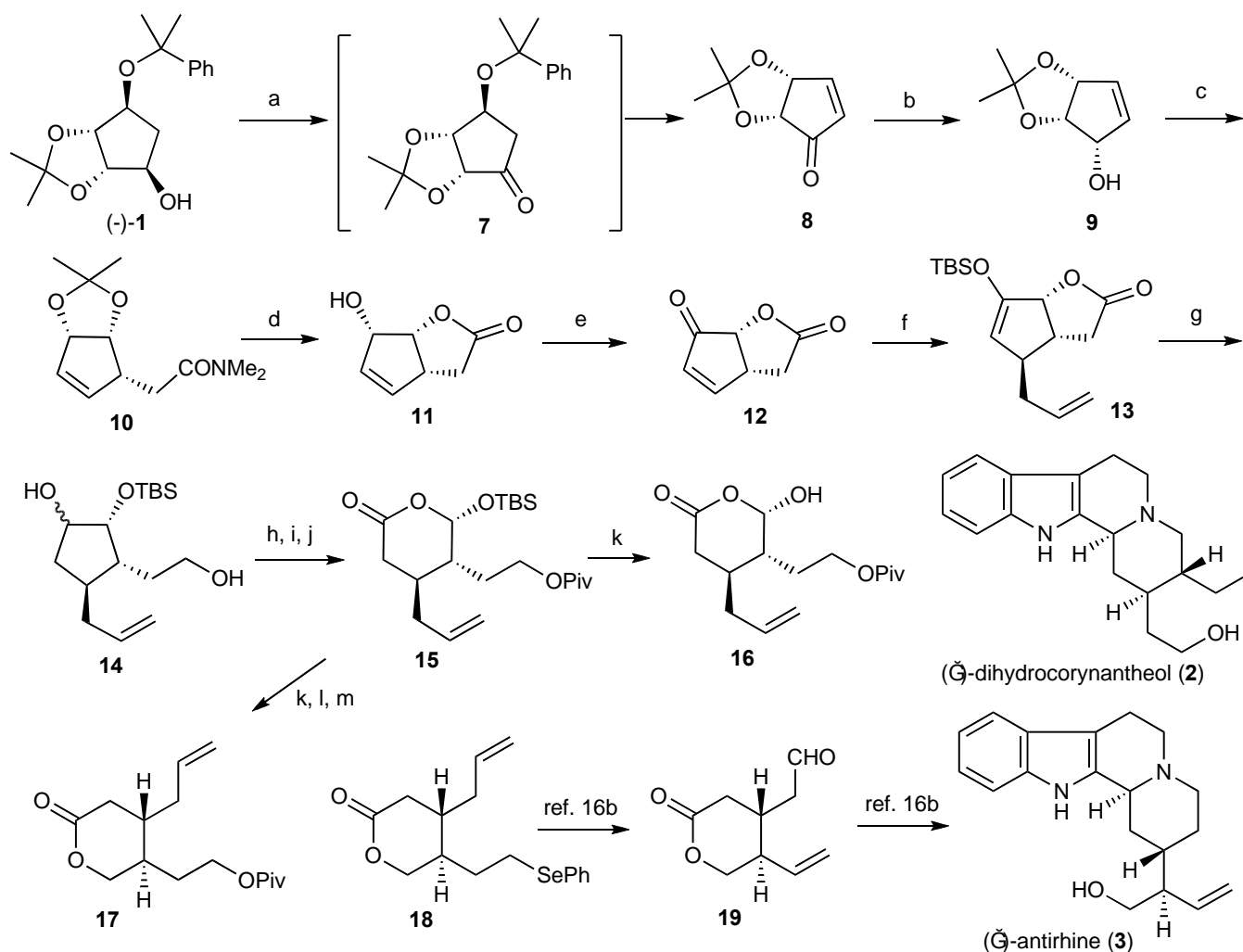


Scheme 2

The strategic point of this synthetic venture is to exploit expedient methods addressing issues on how and when to install the requisite side chains selectively at the right positions on the periphery of the cyclopentane ring and to cleave the exact bond by taking a full advantage of functionalities in **1**.

Our effort to transform (+)-**1** to a key synthetic intermediate of the *corynanthe*-class of indole alkaloids, featuring the 1,2-vicinal stereogenic centers consisting of secondary alkyl carbons, was commenced with the oxidative activation of the chiral building block (+)-**1** to place the base for installation of the two alkyl branches (Scheme 3). Thus, the oxidation of the alcohol (+)-**1** was first carried out using IBX<sup>9</sup> in DMSO at 60 °C to give the enone **8** in 75% via the ketone **7**<sup>10</sup> with the concomitant  $\beta$ -elimination of a cumyl alcohol. Upon treatment with sodium borohydride in the presence of cerium(III) chloride, the enone **8** afforded the cyclopentenol **9** having the all-*cis* oxygen stereochemistry as a sole product via the

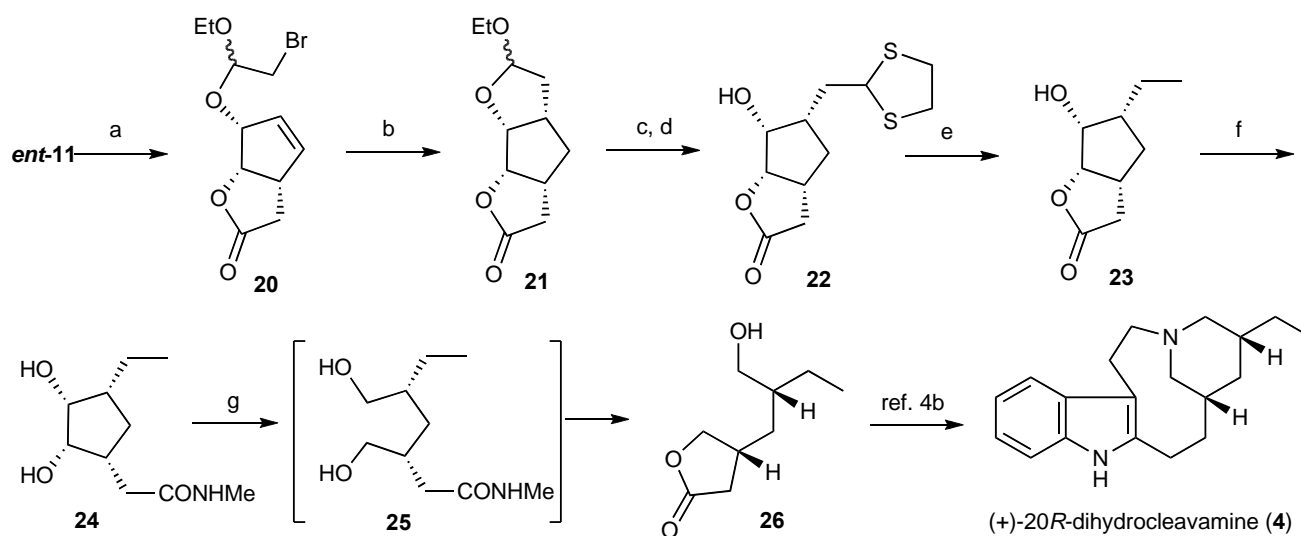
diastereocontrolled delivery of a hydride from the convex-face.<sup>11</sup> The installation of the first C2 branch was then conducted by the Eschenmoser reaction of **9** with dimethylacetamide dimethyl acetal in diphenyl ether at 280 °C to give the single cyclopentene **10** having the acetamide moiety *cis* to the acetonide moiety.<sup>1,12,13</sup> Due to the given stereochemical arrangement, the amide **10** allowed consecutive facile deacetonization and lactonization under acidic condition to give the  $\delta$ -hydroxy- $\gamma$ -lactone **11**, which on treatment with MnO<sub>2</sub> gave the enone **12** with a biased platform suitable for the stereocontrolled installation of the second branch intrinsic the *corynanthe*-family. As expected, reaction of **12** with allyltributylstannane in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C in the presence of TBSOTf furnished the silyl enol ether **13** in 74% yield by concurrent diastereoselective 1,4-addition and *O*-silylation.<sup>14</sup>



**Scheme 3.** Reagents and conditions: (a) IBX, DMSO, 60 °C, 15 h (75%); (b) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, -20 °C (98%); (c) Me<sub>2</sub>NC(OMe)<sub>2</sub>Me, Ph<sub>2</sub>O, reflux, 2 h (98%); (d) 10% HCl, THF (97%); (e) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (quant.); (f) allyltributyltin, TBSOTf, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C (74%); (g) NaBH<sub>4</sub>, EtOH, reflux (77%); (h) PivCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (75%); (i) PCC, MS 4Å, CH<sub>2</sub>Cl<sub>2</sub> (89%); (j) *m*CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> (83%); (k) *aq.* HF, MeCN, (l) NaBH<sub>4</sub>, MeOH, 0 °C; (m) PPTS, toluene (64%, 3 steps).

The task for a regioselective cleavage of the cyclopentane ring of **13** suitable for the *corynanthe*-class of indole alkaloid could be facilitated with an unexpected side reaction provoked by a protecting group. Thus, on treatment with sodium borohydride in boiling EtOH, **13** gave the diol **14** in 77% yield via the concomitant migration of a TBS group to the possible secondary oxyanion generated right after the partial reduction of the  $\gamma$ -lactone **13**. The selective protection of the primary hydroxy group of **14** as the pivalate and PCC oxidation of the remaining secondary hydroxy group and the following Baeyer-Villiger oxidation using *m*CPBA afforded the lactone **15**. On HF-mediated deprotection of TBS group, **15** gave **16**, which on sequential sodium borohydride treatment in MeOH, and PPTS-catalyzed lactonization with azeotropic removal of water afforded the  $\delta$ -lactone **17**,  $[\alpha]_D^{28} +9.23^\circ$  (c 0.86, CHCl<sub>3</sub>). In light of the close topological correlations and the functionalities of **16** and **17** with the non-tryptamine moieties of **2** and **3**, respectively, **16** should be a potential synthon of (–)-dihydrocorynantheol (**2**)<sup>15</sup> and (–)-antirrhine (**3**).<sup>16g</sup>

The synthetic effort directed toward *iboga*-type indole alkaloid was put into practice by setting the exact target to (+)-20*R*-dihydrocleavamine (**4**), where the construction of the characteristic 1,3-vicinal tertiary alkyl centers was accomplished by applying the Stork radical cyclization protocol<sup>17</sup> to the allyl alcohol *ent*-**11** as the key step (Scheme 4). Thus, treatment of *ent*-**11**, prepared from (–)-**1** by employing the same sequence as shown in Scheme 3, with NBS in CH<sub>2</sub>Cl<sub>2</sub> in the presence of ethyl vinyl ether and sodium bicarbonate gave quantitatively the bromoethyl acetal **20**, which on treatment with AIBN in boiling toluene in the presence of Bu<sub>3</sub>SnH furnished the tricyclic lactone **21** in 77% yield.



**Scheme 4.** Reagents and conditions: (a) ethyl vinyl ether, NBS, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> (98%); (b) Bu<sub>3</sub>SnH, AIBN, toluene, reflux (77%); (c) PPTS, MeCN, H<sub>2</sub>O, reflux (92%); (d) HS(CH<sub>2</sub>)<sub>2</sub>SH, BF<sub>3</sub>·OEt<sub>2</sub>, (quant.); (e) Raney Ni, EtOH (78%); (f) MeNH<sub>2</sub>, AlMe<sub>3</sub>, THF, reflux (74%); (g) NaIO<sub>4</sub>, THF, H<sub>2</sub>O then NaBH<sub>4</sub>, then 10% HCl (64%).

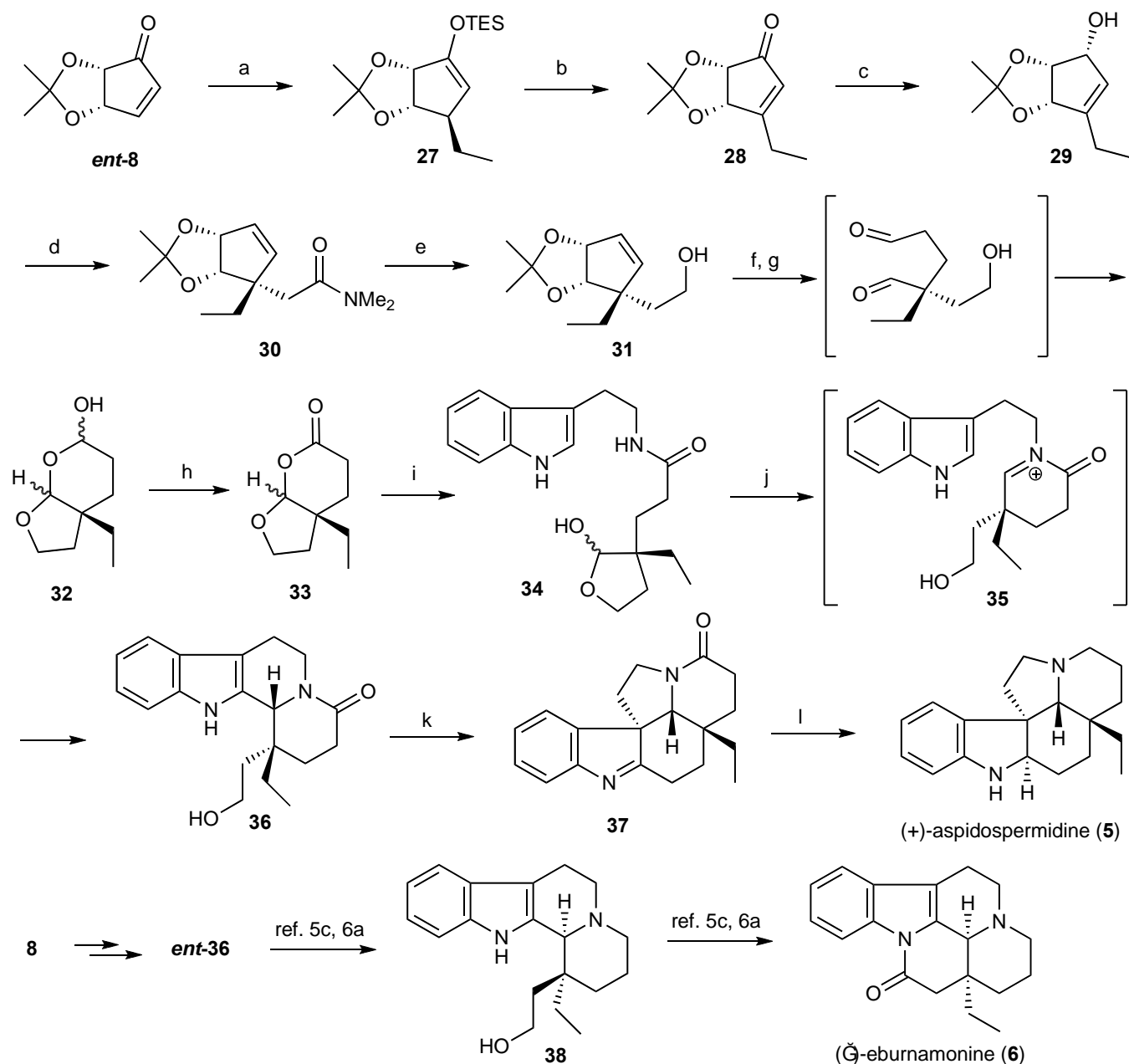
After acidic hydrolysis of the acetal moiety of **21**, the resulting lactol was converted to the dithiane **22** on treatment with ethanedithiol and  $\text{BF}_3 \cdot \text{OEt}_2$ . Upon exposure to Raney-Nickel in EtOH, **22** furnished the hydroxy-lactone **23** with the requisite 20*R*-ethyl group being arranged in 78% yield. Then, the hydroxy-lactone **23** was exposed to the complex generated from methylamine hydrochloride and trimethylaluminum in THF at reflux to give the dihydroxy-amide **24**.<sup>18</sup> On sequential periodate cleavage and borohydride reduction in the same flask, **24** afforded the lactone **26**,  $[\alpha]_{\text{D}}^{31} -0.47$  (c 0.11,  $\text{CHCl}_3$ ) {lit.,  $[\alpha]_{\text{D}}^{26} -0.5$  (c 1.0,  $\text{CHCl}_3$ )<sup>4b</sup>}, via diol **25** through a concurrent cyclization during the acidic work up. Since **26** has been transformed into (+)-20*R*-dihydrocleavamine (**4**), this constitutes the development of new formal route to this alkaloid.<sup>4b</sup>

Exploration of a route to *aspidosperma*-type indole alkaloid was carried out targeting (+)-aspidospermidine (**5**) with the intention of adopting the Harley-Mason's protocol.<sup>8</sup>

The synthesis was commenced with the formal substitution of the vinylic hydrogen of *ent*-**8** with an ethyl group to prepare for the construction of the quarternary carbon characteristic to *aspidosperma*-family (Scheme 5). The task was executed via a sequence involving the conjugate addition of a cuprate generated from ethylmagnesium bromide in THF containing HMPA in the presence of copper(I) iodide and triethylsilyl chloride at  $-40$  °C, followed by the *in situ* trapping of the enolate with triethylsilyl chloride, and the subsequent oxidation of the resulting silyl enol ether **27** by the palladium-catalyzed protocol developed by Ito and Saegusa<sup>19</sup> to furnish the  $\beta$ -ethyl enone **28** in 89%. The reduction of **28** with sodium borohydride in MeOH at  $-40$  °C in the presence of cerium(III) chloride gave the *endo*-allyl alcohol **29** as the only product by convex-face selective 1,2-reduction. The Eschenmoser rearrangement reaction<sup>1,12,13</sup> of **29** was carried in boiling diphenyl ether ( $\sim 280$  °C) to give the acetamide **30** having the desired quarternary center in 86% yield as the single product. The acetamide moiety thus arranged was transformed into the hydroxyethyl handle, which is essential for the Harley-Mason reaction, by treating **30** with  $\text{LiEt}_3\text{BH}$ <sup>20</sup> in THF.

Having served its dual purpose as a stereocontrolling element and a protecting group, the dioxabicyclo[3.3.0]octane moiety of **31** was converted into the two side chains of the secologanin-derived C9 unit suitable for merger with a tryptamine. Thus, posterior to the hydrogenation of **31**, the treatment of the resulting product with  $\text{HIO}_4$  in 1,4-dioxane- $\text{H}_2\text{O}$  afforded the dioxabicyclo[4.3.0]nonane lactol **32**, via the sequential hydrolysis of the acetonide moiety, the oxidative cleavage of the resulting 1,2-glycol, and further spontaneous cyclization, which on oxidation with cat. TPAP and NMO<sup>21</sup> yielded the dioxabicyclo[4.3.0]nonane lactone **33**, as an armed form of the key C9 unit. The projected merger was then conducted by treating **33** with tryptamine in boiling toluene to give the known secondary amide **34**, hereby establishing the formal synthesis<sup>6a,c</sup> of aspidospermidine. As a result of our serious attack to

accomplish the synthesis, we found efficient conditions for the promotion of the Pictet-Spengler cyclization of **34**. Thus, on warming in phenol<sup>22</sup> with a catalytic amount of H<sub>2</sub>SO<sub>4</sub> at 50 °C for 1 h, **34** induced diastereoselective cyclization to give **36** in 70% yield as a 10:1 mixture with C(3) β-epimer as the major product.<sup>23</sup>



**Scheme 5. Reagents and conditions:** (a) EtMgBr, CuI, HMPA, TESCl, THF, -78 to -40 °C; (b) Pd(OAc)<sub>2</sub>, O<sub>2</sub>, DMSO, 50 °C, 9 h (89%, 2 steps); (c) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, -40 °C (90%); (d) Me<sub>2</sub>NC(OMe)<sub>2</sub>Me, Ph<sub>2</sub>O, reflux, 2 h (86%); (e) LiEt<sub>3</sub>BH, THF, 0 °C (quant.); (f) H<sub>2</sub>, 10% Pd-C, AcOEt (quant.); (g) HIO<sub>4</sub>·2H<sub>2</sub>O, dioxane-H<sub>2</sub>O (1:1), rt; (h) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, rt (94%, 2 steps); (i) tryptamine, toluene, reflux, 2 h; (j) cat. H<sub>2</sub>SO<sub>4</sub>, phenol, 50 °C, 1 h (70%, 2 steps); (k) 40% aq. H<sub>2</sub>SO<sub>4</sub>, 110 °C, 1.5 h; (l) LiAlH<sub>4</sub>, THF, reflux, 2 h (51%, 2 steps).

Note that the well-precedent protocol required 48 h refluxing in acetic acid for the Pictet-Spengler reaction to give a 1:1 mixture of the C(3) $\alpha$ , and  $\beta$ -epimers as their acetate in moderate (up to 50%) yield, which required the subsequent alkaline hydrolysis to detach the acetate moiety. The conversion of the alcohol **36** to (+)-aspidospermidine (**5**) was carried out as described by Harley-Mason and Kaplan: treatment<sup>7</sup> in 40% H<sub>2</sub>SO<sub>4</sub> at 100-110 °C for 1.5 h to give **37**, and immediate reduction of **37** with LiAlH<sub>4</sub> in refluxing THF to give (+)-aspidospermidine (**5**) in 51% yield. The spectral data (<sup>1</sup>H and <sup>13</sup>C NMR, IR, MS), mp (115-118 °C) and specific rotation of synthetic aspidospermidine [ $\alpha$ ]<sub>D</sub><sup>23</sup> +16.4° (c 1.01 EtOH) were consistent with reported values<sup>22</sup> (mp 120-121 °C, [ $\alpha$ ]<sub>D</sub><sup>23</sup> +17.0 (c 0.60, EtOH)). The present synthesis implies development of a new diastereo- and enantiocontrolled synthesis of eburnamonine, the medicinally important *eburnane*-class of indole alkaloid, since the starting ketone **1** is available in both enantiomeric form and the transformation of **36** to eburnamonine (**6**) via **38**<sup>5c,6a</sup> has been established.

In conclusion, we have demonstrated the transformation of **1** to the key synthetic intermediates of *corynanthe*, *iboga*, and *aspidosperma*-class of monoterpene indole alkaloids which led up to a formal synthesis of (+)-20*R*-dihydrocleavamine, (–)-eburnamonine, and a total synthesis of (+)-aspidospermidine (**2**), thereby extending the utility of **1** as a chiral building block.

## REFERENCES AND NOTES

1. H. Nakashima, M. Sato, T. Taniguchi, and K. Ogasawara, *Synthesis*, 2000, 817.
2. (a) H. Nakashima, M. Sato, T. Taniguchi, and K. Ogasawara, *Tetrahedron Lett.*, 2000, **41**, 2639. (b) K. Tanaka, H. Nakashima, T. Taniguchi, and K. Ogasawara, *Org. Lett.*, 2000, **2**, 1915. (c) K. Tanaka, T. Taniguchi, and K. Ogasawara, *Tetrahedron Lett.*, 2001, **42**, 1049. (d) M. Hayashi, T. Unno, M. Takahashi, and K. Ogasawara, *Tetrahedron Lett.*, 2002, **43**, 1461.
3. (a) J. Stöckigt and M. Ruppert, 'Comprehensive Natural Products,' Vol. 4, ed. by D. Barton and K. Nakanishi, Elsevier, New York, 1999, 109. (b) J. E. Saxton, 'The Alkaloids,' Vol. 51, ed. by G. A. Cordell, Academic Press, New York, 1998, Chapter 1.
4. Enantiocontrolled synthesis of (+)-20*R*-15, 20-dihydrocleavamine, see (a) B. Danieli, G. Lesma, D. Passarella and A. Silvani, *Tetrahedron Lett.*, 2000, **41**, 3489. (b) R. M. Kanada and K. Ogasawara, *Tetrahedron Lett.*, 2001, **42**, 7311. (c) M. Amat, C. Escolano, O. Lozano, N. Llor, and J. Bosch, *Org. Lett.*, 2003, **5**, 3139.
5. For selected total synthesis of (–)-eburnamonine, see (a) S. Takano, M. Yonaga, M. Morimoto, and K. Ogasawara, *J. Chem. Soc., Perkin Trans. 1*, 1985, 305. (b) A. G. Schultz and L. Pettus, *J. Org. Chem.*, 1997, **62**, 6855. (c) A. G. H. Wee and Q. Yu, *Tetrahedron Lett.*, 2000, **41**, 587. (d) W. G. H. Andrew and Y. Qing, *J. Org. Chem.*, 2001, **66**, 8935. (e) Y. Murakami, M. Shindo, and K. Shishido,

- [Synlett, 2005, 664](#).
6. For selected enantiocontrolled synthesis of aspidospermidine, see (a) M. Node, H. Nagasawa, and K. Fuji, [J. Org. Chem., 1990, 55, 517](#). (b) D. Desmaële and J. d'Angelo, [J. Org. Chem., 1994, 59, 2292](#). (c) A. G. Schultz and L. Pettus, [J. Org. Chem., 1997, 62, 6855](#). (d) S. A. Kozmin, T. Iwama, Y. Huang, and V. H. Rawal, [J. Am. Chem. Soc., 2002, 124, 4628](#). (e) J. P. Marino, M. B. Rubio, G. Cao, and A. de Bois, [J. Am. Chem. Soc., 2002, 124, 13398](#). (f) R. Iyengar, K. Schildknecht, and J. Aubé, [Org. Lett., 2000, 2, 1625](#).
  7. For recent total synthesis of Aspidosperma alkaloids, see (a) F. He, Y. Bo, J. D. Altom, and E. J. Corey, [J. Am. Chem. Soc., 1999, 121, 6771](#). (b) M. A. Toczko and C. H. Heathcock, [J. Org. Chem., 2000, 65, 2642](#). (c) Y. Fukuda, M. Shindo, and K. Shishido, [Org. Lett., 2003, 5, 749](#). (d) L. A. Sharp and S. Z. Zard, [Org. Lett., 2006, 8, 831](#). (e) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams, and N. Oram, [Angew. Chem. Int. Ed., 2007, 46, 6159](#).
  8. J. Harley-Mason and M. Kaplan, [Chem. Commun., 1967, 915](#).
  9. (a) M. Frigerio and M. Santagosino, [Tetrahedron Lett., 1994, 35, 8019](#). (b) M. Frigerio, M. Santagosino, S. Sputore, and G. Palmisano, [J. Org. Chem., 1995, 60, 7272](#).
  10. Previously, the conversion of **1** to **8** was conducted by a two step sequence consisting of (i) Dess-Martin periodinane-mediated oxidation to give **7**, and (ii) warming **7** in acetic acid to promote the  $\beta$ -elimination of a cumyl alcohol; see ref. 1. The facile one-pot conversion of **1** to **8** features the inherent acidic nature of IBX in DMSO. For the discussion on p*K*<sub>a</sub> of IBX, see M. J. Gallen, R. Goumont, T. Clark, F. Terrier, and C. M. Williams, [Angew. Chem. Int. Ed., 2006, 45, 2929](#).
  11. (a) J.-L. Luche, [J. Am. Chem. Soc., 1978, 100, 2226](#). (b) A. L. Gemal and J.-L. Luche, [J. Am. Chem. Soc., 1981, 103, 5454](#).
  12. A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, [Helv. Chim. Acta, 1964, 47, 2425](#).
  13. (a) H. Nakashima, M. Sato, T. Taniguchi, and K. Ogasawara, [Synlett, 1999, 1754](#). (b) M. Hayashi, T. Unno, M. Takahashi, and K. Ogasawara, [Tetrahedron Lett., 2002, 43, 1461](#).
  14. S. Kim and J. M. Lee, [Synth. Commun., 1991, 21, 25](#).
  15. For selected synthesis of (–)-dihydrocorynantheol; (a) T. Suzuki, E. Sato, K. Unno, and T. Kametani, [Heterocycles, 1985, 23, 835](#). (b) R. L. Beard and A. I. Meyers, [J. Org. Chem., 1991, 56, 2091](#). (c) M. Ohba, T. Ohashi, and T. Fuji, [Heterocycles, 1991, 32, 319](#). (d) T. Itoh, M. Yokota, K. Miyauchi, K. Nagata, and A. Ohsawa, [Org. Lett., 2006, 8, 1533](#). (e) A. Deiters, M. Pettersson, and S. F. Martin, [J. Org. Chem., 2006, 71, 6547](#). (f) A. Tosaka, S. Itoh, N. Miyaszawa, M. Shibuya, K. Ogasawara, and Y. Iwabuchi, [Heterocycles, 2006, 70, 153](#).
  16. For selected synthesis of antirhine, (±)-Antirhine: (a) S. Takano, M. Takahashi, and K. Ogasawara, [J. Am. Chem. Soc., 1980, 102, 4282](#). (–)-Antirhine: (b) S. Takano, N. Tamura, and K. Ogasawara, [J.](#)

- [Chem. Soc., Chem. Commun., 1981, 22, 1155](#). (c) T. Suzuki, E. Sato, K. Unno, and T. Kametani, [Heterocycles, 1985, 23, 839](#). (d) T. Suzuki, E. Sato, K. Unno, and T. Kametani, [Chem. Pharm. Bull., 1986, 34, 3135](#). (e) A. Pancrazi, J. Kervagoret, and Q. Khuong-Huu, [Tetrahedron Lett., 1991, 32, 4483](#). (f) B. Danieli, G. Lesma, M. Mauro, G. Palmisano, and D. Passarella, *Tetrahedron Lett.*, 1994, **50**, 8837. (g) M. Kawamura and K. Ogasawara, [Tetrahedron Lett., 1995, 36, 3369](#).
17. (a) G. Stork and N. H. Baine, [J. Am. Chem. Soc., 1982, 104, 2321](#). (b) G. Stork and R. Mook, Jr., [J. Am. Chem. Soc., 1983, 105, 3720](#).
18. A. Basha, M. Lipton, and S. M. Weinreb, [Tetrahedron Lett., 1977, 18, 4171](#).
19. Y. Ito, T. Hirao, and T. Saegusa, [J. Org. Chem., 1978, 43, 1011](#).
20. (a) H. C. Brown, S. C. Kim, and S. Krishnamuthy, [J. Org. Chem., 1980, 45, 1](#). (b) H. Tanaka and K. Ogasawara, [Tetrahedron Lett., 2002, 43, 4417](#).
21. S. V. Ley, J. Norman, W. P. Griffith, and S. P. Marsden, [Synthesis, 1994, 639](#).
22. S. Torii, H. Tanaka, M. Taniguchi, and Y. Kameyama, [J. Org. Chem., 1991, 56, 3633](#).
23. The prolongation of reaction time resulted in the attenuation of the diastereoselectivity in the Pictet-Spengler reaction of **34**, suggesting that C(3)  $\beta$ -**36** is the kinetically favored product.
24. G. F. Smith and M. A. Wahid, [J. Chem. Soc., 1963, 4002](#).