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Total Syntheses of (–)-Minovincine and (–)-Aspidofractinine Using a Sequence of Cascade Reactions

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To the memory of Prof. Dr. Georg Fráter

Abstract: We report eight-step syntheses of (–)- minovincine and (–)-aspidofractinine using easily available and inexpensive reagents and catalyst. A key element of the strategy was the utilization of the chain of cascade reactions to rapidly construct the penta- and hexacyclic frameworks. These cascade transformations included organocatalytic Michael-aldol condensation, a multistep anionic Michael-S_N2 cascade reaction and Mannich reaction interrupted Fischer indolization. To streamline the synthetic routes, we also investigated the deliberate use of steric effect to secure various chemo- and regioselective transformations.

The aspidosperma family of alkaloids continues to attract enhanced interest owing to their medical potential and intriguing chemical structure.[1] Their stereochemical complexities present an intrinsic synthetic challenge and their polycyclic, cage-like structures provide much latitude for advancing different synthetic strategies. As a result, this class of compounds has frequently served as a benchmark target for the development of innovative synthetic methodologies and strategies.[2] In particular, aspidospermanes have often provided inspiration for the synthetic community to devise efficient catalytic approaches that allow the stereoselective construction of quaternary carbon stereocenters (C-5 and C-12 in Figure 1). The emerging thrust-power of these asymmetric methodologies has not only enriched the aspidosperma chemistry, but also enabled to pursuit concise synthetic strategies and collective synthesis of structurally related aspidosperma alkaloids.[3]

There is a distinct aspidosperma alkaloid, (–)-minovincine (**1**), possessing a C-20 oxygenation that is not common within this class of alkaloids. With this subtle, but remarkable structural modification, this alkaloid is evolved into a biogenetic turntable toward more complex pleiocarpine-refractine classes of alkaloids (e.g. **2**, **3** in Figure 1). Additionally, this unique aspidospermane derivative can be transformed to pauciflorine[4] and eburnane[5] type alkaloids (**4**, **5** in Figure 1) in few chemical steps. Owing to the apparent synthetic significance of minovincine (**1**), it has been an attractive research target since its isolation[6] in 1962.[7] Interestingly, and despite the advances of catalytic asymmetric methodologies, only two enantioselective approaches have been reported by MacMillan[8] and Nishida[9]. One rationale for this relative paucity in synthetic routes is the shortcomings in the existing repository of asymmetric protocols that can concisely deliver the aspidosperma skeleton with oxidized exocyclic functionality in position C-5.

Stimulated by the synthetic challenges of (–)-minovincine (**1**), with its added (bio)synthetic potential, we devoted ourselves to develop a concise and scalable route of (–)-minovincine (**1**). Our hope was also to expand our synthetic strategy toward topologically different, but minovincine derived natural products. Therefore, a refractine type alkaloid was also targeted, the hexacyclic (–)-aspidofractinine (**6**). As an overarching goal, we aimed to devise streamlined synthetic routes that would collaterally achieve greater level of "ideality"[10] and synthetic practicality[11]. Thus, three interwoven guidelines directed our synthetic design: (1) to implement sequence of cascade reactions[12] for the rapid construction of the penta- and hexacyclic frameworks (2) to minimize protecting group manipulations and steer the selectivity of reactions by steric effect[13] (3) to avoid exotic, toxic and expensive reagents or catalysts.

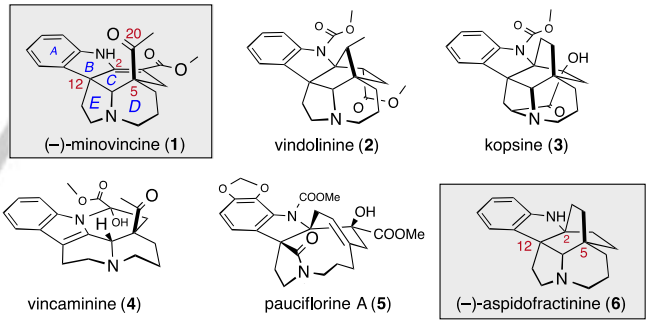

Figure 1. Structure of (–)-minovincine (**1**), (–)-aspidofractinine (**6**) and related alkaloids.

Recently, our laboratory developed a strategy for the concise and diastereoselective synthesis of cis- and trans-decaline subunits of terpenoids.[14] Key to the strategy was an organocatalyzed Robinson annulation reaction that afforded a chiral enone building block with quaternary stereogenic center. As an outgrowth of these studies, we were intrigued to develop an analogous chiral building block **7** that might confer synthetic practicality in aspidospermane chemistry. Our retrosynthetic plan adopted in this investigation is illustrated in Scheme 1. We envisioned tricyclic **8**, a modified Stork's tricyclic ketone[15], to serve as an advanced intermediate en route to **1** and **6**. We also expected that the C-5 ester functionality of **8** can be selectively transformed into the requisite exocyclic keto group to establish the correct functionality in minovincine (**1**). Furthermore, on the grounds of proposed biosynthetic pathway of aspidofractinine (**6**),[16] our hope was that its "supercaged" skeleton might be

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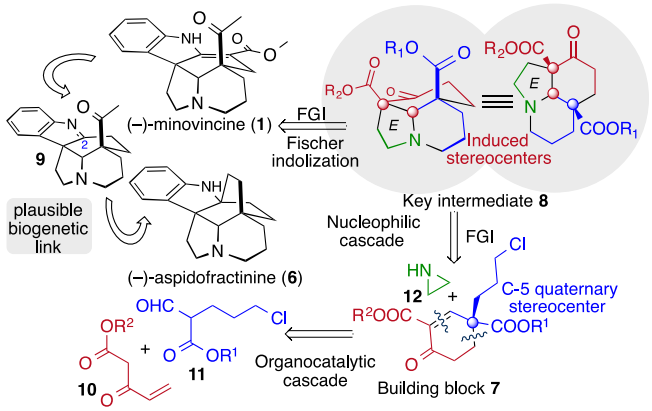
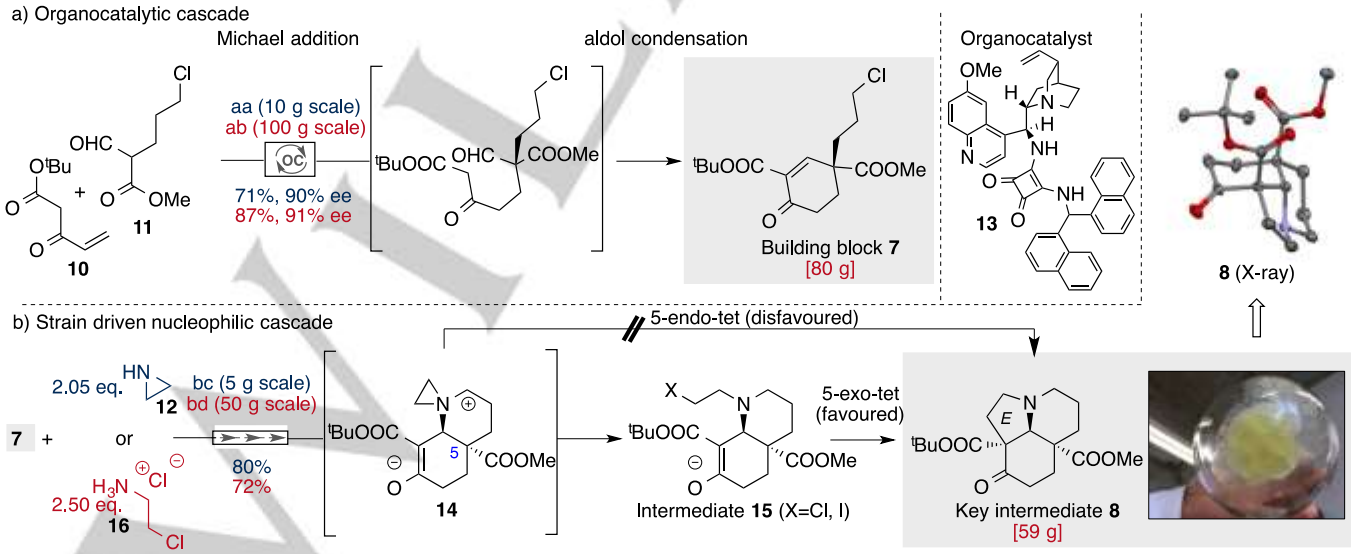
secured through the interception of C-2 carbon atom of the transient iminium ion of **9** by its acetyl functionality. Finally, we aspired to construct the desired tricyclic ketone **8** in a concise way to provide opportunity for a scalable process of this advanced intermediate. So, we devised a short synthetic route through the organocatalytic Robinson annulation reaction of **10** and **11** to give multifunctional enone **7** followed by a multistep nucleophilic cascade reaction of aziridine (**12**). Thus, we aimed the early introduction of the C-5 quaternary center and used that center to direct the relative configuration of further functionalization around the C ring.



Scheme 1. Retrosynthetic analysis of (–)-minovincine (**1**) and (–)-aspidofractinine (**6**).

As a first foray, we sought to develop an efficient synthesis of the desired enone **7** with the requisite quaternary stereogenic center. Specifically, we strived to merge the easily available Nazarov reagent **10** and ω-chloro-formylpentenoate **11** using the previously reported quinine-squaramide organocatalyst **13**[14] (Scheme 2). Gratifyingly, this Michael addition-aldol condensation organocascade reaction afforded the envisioned enone **7** as a sole product. Using the optimized reaction condition (dioxane, room temperature, 2 mol% catalyst) the chiral building block **7** was constructed in 71% yield and 90% ee (Scheme 2). Notably, the catalyst tolerated the presence of primary alkyl chloride functional group, the alkylative inhibition of the catalyst was not detected. This method proved also to be amenable for scale up, ultimately allowing access to 80 g of enone **7**.

With a robust approach to **7** in hand, we were poised to examine the feasibility of the nucleophilic cascade strategy toward the tricyclic ketone **8**. Pleasingly, the envisioned multistep reaction occurred smoothly and delivered the tricyclic ketone **8** with the correct configuration in high efficiency and diastereoselectivity (Scheme 2: **8**, X-ray)[17]. Although the diastereoselectivity of the cascade was excellent, the exact mechanism by which this is achieved is not unequivocal. To begin with, the product of the first aziridine adduct could not be detected by NMR, suggesting that the rate of the subsequent cyclization is relatively fast. Thus, the reaction started either by the aza-Michael addition of aziridine (**12**) on the double activated enone **7** or by the nucleophilic substitution of aziridine (**12**) on the alkyl halide part of the enone **7**. Regardless of the reaction sequence, the stereochemical outcome is determined by the π-facial diastereoselectivity of the aza-Michael addition. This type of Michael-S_N2 or S_N2-Michael annulation thus establishes a preference for trans addition with the C-5 carboxylic substituents of **14**.[18] As a 5-endo-tet cyclization is less probable,[19] the presumed zwitterionic aziridinium intermediate **14** was expected to undergo a ring opening with halogenides. This mechanistic manifold was corroborated by the isolation of **15** from the reaction mixture.[20] Once generated, the arising ethyl halogenide moiety was then quenched by the enolate, closing the cascade process and generating a quaternary stereogenic center and the E ring in parallel. As a less harmful and hazardous synthetic precursor of aziridine (**12**), 2-chloroethylamine (**16**) was also probed. To our delight, the intriguing nucleophilic cascade proceeded also well with 2-chloroethylamine (**16**) in the presence of DIPEA, which allowed us to conduct the process in a batch of 80 g with a 72% yield.



Scheme 2. Rapid construction of key intermediate **8** via relay cascade reactions. Reaction conditions: aa) **10**+**11** (1.13:1.0) (2 mol% **13**) dioxane, r.t.; ab) **10**+**11** (1.1:1.0) (3 mol% **13**), dioxane, r.t.; ba) KI, CH_2Cl_2, rt.; bb) DIPEA, KI, CH_2Cl_2, r.t.; DIPEA= diisopropylethylamine.

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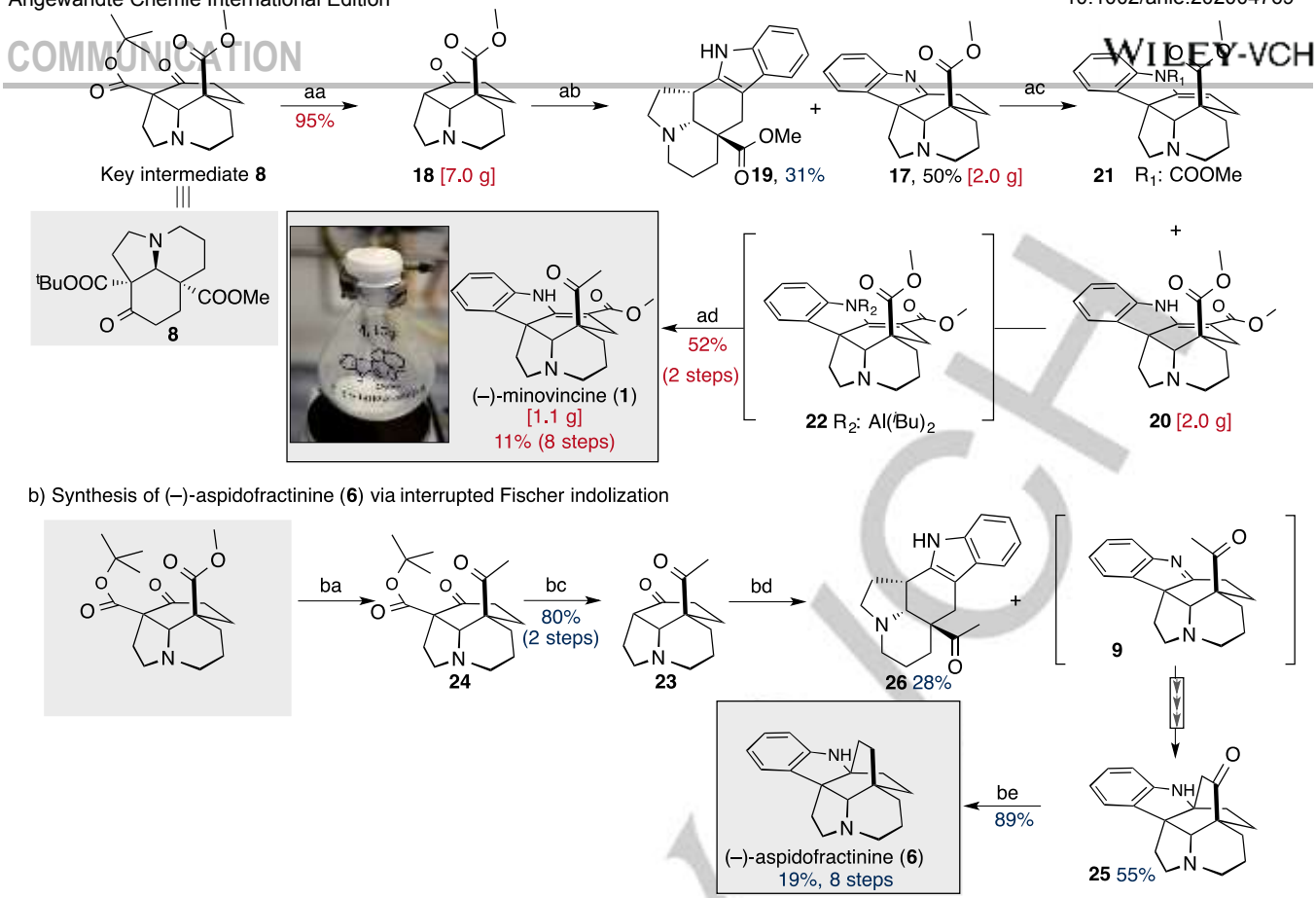

Scheme 3. Syntheses of (–)-minovincine (**1**) and (–)-aspidofractinine (**6**). Reaction conditions: aa) aq. H_2SO_4 (50 V/V%), dioxane, r.t.; ab) $PhNHNH_2$ then BF_3•OEt_2, MeOH, 70 °C; ac) $^iPr_2NH$, LDA, CNCOOMe, THF, -78 °C; ad) Al^iBu_3, THF, -78 °C to r.t. then $TMSCH_2Li$; ba) $TMSCH_2Li$, THF, r.t.; bb) aq. H_2SO_4 (50 V/V%), dioxane, r.t.; bc) $PhNHNH_2$ then BF_3•OEt_2, EtOH, 85 °C; bd) N_2H_4•H_2O, KOH, DEG, 130 to 210 °C, LDA= lithium diisopropylamide, TMS= trimethylsilyl, THF= tetrahydrofuran, DEG= diethyleneglycol.

Given the ready availability of tricyclic ketone **8**, the scalable synthesis of (–)-minovincine (**1**) was addressed by using the classical Fischer indole synthesis[21] (Scheme 3). The synthesis of indolenine **17** was straightforward, proceeded without incident. Thus, following selective deprotection of tBu-ester, the resulting β-oxo carboxylic acid spontaneously decarboxylated, affording ketone **18** in 95% yield in 7 gram scale. Subsequent treatment of product **18** with phenylhydrazine generated aspidospermane-type indolenine **17** and its structural isomer **19** in 50% and 31% yields, respectively. Having achieved the construction of pentacyclic **17**, what remained for completing the synthesis of minovincine was the installation of C-3 methoxycarbonyl and C-5 acetyl groups. During these endeavors, our priority was to minimize the functional group manipulations to shorten the synthetic route and enhance its practicality. First, methyl cyanoformate, also known as Mander reagent, was used to append the methoxycarbonyl group into C-3 position of the indolenine **20**. Importantly, some N-carboxylated isomer **21** also formed that cannot be separated by chromatography (**20**:**21** ratio was 6:1). Then, we turned our attention to the regioselective transformation of the C-5 methoxycarbonyl group to the requisite acetyl moiety. While conversion of the methyl ester **20** to a methyl ketone was not successful with standard reagents (MeLi•LiBr and $TMSCH_2MgCl$), $TMSCH_2Li$ proved to be a competent reagent to effect the desired transformation[22] Although our initial attempts with $TMSCH_2Li$ resulted in poor yields, we anticipated that the addition of TRIBAL to **20** would improve the selectivity of the reaction as a transient protecting group with dual roles. This strong base would not only exert a charge control over C-3 methoxycarbonyl via N-H deprotonation, but the di-isobutyl aluminium adduct **22** would secure an enhanced steric shielding around the C-3 methoxycarbonyl moiety.[20] Gratifyingly, by employing TRIBAL additive, a 52% yield (for two steps) of (–)-minovincine (**1**) could be obtained on a 1.10 gram scale. Overall, the gram-scale synthesis of (–)-minovincine (**1**) was accomplished in an overall yield of 11% by an eight-step sequence. By virtue of (bio)synthetic potential of minovincine, this scalable route seems to provide a rapid access toward structurally related, more complex indole alkaloids.

Aspidofractinine is thought to originate from **9** that is derived from minovincine via an ester hydrolysis followed by decarboxylation (Scheme 1).[1,16] While several routes have been developed to construct racemic aspidofractinine,[23,24] its only asymmetric synthesis was reported by Spino[25] in 2009. The relative ease of our minovincine synthesis served us an impetus for developing a biosynthetically inspired synthesis of (–)-aspidofractinine (**6**). Specifically, we envisioned an interrupted Fischer indolization[26] by the pendant acetyl nucleophile. Therefore, we set out to prepare a C-5 acetyl substituted tricyclic ketone **23** from the previously synthesized advanced intermediate **8**. We reasoned that the steric hindrance embedded in this key intermediate **8** can be exploited for chemo- and regioselective transformation, thus, obviating the need of protecting group manipulation. This scenario proved to be viable, affording a simple route to **24**. Thus, treatment of **8**

with $TMSCH_2Li$ (rt, 1h) followed by ester hydrolysis and decarboxylation resulted in the selective generation of **23** with 80% overall yield. Corroborating the importance of steric effect, the decarboxylated, thus sterically less crowded analog **18** was also reacted with $TMSCH_2Li$ under the same condition. Importantly, that reaction resulted in a complex mixture.[20]

Next, the feasibility of the interrupted Fischer indolization was investigated to construct the "supercaged" aspidofractinine framework. To our delight, the Fischer indole-Mannich cascade reaction occurred smoothly to afford the corresponding oxo-aspidofractinine **25** in a 55% yield (alongside with its isomer **26**) via a presumed indolenine intermediate **9**. Several significant features of the reactions shown in Scheme 3 should be noted. Though there are scattered examples of interrupted Fischer indolization in the literature, a Mannich reaction coupled strategy has not been utilized, to best of our knowledge. Furthermore, the successful implementation of the trans annular Mannich-Fischer indolization process led to the formation of three new bonds and two additional quaternary stereogenic centers. Moreover, based on the notion that C-20 derived indole formation was not detected we surmised that the steric effect secured again the regioselectivity. As the final step of the synthetic route, the substrate **25** was exposed to hydrazine to furnish (–)-aspidofractinine (**6**) in 89% yield.

In conclusion, we have developed eight-step synthetic routes toward (–)-minovincine (**1**) and (–)-aspidofractinine (**6**) with 11% and 19% overall yields, respectively. Key to the success was the strategic implementation of a chain of cascade reactions, including organocatalytic Michael-aldol condensation, multistep anionic Michael-S_N2 cascade reactions and Mannich reaction interrupted Fischer indolization. Importantly, four contiguous stereogenic centers were created in those steps with excellent absolute and relative stereochemical control. Both the employed chain of cascade reactions and the steric effect steered chemo- and regioselective reactions contributed immeasurably for bringing not only synthetic brevity but also improved practicality. Thus, the advanced building block **8** having a quaternary stereogenic center could be synthesized in 60 g scale. The (–)-minovincine (**1**) was delivered in gram scale and the "supercaged" (–)-aspidofractinine (**6**) has become accessible via excessively short manner. Furthermore, the synthetic convenience to utilize easily available, inexpensive reagents adds further practical appeal. We are currently pursuing this synthetic strategy in the total synthesis of structurally related members of aspidospermanes, the results will be reported in due course.

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Keywords: alkaloids • asymmetric catalysis • biomimetic synthesis • total synthesis • organocatalysis

[1] Reviews on Aspidosperma and related alkaloids: a) J. E. Saxton in *Chemistry of Heterocyclic Compounds Vol. 25.,* Wiley-Interscience, New York, **1983**, pp. 331–437; b) J. E. Saxton in *The Alkaloids: Chemistry and Biology, Vol 51.,* (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, pp. 1–197.

[2] Reviews on Synthesis of Aspidosperma and related alkaloids a) J. E. Saxton in *The Alkaloids: Chemistry and Biology, Vol 50.,* (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, pp. 343–376; b) J. M. Lopchuk in *Progress in Heterocyclic Chemistry, Vol. 23.*, (Eds.: G. W. Gribble, J. A. Joule) Elsevier, Oxford, **2011**, pp. 1–25; c) J. Hájícek, *Collect. Czech. Chem. Commun.* **2004**, *69*, 1681–1767; d) J. Hájícek, *Collect. Czech. Chem. Commun.* **2007**, *72*, 821–898; e) B. P. Pritchett, B. M. Stoltz, *Nat. Prod. Rep.* **2018**, *35*, 559–574; f) Y. Wang, F. Xie, B. Lin, M. Cheng, Y. Liu, *Chem. Eur. J.* **2018**, *24*, 14302–14315; g) J. M. Saya, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2019**, *25*, 8916–8935.

[3] a) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183–188; Z. Li, S. Zhang, S. Wu, X. Shen, L. Zou, F. Wang, X. Li, F. Peng, H. Zhang, Z. Shao, *Angew. Chem.* **2013**, *125*, 4211–4215; *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121; b) M. Mewald, J. W. Medley, M. Movassaghi, *Angew. Chem.* **2014**, *126*, 11818–11823; *Angew. Chem. Int. Ed.* **2014**, *53*, 11634–11639; c) Z. Xu, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 6712–6724; d) K. L. White, M. Movassaghi, *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389; e) P. W. Tan, J. Seayed, D. J. Dixon, *Angew. Chem.* **2016**, *128*, 13634–13638; *Angew. Chem. Int. Ed.* **2016**, *55*, 13146–13440; f) B. P. Pritchett, J. Kikuchi, Y. Numajiri, B. M. Stoltz, *Angew. Chem.* **2016**, *128*, 13727–13730; *Angew. Chem. Int. Ed.* **2016**, *55*, 13529–13532; g) X.-Y., Liu, Y. Qin, Acc. Chem. Res. 2019, 52, 1877–1891

[4] M. E. Kuehne, Y-L. Li, *Org. Lett.* **1999**, *1*, 1749–1750.

[5] Gy. Kalaus, L. Léder, I. Greiner, M. Kajtár-Peredy, K. Vékey, L. Szabó, Cs. Szántay, *Tetrahedron* **2003**, *59*, 5661–5666.

[6] Isolation of (-) and (+) minovincine: a) M. Plat, J. LeMen, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, C., Djerassi, *Bull. Chem. Soc. Chim. Fr.* **1962**, 2237–2241; b) M. P. Cava, S. S. Tjoa, Q. A. Ahmed, A. I. Da Rocha, *J. Org. Chem.* **1968**, *33*, 1055–1059.

[7] Total Syntheses of (±) minovincine: a) M. E. Kuehne, W. G. Earley, *Tetrahedron* **1983**, *39*, 3707–3714; b) M. E. Kuehne, W. G. Earley, *Tetrahedron* **1983**, *39*, 3715–3717; c) Gy. Kalaus, I. Juhász, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó, Cs. Szántay, *J. Org. Chem.* **1997**, *62*, 9188–9191;

[8] B. N. Laforteza, M. Pickworth, D. W. C. MacMillan, *Angew. Chem.* **2013**, *125*, 11479–11482; *Angew. Chem. Int. Ed.* **2013**, *52*, 11269–11272.

[9] T. Morikawa, S. Harada, A. Nishida, *J. Org. Chem.* **2015**, *80*, 8859–8867.

[10] a) J. B. Hendrickson *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800; b) P. A. Wender, B. L. Miller *Nature* **2009**, *460*, 197–201; c) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657–4673; d) P. Wender, *Nat. Prod. Prep.* **2014**, *31*, 433–440.

[11] a) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021; b) C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep.* **2014**, *31*, 419–432; c) I. S. Young, P. S. Baran, *Nature Chem.* **2009**, *1*, 193–205.

[12] a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; b) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; c) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993–3009; d) L. F. Tietze (Ed.) *Domino Reactions: Concepts for Efficient Organic Synthesis*, Wiley-VCH, Weinheim, **2014**

[13] Recent examples on steric effect driven chemo- and regioselective transformation: a) V. V. Patil, G. S. Shankarling, *J. Org. Chem.* **2015**, *80*, 7876–7883; b) G. Meng, M. Szostak, *Angew. Chem.* **2015**, *127*, 14726–14730; *Angew. Chem. Int. Ed.* **2015**, *54*, 14518–14522; c) S. Tuokko, P. M. Pihko, K. Honkala, *Angew. Chem.* **2016**, *127*, 1702–1706; *Angew. Chem. Int. Ed.* **2016**, *55*, 1670–1674; d) M. Balkenhohl, H. Jangra, T. Lenz, M. Ebeling, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem.* **2019**, *131*, 9344–9348; *Angew. Chem Int. Ed.* **2019**, *58*, 9244–9247; e) N. A. Serratore, C. B. Anderson, G. B. Frost, T.-G.

Hoang, S. J. Underwood, P. M. Gemmel, M. A. Hardy, C. J. Douglas, *J. Am. Chem. Soc.* **2018**, *140*, 10025–10033.

[14] B. Berkes, K. Ozsváth, L. Molnár, T. Gáti, T. Holczbauer, Gy. Kardos, T. Soós, *Chem. Eur. J.* **2016**, *22*, 18101–18106.

[15] G. Stork, J. E. Dolfini, *J. Am. Chem. Soc.***1963**, *85*, 2872–2873.

[16] H. K. Schnoes, K. Biemann, *J. Am. Chem. Soc.***1964**, *86*, 5693–5694.

[17] CCDC 1988772 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures"

[18] In an analogous reaction, the anionic Deslongchamp annulation resulted in a product with a same, trans to the C-5 carboxylic ester, diastereoselectivity, for details see ref 14.

[19] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

[20] For details see Supporting Information.

[21] Recent review on Fischer indole reaction: M. M. Heravi, S. Rohani, V. Zadsirjan, N. Zahedi, *RSC Adv.* **2017**, *7*, 52852–52887.

[22] M. Demuth, *Helv. Chim. Acta* **1978**, *61*, 3136–3138.

[23] Total syntheses of (±) aspidofractinine: a) Y. Ban, Y. Honma, T. Oishi, *Tetrahedron Lett.* **1976**, *14*, 1111–1114; b) H. Kinoshita, T. Ohnuma, T. Oishi, Y. Ban, *Chem. Lett.* **1986**, 927–930; c) M. Dufour, J-C. Gramain, H.-P. Husson, M.-E. Sinibaldi, Y. Troin, *Tetrahedron Lett.* **1989**, *30*, 3429–3432; d) D. Cartier, M. Quahrani, J. Lévy, *Tetrahedron Lett.* **1989**, *30*, 1951–1954; e) E. Wenkert, S. Liu, *J. Org. Chem.* **1994**, *59*, 7677–7682.

[24] Recent formal syntheses of aspidofractinine: a) P. Zhao, Z. Sun, M. Mo, F. Peng, Z. Shao, *Org. Lett.* **2014**, *16*, 4178–4181; b) J. M. Saya, T. R. Roose, J. J. Peek, B. Weijers, T. J. S. de Waal, C. M. L. Vande Velde, R. V. A. Orru, E. Ruijter, *Angew. Chem.* **2018**, *130*, 15452–15456; *Angew. Chem. Int. Ed.* **2018**, *57*, 15232–15236.

[25] D. Gagnon, C. Spino, *J. Org. Chem*. **2009**, *74*, 6035–6041.

[26] Recent applications: a) B. W. Boal, A. W. Schammel, N. K. Garg, *Org. Lett.* **2009**, *11*, 3458–3461; b) A. W. Schammel, G. Chiou, N. K. Garg, *Org. Lett.* **2012**, *14*, 4556–4559; c) Review on interrupted Fisher indolization: M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 2856–2881.

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Entry for the Table of Contents

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Page No. – Page No.

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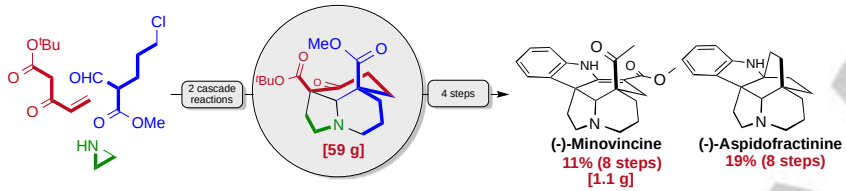

Excessively concise syntheses of (–)-minovincine and (–)-aspidofractinine were accomplished via the strategic use of chain of cascade reactions and steric control.