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Assembly of multicyclic isoquinoline scaffolds from pyridines: formal total synthesis of fredericamycin A†

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The construction of an isoquinoline skeleton typically starts with benzene derivatives as substrates with the assistance of acids or transition metals. Disclosed here is a concise approach to prepare isoquinoline analogues by starting with pyridines to react with β-ethoxy α,β-unsaturated carbonyl compounds under basic conditions. Multiple substitution patterns and a relatively large number of functional groups (including those sensitive to acidic conditions) can be tolerated in our method. In particular, our protocol allows for efficient access to tricyclic isoquinolines found in hundreds of natural products with interesting bioactivities. The efficiency and operational simplicity of introducing structural complexity into the isoquinoline frameworks can likely enable the collective synthesis of a large set of natural products. Here we show that fredericamycin A could be obtained *via* a short route by using our isoquinoline synthesis as a key step.

Isoquinolines and their derivatives are common structural motifs in numerous natural products. Among them, the analogues of isoquinolines fused with rings from the benzene side such as 8-hydroxyisoquinolin-1[2*H*]-one (Fig. 1a) have been found in hundreds of natural products with interesting bioactivities.[1] For example, fredericamycin A and the related family members, isolated from *Streptomyces griseus*, show both antimicrobial and anti-tumor activities.[2] Ericamycin is a natural product isolated in the culture of *Streptomyces varius* n. sp. with anti-staphylococcal activities.[3] Due to the widespread presence of isoquinolines in both natural and synthetic molecules, numerous approaches have been developed to assemble this class of scaffolds.[4] The dominated strategies reported to date focus on forming the new pyridine ring of isoquinolines (Fig. 1b, left part). Classic methods include Bischler–Napieralski isoquinoline synthesis,[4a,b] Pictet–Gams isoquinoline synthesis,[4a] and Pomeranz–Fritsch reaction.[4a] These reactions, proven to be useful since as early as 1893,[5] have their own merits and limitations. For instance, high reaction temperature (*e.g.* reflux in toluene) and strong acids are typically required and thus functional group tolerance can become challenging. On the other side, the introduction of structural complexities and substitution patterns is constrained as the substrates have to be pre-settled to favor the formation of pyridine moieties. Here we report a new approach to prepare isoquinoline scaffolds by constructing a new benzene ring (Fig. 1b, right part).[6] Our method starts with pyridine derivatives as the substrates to react with readily available β-ethoxy α,β-unsaturated carbonyl compounds. The reaction cascade involves five main plausible mechanistic processes (Michael addition, Dieckmann condensation, elimination, aromatization and *in situ* methylation) to furnish isoquinoline-based products with medium to good yields. The tricyclic isoquinoline-containing products might serve as formal common starting points for rapid total synthesis of a large number of natural products, such as those exemplified in Fig. 1a. In the present study, we demonstrate that starting from the tricyclic isoquinoline adduct **6a** prepared using our method, fredericamycin A can be synthesized in 8 steps (Fig. 1c). Our strategy for isoquinoline assembly offers complementary and in certain cases better solutions not readily provided by the classic methods. We expect our method to find impressive applications in concise modular synthesis of complex natural products and molecular libraries, especially those bearing isoquinoline units fused with additional cyclic structures.

Our design and initial studies are illustrated in Scheme 1.[7] We first used pyridine **1a** to react with α-substituted cycloenones (**2a–2d**), in the hope of obtaining isoquinoline **3a** as the target product (Scheme 1a). The use of **2a** and **2b** was inspired

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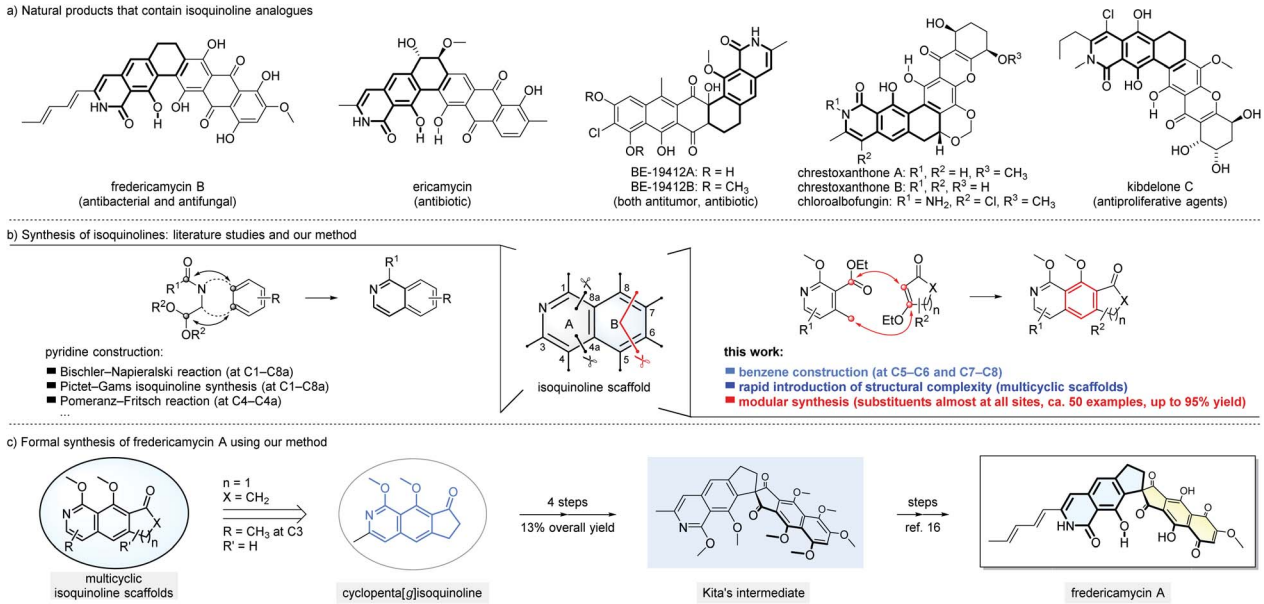
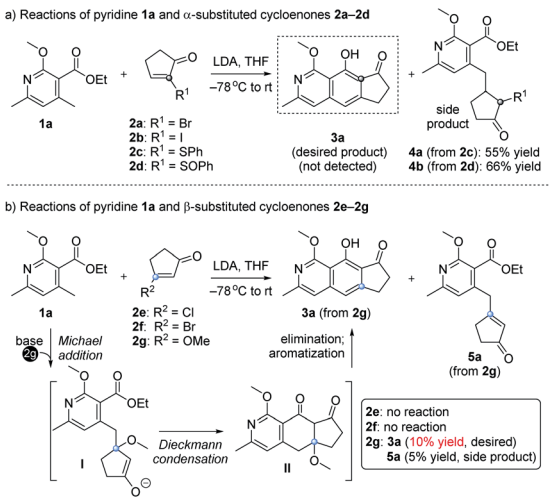


Fig. 1 Isoquinoline analogues and their synthesis.

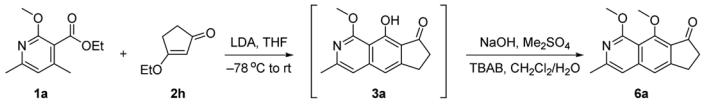


Scheme 1 Proposed routes and initial studies for isoquinoline synthesis.

by studies from Tamura, in which α-Br in 1,4-naphthoquinone was used as a leaving group to form an aromatic ring.[8] Unfortunately, no product was formed and most of the starting materials were recovered. When SPh (**2c**) or SOPh (**2d**) was incorporated at the α site of the cycloenone, side products **4a** and **4b** were isolated respectively in moderate yields. The Michael products **4a** and **4b** could not be further transformed into our desired cyclic product **3a** under various conditions. We then studied the use of β-substituted cycloenones (**2e–2g**) to react with **1a** (Scheme 1b). No reactions were observed when **2e** or **2f** was used. To our delight, when the halogen of **2e**/**2f** was replaced with a methoxy unit (OCH_3, substrate **2g**), an encouraging amount of annulation product **3a** was detected (10% yield). A side product **5a** was also obtained (5% yield) in this initial study and it couldn't be further transformed into the annulation product **3a** under various alkaline conditions. It is noteworthy that, while β-alkoxy cycloenones (specifically, only β-alkoxy cyclohexenones) have been used in Staunton–Weinreb annulation[9] to prepare fused aromatic compounds, no examples for those containing a heterocyclic aromatic ring were reported.[10] Even for the construction of an aromatic ring without any heteroatom, low yields (mostly ranging from 0 to 30%) often occurred for this type of annulation starting with β-alkoxy cycloenones,[9] which severely hampered its usage in Staunton–Weinreb annulation for the total synthesis of natural products. Our initial results showcased the possibility of direct assembly of isoquinoline scaffolds from β-methoxy cyclopentenone for the first time, though also in a low yield of 10%.

With the initial results in hand, we performed additional condition optimization (Table 1). The best conditions (Table 1, entry 1) involve the deprotonation of **1a** with LDA at −78 °C, warming the reaction mixture to room temperature in 10 minutes after the completion of slow addition of **2h**, and most importantly, *in situ* methylation of the hydroxyl group of phenol **3a**, which accounts for the relatively high yield of adducts **6a** (72% yield). Without methylation, the phenol adduct **3a** was isolated only in 14% yield (entry 2).[11] The β-methoxy cyclopentenone **2g** could also react to give **6a** in a lower yield of 65% (entry 3). Other bases [such as triethylenediamine (DABCO), diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), lithium bis(trimethylsilyl)amide (LiHMDS) and potassium bis(trimethylsilyl)amide (KHMDS)] gave poorer results with yields ranging from 0 to 42% (entry 4). When THF was changed to other solvents, lower yields (<41%) were obtained (entry 5). Revising the ratio of **1a** to **2h** from 1 : 1.5 to 1.5 : 1 delivered **6a** in 39% to 54% yields (entries 6–8). Lower reaction temperature (*e.g.* −78 °C) could not improve the outcome of this cascade transformation, but gave 23% yield of

Table 1 Screening of conditions[a]

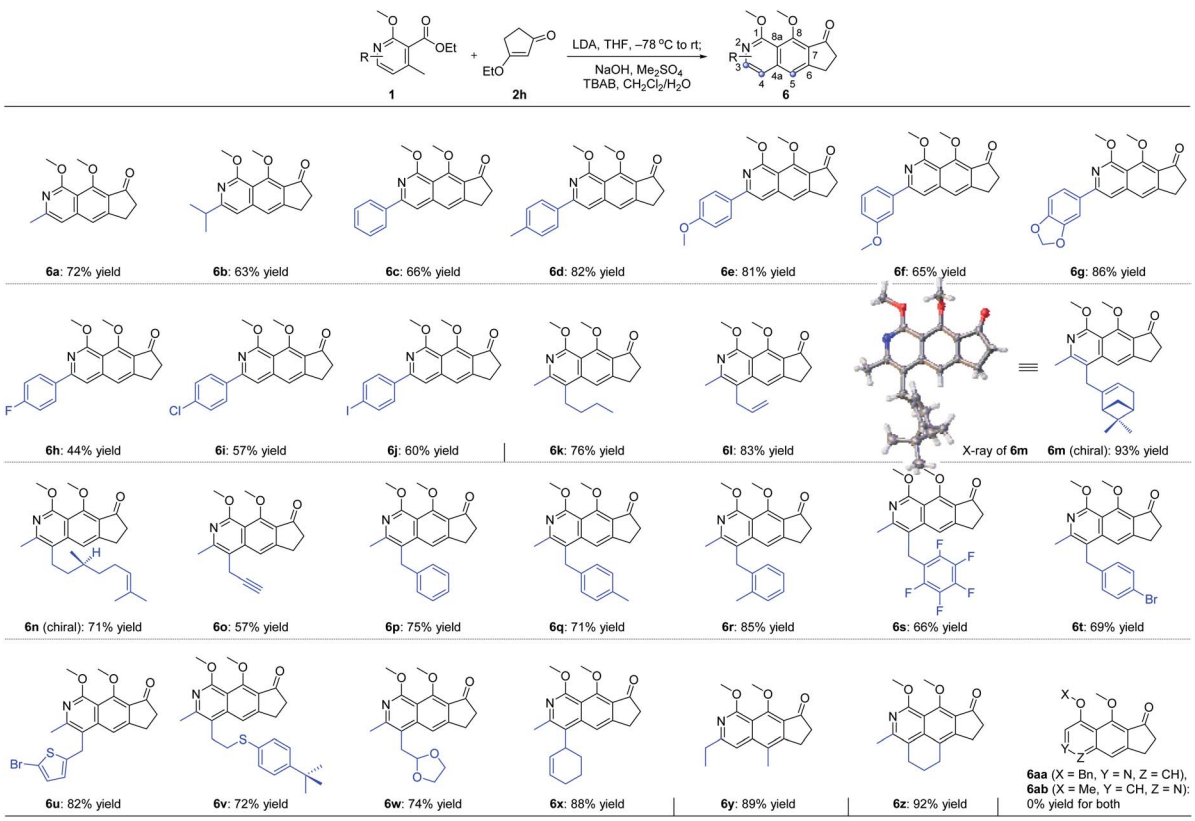


Entry	Variation from standard conditions	Yield[b] (%)
1	None	72
2	Without methylation	14
3	OCH_3 instead of OEt in **2h**	65
4	DABCO, DBU, DMAP, LiHMDS and KHMDS instead of LDA	0–42
5	Other solvents in step 1	<41
6	**1a** : **2h** = 1 : 1	39
7	**1a** : **2h** = 1.5 : 1	54
8	**1a** : **2h** = 1 : 1.5	42
9[c]	−78 °C for step 1	23
10	H instead of OCH_3 in **1a**	0

[a] Standard conditions: **1a** (0.2 mmol) and LDA (0.2 mmol) reacted in THF at −78 °C for 1 h; **2h** (0.1 mmol) was added dropwise to the mixture before warming up to rt in 10 min. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl after completion monitored by TLC. After the removal of solvents, the crude residue was treated directly with TBAB (0.2 eq.), NaOH (2.0 eq.) in water (1 mL), and Me_2SO_4 (4.0 eq.) in CH_2Cl_2 (1 mL). [b] Isolated yield. [c] Recovered starting material **2h**: 16% yield.

6a together with 16% yield of recovered starting material **2h** (entry 9). Long exposure to low temperature in step 1 could also lead to a considerable amount of the undesired elimination product **5a** (*ca.* 29% yield), which was decomposed under the following methylation conditions (step 2). No product was observed in the absence of the methoxy group in **1a** as it could stabilize the transition state *via* the formation of a metallate complex (entry 10).

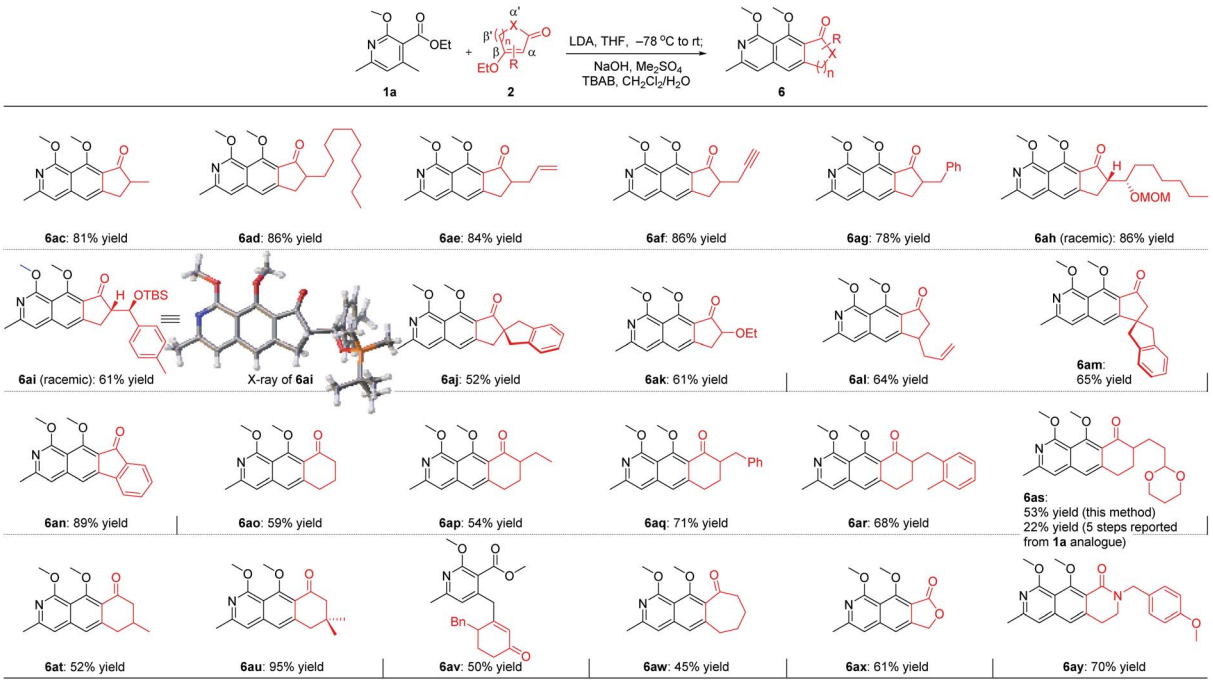
With the optimal reaction conditions in hand, we next examined the scope of the pyridine derivatives **1**. As we can see



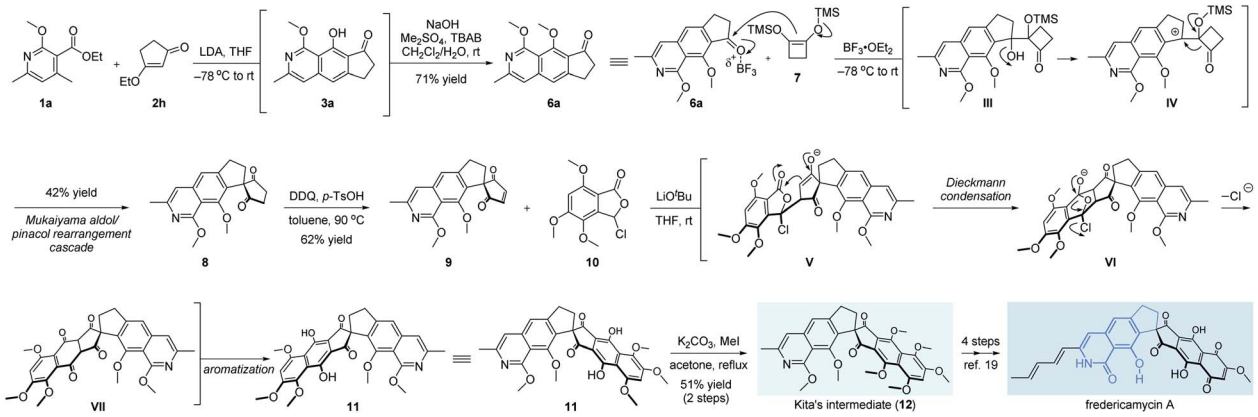
Scheme 2 Scope of pyridine derivatives.

from Scheme 2, substrates with the aliphatic substituents at C3 could afford the corresponding tricyclic isoquinoline products (**6a** and **6b**) in acceptable yields. Besides, the incorporation of an aromatic ring at this site (**6c–6j**) also works well for this transformation, wherein electron-rich aromatic rings (**6c–6g**) could give higher yields than the corresponding electron-deficient ones (**6h–6j**). It should be noted that the relatively lower yield of 44% for **6h** was partially due to the slow reaction rate as the recovered starting material was always detected in this transformation. When it comes to C4 substitution, the isoquinoline products with broad structural diversities such as alkyl (**6k**), alkenyl (**6l–6n**),[12] alkynyl (**6o**), benzyl derivatives with different substituents on the phenyl ring (**6p–6t**), hetero-aromatic ring (**6u**) and thioether (**6v**) could be obtained in 57–93% yields. Moreover, substrates bearing acid-hydrolyzable functionalities (**6w**) and with a relatively bulky secondary substituent (**6x**) also worked well under the optimized reaction conditions. Next, we examined the possibility of introducing a side chain at C5. To our delight, the substrate with an ethyl group instead of the methyl group on the aromatic ring reacted smoothly to deliver the corresponding isoquinoline **6y** in 89% yield. Further study revealed that the exposure of the bicyclic substrate 5,6,7,8-tetrahydroisoquinoline derivative to the optimized reaction conditions could furnish the polycyclic product **6z** in 92% yield. Finally, we relocated the nitrogen atom in the pyridine ring. The experimental results indicated that the substrate with nitrogen atom located at C3 can't react to form the corresponding isoquinoline **6aa**, possibly due to the mismatched dipole orientation. When the nitrogen atom was sited at the *ortho*-position of the methyl group in the aromatic ring, quinoline **6ab** could not be detected either under the optimized reaction conditions. The control experiments showcased the decisive influence of the location of nitrogen atom in the aromatic ring on the reactivity of this cascade transformation.

For the five-membered cycloenone derivatives **2** (Scheme 3), substrates with different substituents at the α′ position work well for this transformation (**6ac–6ak**),[12] of which the incorporation of a quaternary carbon center (**6aj**) and a heteroatom (**6ak**) at this site was included. The introduction of an allyl group at the β′ position in cyclopentenone proved to be viable for this transformation, delivering **6al** in 64% yield. More encouragingly, when the sterically hindered substrate with a quaternary carbon center located at the γ site was exposed to the optimized reaction conditions, the isoquinoline **6am** was obtained in 65% yield. This is challenging, considering the fact that the reacting site is just adjacent to a sterically bulky all-carbon quaternary stereocenter. Bicyclic 3-ethoxy-1*H*-inden-1-one is also suitable for this cascade transformation, giving the tetracyclic 10*H*-indeno[1,2-*g*]isoquinolin-10-one derivative **6an** in 89% yield. When it comes to six-membered cycloenone derivatives (**6ao–6au**), substrates with substituents at α′ and β′ positions all worked smoothly to provide the corresponding isoquinoline products in moderate to high yields. Notably, Kita reported a 5-step reaction sequence to get the tricyclic benzo[*g*]isoquinoline-derived product **6as** starting from the **1a** analogue in an overall yield of 22%.[6b] Using our developed method, **6as** could be easily obtained in 53% yield from **1a**. Unexpectedly, a side product **6av** was isolated in moderate yield when it comes to the γ-substituted substrate. Further study revealed that cyclohept-2-en-1-one with a medium-sized ring (**6aw**), lactone (**6ax**), and lactam (**6ay**) all worked well for this annulation cascade, which significantly expanded the substrate scope of this powerful cascade transformation.



Scheme 3 Scope of cycloenone derivatives and more.



Scheme 4 Formal synthesis of fredericamycin A.

Finally, fredericamycin A was selected further as the target molecule to verify the flexibility of our method in the total synthesis of natural products, especially those containing 8-hydroxyisoquinolin-1[2*H*]-one units.[13] Since its first isolation in 1981, fredericamycin A attracted much attention from the synthetic community due to its interesting chemical structure and significant anti-tumor activity.[2,14,15] The synthetic route was inspired by the expeditious work from Bach.[16a] As shown in Scheme 4, we started our synthetic attempts with our developed multifold reaction sequence of pyridine **1a** and β-ethoxy enone **2h**, delivering the corresponding methyl ether **6a** on a gram scale. To the best of our knowledge, this is the first example of isoquinoline synthesis directly starting from a pyridine derivative in a single step. The aromatic ketone **6a** was subjected to a Mukaiyama aldol/pinacol rearrangement cascade with cyclobutene **7** to give spiro diketone **8** in 42% yield.[7,16] After oxidation with DDQ, the pivotal synthon **9** was obtained in 62% yield.[7] It should be noted that the addition of *p*-TsOH is necessary for this transformation as a sluggish reaction rate was detected in the absence of an acid. Meanwhile, a four-step access of phthalidyl chloride **10** was developed starting from a commercially available benzoic acid derivative.[7,17] For the crucial Hauser–Kraus annulation[18] between fragments **9** and **10**, we found that the coupling product **11** was not stable and thus protected directly as the corresponding methyl ether. After extensive screening of reaction conditions,[7] LiO^tBu turned out to be the only efficient base for this annulation. Mechanistically, the intermolecular Michael addition of segments **9** and **10** was followed by successive transformations involving Dieckmann condensation of enolate **V**, extrusion of chloride anions from the diketone **VI**, and last aromatization of the advanced intermediate **VII** to afford the hexacyclic diphenol **11** with the full skeleton embedded in fredericamycin A. As far as we know, this is the first example of 3-halophthalide as the Hauser donor instead of the classic sulfonyl- or cyano-containing substrates in Hauser–Kraus annulation, as 3-halophthalide was previously reported not suitable for this annulation.[18a] *In situ* methylation of the newly formed phenol hydroxyls delivered Kita's intermediate **12** in 51% yield in 2 steps. A further 4-step sequence ensured the accomplishment of fredericamycin A.[19] The overall synthetic route clearly showcased the power of ingenious introduction of multifold reaction cascades to realize the best performance from the point of step economy.

Conclusions

In summary, we have developed a concise approach for the rapid assembly of multicyclic isoquinoline scaffolds from pyridines and β-ethoxy α,β-unsaturated carbonyl compounds. In addition to operational simplicity, an intriguing feature of our strategy lies in the facile introduction of substituents and substitution patterns. Specifically, except for a very few cases (such as **6av**), substituents can be installed at all possible sites of our tricyclic isoquinoline molecules. This flexibility of rich substituent incorporation can likely enable framework-based construction of a large class of natural products and their analogues. In the present study, we demonstrate that fredericamycin A can be prepared in a short route, involving tricyclic isoquinoline construction, Mukaiyama aldol/pinacol rearrangement cascade, and Hauser–Kraus-type annulation as key steps. We expect our studies to find use in rapid and scalable preparation of complex natural products and their analogues, providing libraries of sophisticated molecules for bioactivity investigations.

Author contributions

F.-X. W. conducted most of the experiments; T. Z. and Y. L. initiated the study and chose the natural product target; J.-L. Y., Z. L., T. Z., Y. L., S.-C. R. and W.-X. L. performed some of the studies; Z. J. contributed to designs and discussions; Y. R. C. conceptualized and directed the project. All authors contributed to discussions and manuscript preparation.

Conflicts of interest

The authors declare no competing financial interests.

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Notes and references

1 For selected reviews on the biological activities of isoquinoline alkaloids, see: (*a*) M. Iranshahy, R. J. Quinn and M. Iranshahi, *RSC Adv.*, 2014, **4**, 15900–15913; (*b*) Z.-X. Qing, J.-L. Huang, X.-Y. Yang, J.-H. Liu, H.-L. Cao, F. Xiang, P. Cheng and J.-G. Zeng, *Curr. Med. Chem.*, 2018, **25**, 5088–5114; (*c*) X.-F. Shang, C.-J. Yang, S. L. Morris-Natschke, J.-C. Li, X.-D. Yin, Y.-Q. Liu, X. Guo, J.-W. Peng, M. Goto, J.-Y. Zhang and K.-H. Lee, *Med. Res. Rev.*, 2020, **40**, 2212–2289.

2 For the biological activities of fredericamycin A, see: D. J. Warnick-Pickle, K. M. Byrne, R. C. Pandey and R. J. White, *J. Antibiot.*, 1981, **34**, 1402–1407.

3 For the biological activities of ericamycin, see: M. Shimura, S. Kondo, T. Nishio, E. Akita, K. Satoh and T. Hara, *J. Antibiot.*, 1966, **19**, 51–55.

4 For the selected reviews on isoquinoline synthesis, see: (*a*) *Name Reactions in Heterocyclic Chemistry*, ed. J. J. Li and E. J. Corey, John Wiley & Sons, Hoboken, NJ, 2005, pp. 376–385; (*b*) M. M. Heravi, S. Khaghaninejad and N. Nazari, *Adv. Heterocycl. Chem.*, 2014, **112**, 183–234; (*c*) R. He, Z.-T. Huang, Q.-Y. Zheng and C. Wang, *Tetrahedron Lett.*, 2014, **55**, 5705–5713; (*d*) B. Zhang and A. Studer, *Chem. Soc. Rev.*, 2015, **44**, 3505–3521; (*e*) J. Jacob, N. Varghese, S. P Rasheed, S. Agnihotri, V. Sharma and S. Wakode, *World J. Pharm. Pharm. Sci.*, 2016, **5**, 1821–1837.

5 For the first discovery of Bischler–Napieralski isoquinoline synthesis, see: (*a*) A. Bischler and B. Napieralski, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 1903–1908; for the first discovery of the Pomeranz–Fritsch reaction, see: (*b*) P. Fritsch, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 419–422; (*c*) C. Pomeranz, *Monatsh. Chem.*, 1893, **14**, 116–119.

6 For limited examples of isoquinoline synthesis from pyridine *via* multiple steps, see: (*a*) D. L. J. Clive and J. Sedgeworth, *J. Heterocycl. Chem.*, 1987, **24**, 509–511; (*b*) K. Iio, N. G. Ramesh, A. Okajima, K. Higuchi, H. Fujioka, S. Akai and Y. Kita, *J. Org. Chem.*, 2000, **65**, 89–95; (*c*) A. E. Morrison, T. T. Hoang, M. Birepinte and G. B. Dudley, *Org. Lett.*, 2017, **19**, 858–861.

7 For details, see the ESI.†

8 Y. Tamura, A. Wada, M. Sasho and Y. Kita, *Chem. Pharm. Bull.*, 1983, **31**, 2691–2697.

9 For a review on Staunton–Weinreb annulation, see: C. D. Donner, *Tetrahedron*, 2013, **69**, 3747–3773.

10 For one example of annulation involving pyridine and cyclohexenone without substitution at the β site to form pyridine-containing products, see: M. G. Charest, C. D. Lerner, J. D. Brubaker, D. R. Siegel and A. G. Myers, *Science*, 2005, **308**, 395–398.

11 This is interesting as the phenol adduct **3a** itself is stable enough when exposed to air, though a sharp decrease in the yield was observed after purification through column chromatography. If this is a general phenomenon for some (if not all) phenol adducts, low yields previously reported in the reactions involving β-alkoxy cycloenones might be easily explained as all the phenol products in ref. 9 were isolated without *in situ* protection.

12 The absolute configuration of **6m** and the relative configuration of **6ai** were determined by X-ray crystallographic analysis. CCDC 2061702 (**6m**) and CCDC 2061701 (**6ai**)†.

13 For the selected examples on the total synthesis of 8-hydroxyisoquinolin-1[2*H*]-one-containing natural products in the past 10 years, see: (*a*) D. L. Sloman, J. W. Bacon and J. A. Porco, *J. Am. Chem. Soc.*, 2011, **133**, 9952–9955; (*b*) J. R. Butler, C. Wang, J. Bian and J. M. Ready, *J. Am. Chem. Soc.*, 2011, **133**, 9956–9959; (*c*) Y. Wang, C. Wang, J. R. Butler and J. M. Ready, *Angew. Chem., Int. Ed.*, 2013, **52**, 10796; *Angew. Chem.*, 2013, **125**, 10996–10999; (*d*) D. K. Winter, M. A. Endoma-Arias, T. Hudlicky, J. A. Beutler and J. A. Porco, *J. Org. Chem.*, 2013, **78**, 7617–7626; (*e*) J. Rujirawanich, S. Kim, A.-J. Ma, J. R. Butler, Y. Wang, C. Wang, M. Rosen, B. Posner, D. Nijhawan and J. M. Ready, *J. Am. Chem. Soc.*, 2016, **138**, 10561–10570; (*f*) Y. Dai, F. Ma, Y. Shen, T. Xie and S. Gao, *Org. Lett.*, 2018, **20**, 2872–2875; (*g*) A.-J. Ma and J. M. Ready, *Org. Lett.*, 2019, **21**, 1148–1151.

14 For the isolation and characterization of fredericamycin A, see: (*a*) R. C. Pandey, M. W. Toussaint, R. M. Stroshane, C. C. Kalita, A. A. Aszalos, A. L. Garretson, T. T. Wei, K. M. Byrne, R. F. Geoghegan and R. J. White, *J. Antibiot.*, 1981, **34**, 1389–1401; (*b*) R. Misra and R. C. Pandey, *J. Am. Chem. Soc.*, 1982, **104**, 4478–4479; (*c*) R. Misra, R. C. Pandey, B. D. Hilton, P. P. Roller and J. V. Silverton, *J. Antibiot.*, 1987, **40**, 786–802.

15 For synthetic reviews on fredericamycin A, see: (*a*) D. L. J. Clive, Y. Tao, A. Khodabocus, Y.-J. Wu, A. G. Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, M. Cantin, D. R. Cheshire, D. Kellner, G. Kleiner, D. S. Middleton, C. J. Nichols, S. R. Richardson, L. Set and P. G. Vernon, *Stud. Nat. Prod. Chem.*, 1995, **16**, 27–74; (*b*) D. L. Boger, *J.*

Heterocycl. Chem., 1996, **33**, 1519–1531; (*c*) Y. Kita, S. Akai and H. Fujioka, *J. Synth. Org. Chem.*, 1998, **56**, 963–974; (*d*) Y. Kita and H. Fujioka, *Pure Appl. Chem.*, 2007, **79**, 701–713; (*e*) C. D. Turner and M. A. Ciufolini, *Beilstein J. Org. Chem.*, 2011, **7**, 1475–1485; (*f*) S. Kotha and A. Fatma, *Asian J. Org. Chem.*, 2021, **10**, 129–148.

16 For similar reactions on the Mukaiyama aldol/pinacol rearrangement cascade, see: (*a*) J. A. Wendt, P. J. Gauvreau and R. D. Bach, *J. Am. Chem. Soc.*, 1994, **116**, 9921–9926; (*b*) T. J. Jenkins and D. J. Burnell, *J. Org. Chem.*, 1994, **59**, 1485–1491; (*c*) S. N. Crane, T. J. Jenkins and D. J. Burnell, *J. Org. Chem.*, 1997, **62**, 8722–8729; (*d*) S. N. Crane and D. J. Burnell, *J. Org. Chem.*, 1998, **63**, 1352–1355.

17 J. C. Evans, R. C. Klix and R. D. Bach, *J. Org. Chem.*, 1988, **53**, 5519–5527.

18 For a review on Hauser annulation, see: (*a*) D. Mal and P. Pahari, *Chem. Rev.*, 2007, **107**, 1892–1918; for the selected examples on Hauser–Kraus-type annulation in the total synthesis of natural products, see: (*b*) K. C. Nicolaou, H. Zhang, J. S. Chen, J. J. Crawford and L. Pasunoori, *Angew. Chem., Int. Ed.*, 2007, **46**, 4704–4707; (*c*) C. L. Hugelshofer and T. Magauer, *Angew. Chem., Int. Ed.*, 2014, **53**, 11351–11355; (*d*) K. Tatsuta and S. Hosokawa, *Chem. Rec.*, 2014, **14**, 28–40; (*e*) J.-K. Huang, T.-L. Yang Lauderdale and K.-S. Shia, *Org. Lett.*, 2015, **17**, 4248–4251; (*f*) S. Ahn and Y. T. Han, *Tetrahedron Lett.*, 2017, **58**, 4779–4780; (*g*) S. D. Holmbo and S. V. Pronin, *J. Am. Chem. Soc.*, 2018, **140**, 5065–5068; (*h*) S. Wang and G. A. Kraus, *J. Org. Chem.*, 2018, **83**, 15549–15552.

19 In Kita's two reports on the synthesis of fredericamycin A, the overall synthetic routes contain 27 and 25 steps, respectively. For details, see: (*a*) Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, S. Akai and H. Fujioka, *Angew. Chem., Int. Ed.*, 1999, **38**, 683–686; (*b*) Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, K. Ueda, S. Akai and H. Fujioka, *J. Am. Chem. Soc.*, 2001, **123**, 3214–3222.