This is the peer reviewed version of the following article: A. Nakayama, T. Nakamura, T. Zaima, S. Fujimoto, S. Karanjit, K. Namba, Angew. Chem. Int. Ed. 2021, 60, 635., which has been published in final form at https://doi.org/10.1002/anie.202009966. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions. This article may not be enhanced, enriched or otherwise transformed into a derivative work, without express permission from Wiley or by statutory rights under applicable legislation. Copyright notices must not be removed, obscured or modified. The article must be linked to Wiley's version of record on Wiley Online Library and any embedding, framing or otherwise making available the article or pages thereof by third parties from platforms, services and websites other than Wiley Online Library must be prohibited.

WILEY-VCH

COMMUNICATION

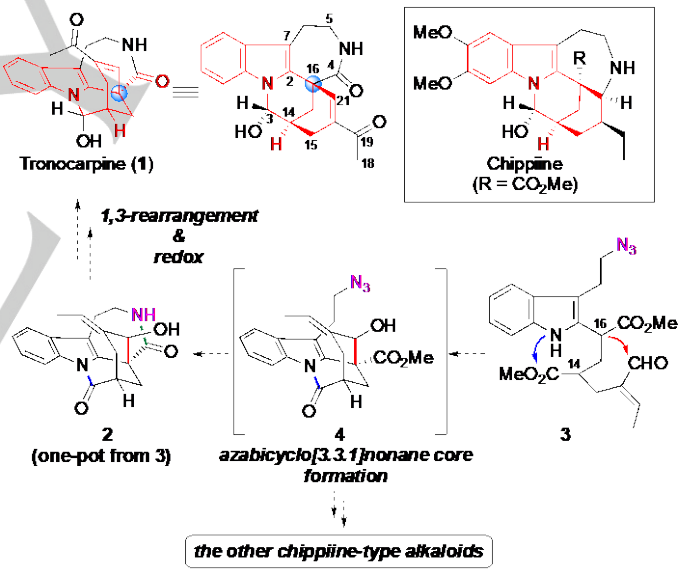
Concise Total Synthesis of Tronocarpine

Atsushi Nakayama*, Tenta Nakamura, Toshihiro Zaima, Saho Fujimoto, Sangita Karanjit, and Kosuke Namba*

Abstract: A concise total synthesis of tronocarpine, a chippiine-type indole alkaloid, was accomplished. The key feature of this total synthesis is a one-pot construction of the pentacyclic skeleton containing an azabicyclo[3.3.1]nonane core by tandem cyclization from an indole derivative having all carbon side chains and functional groups. This tandem cyclization consists of α,β-unsaturated aldehyde formation, intramolecular aldol reaction, six-membered lactamization, azide reduction, and seven-membered lactamization. The stereochemical outcome in this tandem cyclization is controlled by the stereocenter at the C14 position. This strategy can be utilized to synthesize other chippiine-type alkaloids with azabicyclo[3.3.1]nonane skeletons.

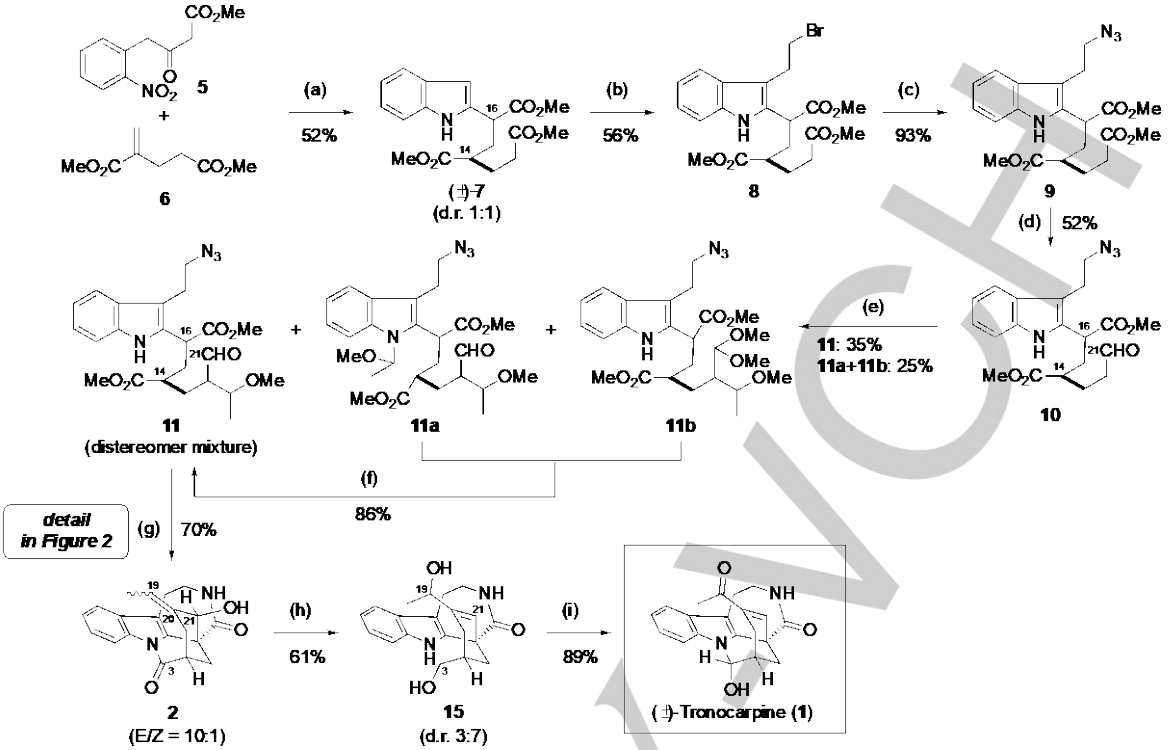
Tabernaemontana corymbosa plants are widely known to produce secondary metabolites, particularly monoterpenoid indole alkaloids with diverse and complex skeletons, and numerous kinds of compounds have been isolated from these metabolites.[1-4] Two prominent examples are the vobasinyl-iboga-type bis-indole alkaloids and chippiine-type indole alkaloids derived from *Tabernaemontana corymbosa,* which are expected to be useful molecules for anticancer treatment because of their unique ability to reverse multidrug resistance.[5] Tronocarpine (**1**), a family member of chippiine-type alkaloids, was isolated by Kam and co-workers in 2000 (Figure 1).[6] The structural features of **1** are a unique pentacyclic skeleton containing six- and seven-membered lactams, three asymmetric centers including a quaternary carbon center (C16) adjacent to the C2 position of the indole, a hemiaminal moiety, and an α,β-unsaturated ketone. Several efforts to synthesize **1** have been reported,[7] most of which have involved the construction of the polycyclic skeleton without the carbon side chains and functional groups in the early stage of synthesis. In 2020, Han and co-workers reported the first asymmetric total synthesis of (+)-**1** from tryptamine using elegant reactions.[8] They constructed the azabicyclo[3.3.1]nonane core by utilizing asymmetric Michael/aldol reactions, and formed the pentacyclic skeleton of **1** in the early stages of the synthesis. The remainder of the carbon side chains were then introduced in the later stages under mild conditions to avoid unexpected side reactions. As Han and co-workers demonstrated, a synthetic strategy that includes the construction, in advance, of a basic carbon skeleton of complex polycyclic ring systems is a reasonable approach for achieving divergent synthesis of related natural products. On the other hand, assembling a fully functionalized skeleton from a chain substrate having all required units at once is more efficient for target-oriented synthesis because it can simplify the synthetic scheme.[9] To realize a more concise total synthesis of **1**, we designed the following synthetic strategy. We envisioned that if α,β-unsaturated aldehyde **3** or its synthetic equivalent having all carbon units of **1** could be synthesized, we could induce tandem intramolecular aldol/lactamization reactions to form the azabicyclo[3.3.1]nonane core (**4** in Figure 1). Then, we could reduce the azide and form a seven-membered lactam to afford the fully functional pentacyclic compound **2** in a one-pot operation, leading to **1**. Moreover, 1,3-rearrangement of the hydroxy group followed by oxidation would yield **1** in rapid fashion. This strategy could applied to synthesize other chippiine-type alkaloids with an azabicyclo[3.3.1]nonane core from **4**.

Figure 1. Structure of tronocarpine (**1**) and synthetic plans for the construction of an azabicyclo[3.3.1]nonane core and pentacyclic skeleton of **1**.



[a] Dr. A. Nakayama, T. Nakamura, T. Zaima, S. Fujimoto, Dr. S. Karanjit, Prof. Dr. K. Namba
Graduate School of Pharmaceutical Sciences
Tokushima University
1-78 Shomachi, Tokushima
Tokushima 770-8505 (Japan)
E-mail: anakaya@tokushima-u.ac.jp
E-mail: namba@tokushima-u.ac.jp
http://www.tokushima-u.ac.jp/ph/faculty/labo/bot/

Supporting information for this article is given via a link at the end of the document.



Scheme 1. Total synthesis of tronocarpine (**1**) through tandem cyclization to construct the pentacyclic skeleton. Reagents and conditions: a) nBu$_3$P, MeCN, RT then Pd/C (20 w/w%), MeOH, H_2 (1 atm), RT, 52% (d.r. 1:1); b) 2-Bromo-1,1-dimethoxyethane, TFA, Et_3SiH, CH_2Cl_2, RT, 56%; c) NaN_3, DMF, 40 °C, 93%; d) DIBAL, CH_2Cl_2, –78 °C, 52%; e) TBSOTf, DIPEA, CH_2Cl_2, 0 °C then acetaldehyde dimethyl acetal, TBSOTf, –78 °C to 0 °C, **11**: 35%, **11a**+**11b**: 25%; (f) Amberlyst®15, Acetone, RT, 86%; g) Na_2CO_3, MeOH, 0 °C to 40 °C then Pd/$CaCO_3$ (50 w/w%), H_2 (1 atm), RT then Na_2CO_3, 35 °C under Ar atmosphere, 70% (E:Z = 10:1 at C19-C20); h) Tf_2NH, $(CH_2Cl)_2$, 0 °C then THF/H_2O (4:1), $NaHCO_3$, $NaBH_4$, 70 °C, 61% (d.r. 3:7); i) Dess-Martin periodinane, CH_2Cl_2, RT then (+)-CSA, THF/H_2O (4:1), RT, 89%. TFA = trifluoroacetic acid, DMF = *N*,*N*-dimethylformamide, DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethansulfonyl, DIPEA = diisopropylethylamine, (+)-CSA = (+)-10-camphorsulfonic acid.

We commenced the synthesis of the preparation of a tandem cyclization precursor **11**, which is a synthetic equivalent of **3** (Scheme 1). The known 1,3-dicarbonyl derivative **5**[10] and α,β-unsaturated ester **6**,[11] which were both prepared in one step from commercially available reagents, were coupled in the presence of tributyl phosphine.[12] Then, the reaction mixture was directly hydrogenated by adding MeOH and Pd/C under a hydrogen atmosphere to afford indole triester derivative (±)-**7** as a 1:1 diastereomeric mixture between C14 and C16. A two-carbon unit was introduced to the C3 position of the indole moiety with the addition of 2-bromo-1,1-dimethoxyethane in the presence of trifluoroacetic acid and triethylsilane to afford bromide **8** in 56% yield.[13] Treatment of **8** with sodium azide in dimethylformamide at 40°C then gave azide triester **9** in excellent yield. To our delight, careful DIBAL reduction of **9** at –78 °C selectively converted the primary ester to aldehyde and afforded aldehyde **10** along with 30% recovery of **9**. Then, we chose Mukaiyama aldol reaction conditions with a silyl enol ether for the introduction of a two-carbon side chain to avoid an intramolecular aldol at the C16 position with the C21 aldehyde moiety. To this end, aldehyde **10** was easily converted to the silyl enol ether by treatment with TBSOTf and diisopropylethylamine. After confirming the formation of the silyl enol ether by monitoring thin-layer chromatography, an additional excess amount (ca. 20 equiv)[14] of acetaldehyde dimethyl acetal and 2 equiv of TBSOTf were added at –78 °C. Then, the reaction mixture was warmed to 0 °C, and the reaction proceeded rapidly to afford the desired aldehyde **11** as an inseparable diastereomeric mixture in 35% yield, along with a mixture of *N*-hemiaminal aldehyde **11a** and dimethyl acetal product **11b** in 25% yield. The mixture of **11a** and **11b** was then converted to **11** in 86% yield by treatment with Amberlyst®15 (see the Supporting Information). As a result, we finally obtained the tandem cyclization precursor **11** in 57% combined yield from **10**. It should be noted that the use of a smaller amount of acetaldehyde dimethyl acetal (approximately equivalent to the amount of the starting material) caused the decomposition of the TBS enol ether taking precedence over the Mukaiyama aldol reaction. On the other hand, a further excessive amount of acetaldehyde dimethyl acetal gave side products, including **11a** and **11b**, without furnishing **11**.

We succeeded in obtaining **11** as a synthetic equivalent of the desired aldehyde **3**, and then examined the tandem cyclization reaction with **11**. The one-pot operation of basic and reductive treatment of **11** gave the desired tandem cyclization (intramolecular aldol reaction, six- and seven-membered lactamization), and the pentacyclic compound **2** with a tronocarpine skeleton was obtained in 70% yield as an inseparable mixture of olefin isomers (E/Z = 10:1).[14] Gratifyingly, all the diastereomers of **11** converged into one diastereomer of **2**. The structure of **2** was determined by 2D-NMR (COSY, HMQC, HMBC, NOESY; see the Supporting Information). The details of this tandem cyclization are shown in Figure 2. First, treatment of

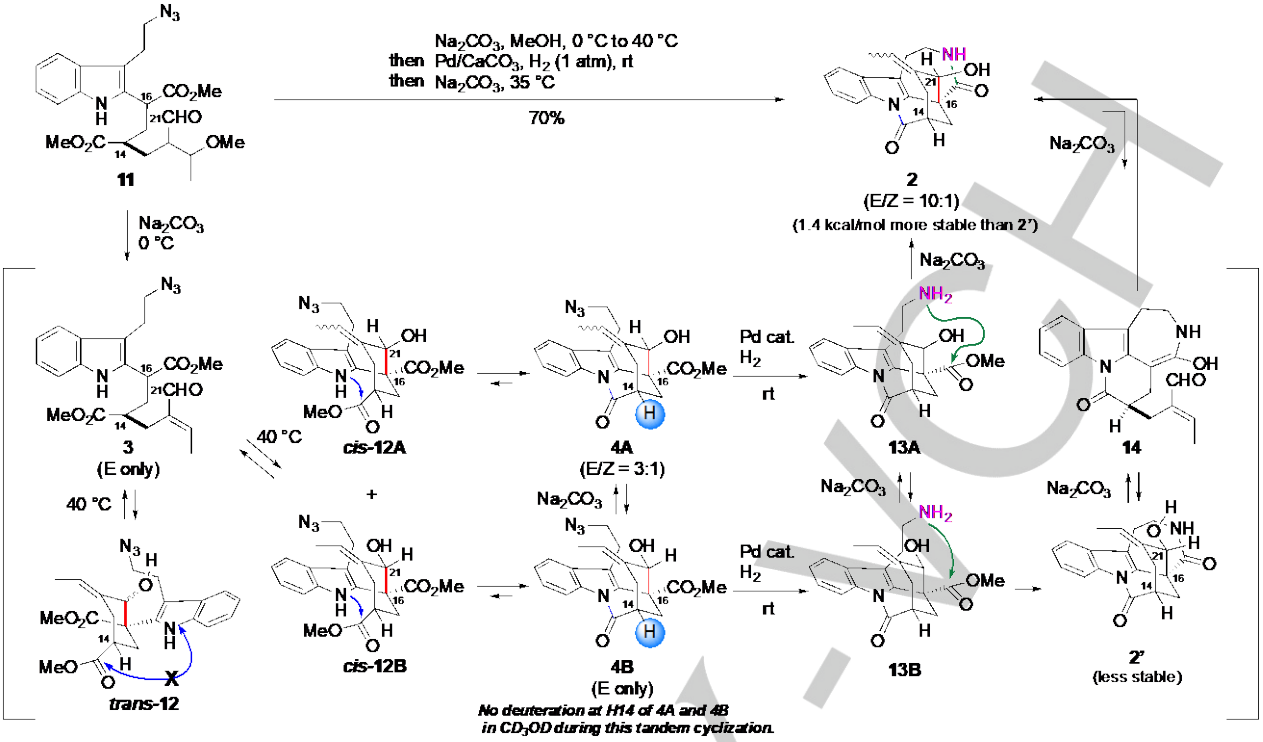


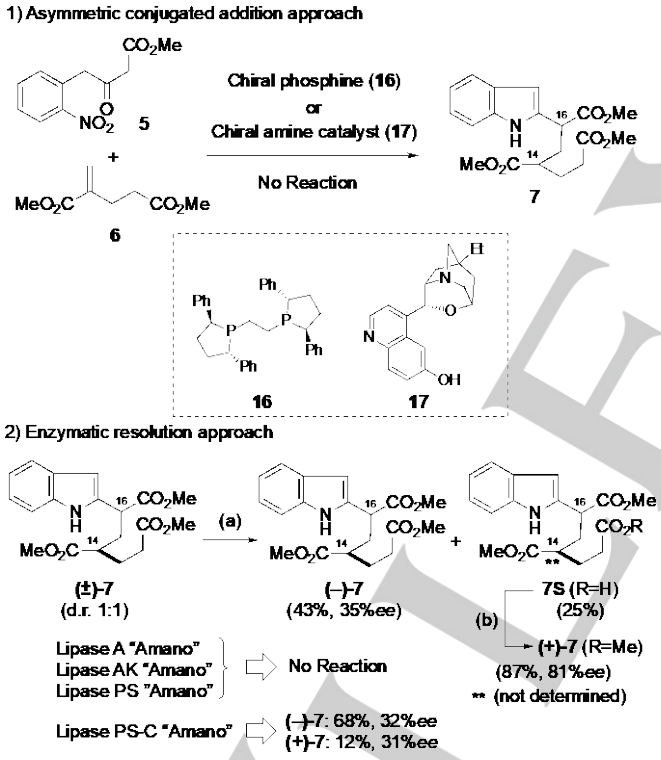
Figure 2. Plausible reaction mechanism of tandem cyclization from **11** to pentacyclic compound **2.**

11 with sodium carbonate at 0 °C led to β-elimination to form α,β-unsaturated aldehyde **3** exclusively in the E-form without any side reactions. Then, warming the reaction mixture to 40 °C induced the next intramolecular aldol reaction. During this aldol reaction, the stereochemistry at the C16 position might not be controlled, and the 1:1 mixture of ***trans*-12** and ***cis*-12** would be generated. The stereochemistry of the hydroxy group at the C21 position should also be a mixture, and there was an equilibrium between ***trans*-12** and ***cis*-12** by the *retro*-aldol reaction. In the case of ***trans*-12**, the distance between the the indole nitrogen and the ester group at the C14 position is too great to allow the formation of a lactam. On the other hand, ***cis*-12A** and ***cis*-12B**, which are epimers at the C21 position, were able to form a six-membered lactam because of the short distance between the reaction positions, affording tetracyclic compounds **4A** and **4B**, respectively. As the lactamization of ***cis*-12** proceeds, the equilibrium would be shifted to ***cis*-12** from ***trans*-12**, and finally all these compounds would be converted to **4A** and **4B**. When the reaction was quenched in this step, **4A** (ca. E/Z = 3:1) and **4B** (all E-form) were obtained in a ca. 1:1 ratio (see the Supporting Information). We also confirmed that **4A** and **4B** were formed in equilibrium under basic conditions by treating the isolated **4B** with sodium carbonate in MeOH and checking the formation of **4A** (see the Supporting Information). In addition, we investigated a suitable base to advance this tandem cyclization and found Na_2CO_3 and K_2CO_3, as well as NaOMe and KOMe, smoothly induced the β-elimination and intramolecular aldol reaction/lactamization. Due to its lower basicity, $NaHCO_3$ did not induce the lactamization, and organic bases such as Et_3N, *i*Pr_2NEt, DBU, and tetramethylguanidine did not prompt the tandem cyclization and give the desired tetracyclic products.

As described above, we developed a powerful method to construct the azabicyclo[3.3.1]nonane skeleton by utilizing this tandem reaction. Then, the azide moiety of **4A** and **4B** was converted to the primary amine successively by directly adding Lindlar catalyst ($Pd/CaCO_3$) under a hydrogen atmosphere in one pot to afford the corresponding products **13A** and **13B**. The subsequent addition of sodium carbonate[15] to the reaction mixture for the acceleration of the seven-membered lactam formation would then potentially afford the pentacyclic compounds **2** and **2'** with a tronocarpine skeleton. However, to our surprise and delight, the pentacyclic compound **2** was finally obtained as a sole isomer at the C21 position under this one-pot tandem cyclization procedure, and the stereochemistry of C21 was determined by a NOESY experiment (see the Supporting Information). The finding that this tandem cyclization gave only **2** could be explained by comparing the thermodynamic stability between **2** and its epimer **2'** at the C21 position by density functional theory (DFT) calculation (Method/Basis set b3lyp/6-31g(d,p)). Based on this calculation, **2** is 1.4 kcal/mol more stable than **2',** and the calculated result was in good agreement with the experimental result. This concordance indicated that aldol/*retro*-aldol reactions can take place between **2** and **2'** via tetracyclic aldehyde **14**, allowing epimer **2'** to converge to the most stable compound **2** entirely. We separately prepared **2'** from **13B** (see the Supporting Information) and confirmed that **2'** could be converted entirely to **2** with Na_2CO_3 in MeOH. In other words, pentacyclic compound **2**, which has a tronocarpine skeleton, could be obtained via equilibrium events in each reaction. Moreover, if the epimerization at the C14 position does not occur under the mild basic conditions of this tandem cyclization, the stereochemistry of the quaternary carbon center

at the C16 position would be controlled by the stereochemistry at the C14 position. To confirm the possibility of epimerization at the C14 position, we conducted the aldol reaction/lactamization tandem reaction in CD_3OD. We confirmed that the proton at the C14 position was not deuterated at all in the NMR experiment, indicating that the C14 position is not epimerized under this tandem cyclization condition. Therefore, the chiral quaternary carbon center at the C16 position of the pentacyclic product **2** can be controlled by the stereochemistry at the C14 position.

We succeeded in constructing the tronocarpine skeleton from commercially available reagents in short order, and finally attempted the functional group transformation from **2** toward the total synthesis of **1** (see Scheme 1). 1,3-Rearrangement of the hydroxy group from the C21 position to the C19 position was achieved by treatment of **2** with bis(trifluoromethane)sulfonimide, and subsequent reduction of the C3 lactam was conducted by direct addition of THF, H_2O, $NaHCO_3$, and an excess amount of sodium borohydride to give primary alcohol **15**. Finally, we accomplished the total synthesis of tronocarpine (**1**) by Dess–Martin oxidation and acidic treatment of the product. All the spectral data were in good agreement with Han's reported data for **1**.



Scheme 2. An attempt for the asymmetric synthesis of triester **7**. Reagents and conditions: a) Novozyme 435 (100 w/w%), MeCN/0.1 M Phosphate buffer (1:2), RT, **(–)-7**: 43%, 35%*ee*, **7S**: 25%; b) $TMSCHN_2$, MeOH/Toluene (1:3), RT, **(+)-7**: 87%, 81%*ee*. TMS = trimethylsilyl.

Having established a highly effective synthetic route to (±)-**1**, we investigated the possibility of rendering this synthesis asymmetric (Scheme 2). Since the stereochemistry at the most important C16 quaternary carbon center is controlled by the stereochemistry at the C14 position, as shown in Figure 2, synthesis of triester **7** with an enantiomerically enriched carbon center at the C14 position was attempted. First, we tried an asymmetric conjugated addition between **5** and **6** with a chiral phosphine or with a quinidine-derived chiral amine catalyst instead of tributyl phosphine. However, the coupling reaction did not proceed, and only starting materials were recovered. We found that only tributyl phosphine catalyzed this reaction in this Morita-Baylis-Hillman-type reaction, and common catalysts such as DMAP and DABCO did not effect this transformation. Next, we attempted an enzymatic kinetic resolution of triester **7**. After extensive investigation (see the Supporting Information), we finally found that enzymatic kinetic resolution with Novozyme 435 gives the desired hydrolyzed product **7S**, and the use of acetonitrile as a co-solvent improved the conversion. Subsequent esterification of **7S** afforded the enantioenriched triester **(+)-7** with 81%*ee*. We also conducted the chiral separation of (±)-**1** for rapid supply of both enantiomers, and obtained optically pure (+)-**1** ($[\alpha]^{28}_D$ +277, *c* = 0.167, CH_2Cl_2) and (–)-**1** ($[\alpha]^{28}_D$ –282, *c* = 0.153, CH_2Cl_2). Thus, our short step synthesis may make it possible to efficiently supply both enantiomers of this natural product for various applications in the field of life science.

In summary, we have developed an efficient synthetic method for constructing the pentacyclic skeleton of tronocarpine (**1**) with an azabicyclo[3.3.1]nonane core, which is a characteristic skeleton of chippiine-type alkaloids, by utilizing a tandem cyclization. In this manner, we achieved the concise total synthesis of (±)-tronocarpine (**1**) in 3.05% overall yield from **5**. The key tandem cyclization step consisted of i) β-elimination, ii) intramolecular aldol reaction, iii) six-membered lactamization, iv) reduction of azide, and v) seven-membered lactamization, all conducted in a one-pot operation. We also developed an enzymatic kinetic resolution of racemic triester **7** to render this synthesis asymmetric. Finally, we established conditions for the chiral separation of racemic **1**. Biological studies and medicinal chemistry research of (+)-**1** and (–)-**1**, as well as other chippiine-type alkaloids are currently underway in our laboratory.

Acknowledgements ((optional))

We deeply thank Prof. Dr. T. Sugai and Prof. Dr. S. Higashibayashi of Keio University for the technical support of the enzymatic kinetic resolution. We thank Novozymes Japan Ltd. for supplying Novozyme 435. This work was supported by JSPS KAKENHI Grant Nos. 20K09396 (A.N.), JP19H02851 (K.N.), and JP16H01156 (K.N.), as well as the Uehara Memorial Foundation, Takeda Science Foundation. We also acknowledge Tokushima University for their financial support of the Research Clusters program of Tokushima University (No. 1802001).

Keywords: total synthesis • natural product •tandem cyclization • equilibrium • alkaloid

[1] B. Danieli, G. Palmisano, In *The Alkaloids*, *Vol.* 27 (Eds.: A. Brossi), Academic Press, Amsterdam, **1986**, pp 1–130.

[2] T.-S. Kam, In *Alkaloids: Chemical ad Biological; Perspectives*, *Vol.* 14 (Eds.: S. W. Pelletier), Pergamon, Amsterdam, **1999**, pp 284–435.

[3] T.-S. Kam, Y.-M. Choo, In *The Alkaloids*, *Vol.* 63 (Eds.: G. A. Cordell), Academic Press, Amsterdam, **2006**, pp 181–337.

[4] For selected papers, see: a) T.-S. Kam, K.-Y. Loh, *Phytochemistry* **1993**, *32*, 1357–1358; b) H. Takayama, S. Suda, M. Kitajima, S. Sakai, D.

Santiarworn, B. Liawruangrath, N. Aimi, *Natural Medicines* **1998**, *52*, 289; c) T.-S. Kam, K.-M. Sim, *Heterocycles* **2001**, *55*, 2405–2412; d) T.-S. Kam, K.-M. Sim, *Helv. Chim. Acta* **2002**, *85*, 1027–1032; e) T.-S. Kam, K.-M. Sim, *J. Nat. Prod.* **2003**, *66*, 11–16; f) K.-H. Lim, O. Hiraku, K. Komiyama, T.-S. Kam, *J. Nat. Prod.* **2008**, *71*, 1591–1594; g) K.-H. Lim, G.-H. Tan, K.-M. Sim, T.-S. Kam, *Phytochemistry* **2009**, *70*, 1182–1186; h) K.-H. Lim, T.-S. Kam, *Helv. Chim. Acta* **2009**, *92*, 1895–1902; i) K.-H. Lim, T. Etoh, M. Hayashi, K. Komiyama, T.-S. Kam, *Tetrahedron Lett.* **2009**, *50*, 752–754; j) C.-E. Nge, C.-Y. Gan, K.-H. Lim, K.-N. Ting, Y.-Y. Low, T.-S. Kam, *Org. Lett.* **2014**, *16*, 6330–6333; k) K.-H. Lim, V. J. Raja, T. D. Bradshaw, S.-H. Lim, Y.-Y. Low, T.-S. Kam, *J. Nat. Prod.* **2015**, *78*, 1129–1138; l) C.-E. Nge, K.-S. Sim, S.-H. Lim, N. F. Thomas, Y.-Y. Low, T.-S. Kam, *J. Nat. Prod.* **2016**, *79*, 2709–2717; m) Y.-X. Yuan, Y. Zhang, L.-L. Guo, Y.-H. Wang, M. Goto, S. L. Morris-Natschke, K.-H. Lee, X.-J. Hao, *Org. Lett.* **2017**, *19*, 4964–4967; n) B.-J. Zhamg, J.-S. Lu, M.-F. Bao, X.-H. Zhong, L. Ni, J. Wu, X.-H. Cai, *Phytochemistry* **2018**, *152*, 125–133; o) Y. Zhang, X. Ding, Y.-X. Yuan, L.-L. Guo, X.-J. Hao, *J. Nat. Prod.* **2020**, *83*, 1432–1439.

[5] a) T.-S. Kam, K. M. Sim, T. Koyano, M. Toyoshima, M. Hayashi, K. Komiyama, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1693–1696; b) T.-S. Kam, K.-M. Sim, H.-S. Pang, T. Koyano, M. Hayashi, K. Komiyama, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4487–4489; c) Y.-Y. Low, K.-H. Lim, Y.-M. Choo, H.-S. Pang, T. Etoh, M. Hayashi, K. Komiyama, T.-S. Kam, *Tetrahedron Lett.* **2010**, *51*, 269–272; d) C.-E. Nge, K.-W. Chong, N. F. Thomas, S.-H. Lim, Y.-Y. Low, T.-S. Kam, *J. Nat. Prod.* **2016**, *79*, 1388–1399.

[6] T.-S. Kam, K.-M. Sim, T.-M. Lim, *Tetrahedron Lett*. **2000**, *41*, 2733–2736.

[7] a) J. Magolan, M. A. Kerr, *Org. Lett.* **2006**, *8*, 4561–4564; b) K. Sapeta, M. A. Kerr, *Org. Lett.* **2009**, *11*, 2081–2084; c) P. E. Reyes- GutiØrrez, R. O. Torres-Ochoa, R. Martínez, L. D. Miranda, *Org. Biomol. Chem.* **2009**, *7*, 1388–1396; d) D. Du, L. Li, Z. Wang, *J. Org. Chem.* **2009**, *74*, 4379–4382; e) R. O. Torres-Ochoa, P. E. Reyes- GutiØrrez, R. Martínez, *Eur. J. Org. Chem*. **2014**, 48–52; f) D. A. Contreras-Cruz, M. CastaÇón-García, E. Becerril-Rodríguez, L. D. Miranda, *Synthesis* **2020**, *52*, 246–252.

[8] D.-X. Tan, J. Zhou, C.-Y. Liu, F.-S. Han, *Angew. Chem. Int. Ed.* **2020**, *59*, 3834–3839.

[9] For selected recent papers, especially for alkaloid synthesis, see: a) D. Shan, Y. Gao, Y. Jia, *Angew. Chem. Int. Ed.* **2013**, *52*, 4902–4905; b) H. Mizoguchi, H. Oikawa, H. Oguri, *Nat. Chem.* **2014**, *6*, 57–63; c) J. Carreras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2014**, *53*, 4896–4899; d) M. Azuma, T. Yoshikawa, N. Kogure, M. Kitajima, H. Takayama, *J. Am. Chem. Soc.* **2014**, *136*, 11618–11621; e) A. S. Lee, B. B. Liau, M. D. Shair, *J. Am. Chem. Soc.* **2014**, *136*, 13442–13452; f) K. Popov, A. Hoang, P. Somfai, *Angew. Chem. Int. Ed.* **2016**, *55*. 1801–1804; g) S. L. Drew, A. Lawrence, M. S. Sherburn, *Chem. Sci.* **2015**, *6*, 3886–3890; h) P. W. Tan, J. Seayad, D. J. Dixon, *Angew. Chem. Int. Ed.* **2016**, *55*, 13436–13440; i) S. Chu, N. Münster, T. Balan, M. D. Smith, *Angew. Chem. Int. Ed.* **2016**, *55*, 14306–14309; j) X. Ju, C. M. Beaudry, *Angew. Chem. Int. Ed.* **2019**, *58*, 6752–6755; k) B. Zhang, X. Wang, C. Li, *J. Am. Chem. Soc.* **2020**, *142*, 3269–3274; l) J. J. Dotson, J. L. Bachman, M. A. Garcia-Garibay, N. K. Garg, *J. Am. Chem. Soc.* **2020**, *142*, 11685–11690.

[10] K. M. Allan, B. D. Hong, B. M. Stoltz, *Org. Biomol. Chem*. **2009**, *7*, 4960–4964.

[11] Y. Feng, J. K. Coward, *J. Med. Chem.* **2006**, *49*, 770–788.

[12] C. Gimbert, M. Lumbierres, C. Marchi, M. M.-Mañas, R. M. Sebastiån, A. Vallribera, *Tetrahedron* **2005**, *61*, 8598–8605.

[13] M. Righi, F. Topi, S. Bartolucci, A. Bedini, G. Piersanti, *J. Org. Chem*. **2012**, *77*, 6351–6357.

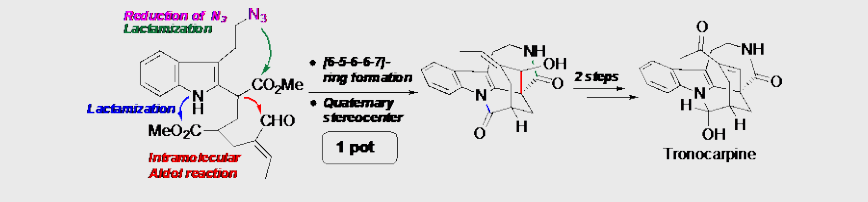
[14] The ratio of E/Z isomers of compound **2** is considered to be correlated with the E/Z ratio of compounds **13A** and **13B** in the reaction mixture before the final seven-membered lactamization. We consider that the E/Z ratio of **4A** was converged to 3:1 in the first intramolecular aldol reaction. On the other hand, the olefin of **4B** was only the E-form. The total E/Z ratio further changed during the subsequent conversion of **4A** and **4B** to **13A** and **13B** through the equilibrium between **4A** and **4B**. Isomerization of the olefin should occur during the equilibrium of the tandem cyclization by repeated addition-elimination reaction of MeOH with the α,β-unsaturated aldehyde of the retro aldol product of **4A** at 40 °C, and the final E/Z ratio would depend on the reaction conditions and time.

[15] T. Ohshima, Y. Hayashi, K. Agura, Y. Fujii, A. Yoshiyama, K. Mashima, *Chem. Commun*. **2012**, *48*, 5434–5436.

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



A concise total synthesis of a chippiine-type alkaloid, tronocarpine, was accomplished. The key feature of this total synthesis is the construction of the key pentacyclic skeleton with an azabicyclo[3.3.1]nonane core, which required a one-pot process of i) β-elimination, ii) intramolecular aldol reaction, iii) six-membered lactamization, iv) azide reduction, and v) seven-membered lactamization.

Atsushi Nakayama, Tenta Nakamura, Toshihiro Zaima, Saho Fujimoto, Sangita Karanjit, and Kosuke Namba**

Page No. – Page No.

Concise Total Synthesis of Tronocarpine

WILEY-VCH