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Publication date:
2023-02

Permanent link:
https://doi.org/10.3929/ethz-b-000599316

Originally published in:
Helvetica Chimica Acta 106(2), https://doi.org/10.1002/hlca.202200171

doi.org/10.1002/hlca.202200171

RESEARCH ARTICLE

HELVETICA chimica acta

Synthesis of the Multidrug Reversal Agent Ko143 and Its Parent Natural Product Fumitremorgin C

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In memory of *Jack Dunitz*

Ko143 is a tetracyclic, synthetic analog of the fungal metabolite fumitremorgin C. Ko143 is a potent and specific inhibitor of the membrane-bound efflux transporter ABCG2, and it reverses ABCG2-mediated drug resistance in cancer cells. Here, we describe an improved synthesis of Ko143 that relies on the highly selective, substrate-controlled reduction of an imine that is formed in a *Bischler–Napieralski* reaction with the amide derived from 6-methoxy-L-tryptophan methyl ester and isovaleric acid as a key step. We have also developed a new route to 6-methoxy-L-tryptophan methyl ester from Cbz-L-aspartic acid methyl ester, *m*-anisidine and differently substituted benzaldehydes. With *p*-nitrobenzaldehyde as one of the starting materials, this route gave access to 6-methoxy-L-tryptophan methyl ester in five steps and 20% overall yield; however, it is less efficient than a previously reported synthesis of 6-methoxy-L-tryptophan methyl ester from 6-methoxy indole.

Keywords: *Bischler–Napieralski* reaction, drug design, drug resistance, fumitremorgin C, inhibitors, Ko143, stereoselective synthesis.

Introduction

Fumitremorgin C (**1**; *Figure 1*) is a pentacyclic indole alkaloid that was first isolated from a strain of *Aspergillus fumigatus* by *Cole* and co-workers in 1977.[1] Since then, compound **1** has been isolated multiple times from other species of *A. fumigatus* and also from organisms belonging to other fungal genera.[2] Structurally, compound **1** is based on L-tryptophan and L-proline as the constituent amino acids and contains one prenyl unit that provides the connection between the indole moiety and a diketopiperazine ring.[12]

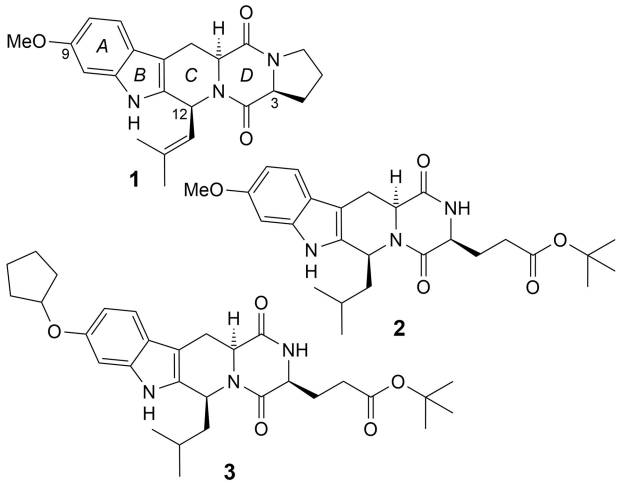
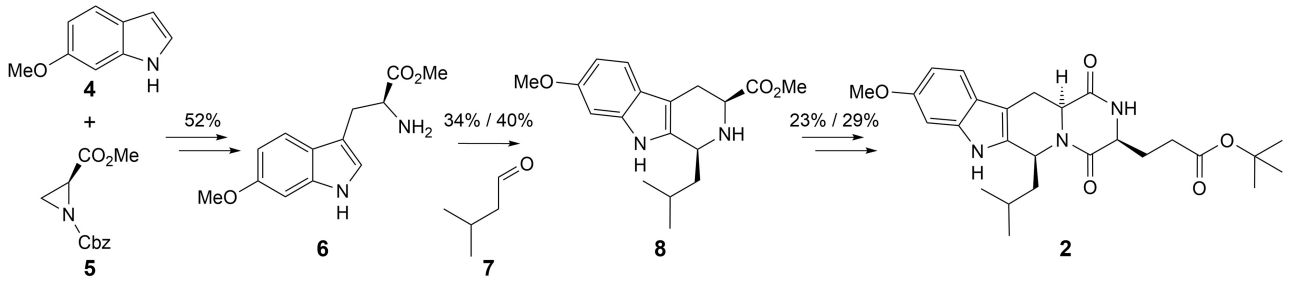


Figure 1. Structures of the natural product fumitremorgin C (**1**) and of fumitremorgin-derived ABCG2 inhibitors Ko143 (**2**) and MZ29 (**3**).

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.202200171

[1] While ref. [1] describes the first isolation of fumitremorgin C (**1**), its structure was only reported later.[3]

[2] The absolute configuration of fumitremorgin C (**1**) can be inferred from the established configuration of fumitremorgins A and B based on biosynthetic considerations.[2,4]



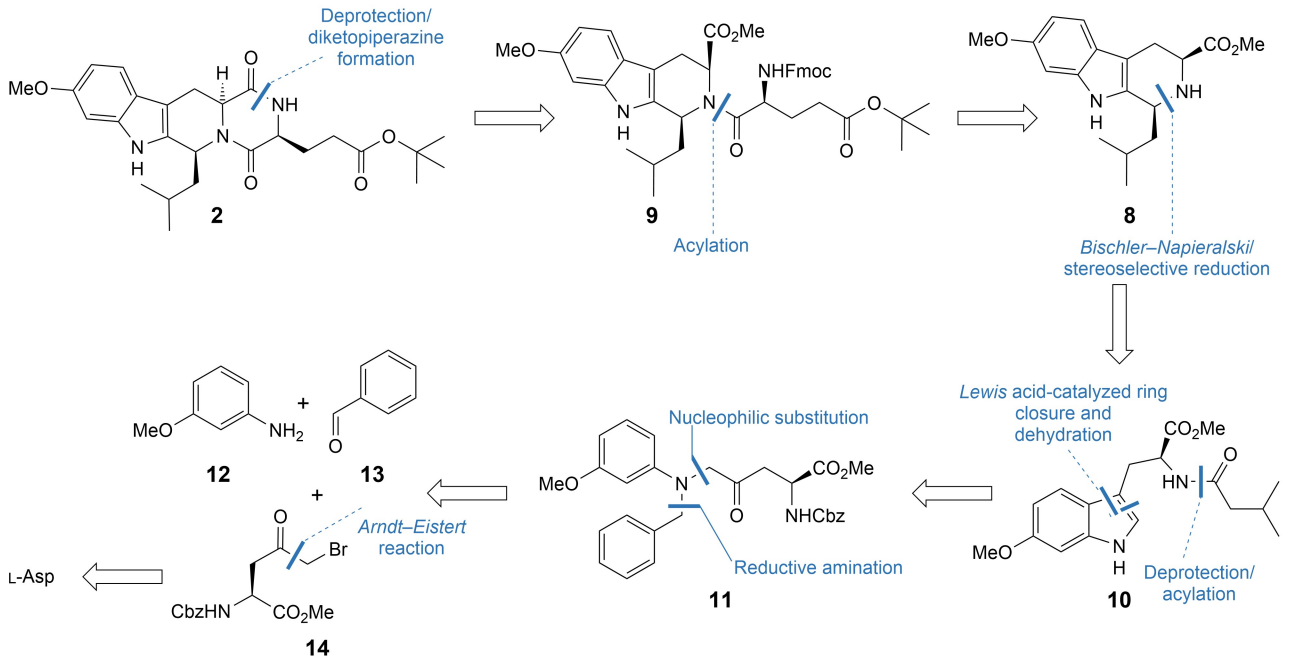
Scheme 1. Synthesis of Ko-143 (**2**) according to *Li*.[18]

Fumitremorgin C (**1**) is a mammalian cell cycle inhibitor[5] and it reverses multidrug resistance in cancer cells whose resistance phenotype is based on drug efflux by the multidrug transporter ABCG2 (also known as breast cancer resistance protein 1, BCRP1).[6,7] While its neurotoxicity precludes the use of **1** as a multidrug-reversal agent *in vivo*, a number of synthetic analogs have been developed that are devoid of neurotoxic effects and that are more potent inhibitors of ABCG2 than **1** itself. The most prominent of these is Ko143 (**2**; *Figure 1*),[8] which incorporates a glutamic acid-derived C(3) side chain in place of the proline-derived pyrrolidine ring in the natural product. We have recently described a series of potent ABCG2 inhibitors related to Ko143 (**2**), including MZ29 (**3**; *Figure 1*);[9] for the latter, the first inhibitor-bound structure of ABCG2 was obtained by *Locher* and co-workers in a collaboration with our group.[9]

The chemistry of fumitremorgin-type structures has been explored in some detail, including two total syntheses of fumitremorgin C (**1**),[10,11] several syntheses of C(9)-demethoxy fumitremorgin C,[12–17] and two stereoselective syntheses of Ko143 (**2**).[18] In the majority of these syntheses, the *C*-ring of the polycyclic scaffold (*Figure 1*) was established in a *Pictet–Spengler* reaction with the methyl ester of L-tryptophan or 6-methoxy-L-tryptophan, respectively, giving rise to diastereomeric product mixtures at C(12). As an exception from this theme, the first total synthesis of fumitremorgin C (**1**) by *Ottenheijm* and co-workers[11] proceeded through (racemic) 6-methoxy-*N*-hydroxy D/L-tryptophan as an early intermediate; the synthesis produced **1** in ten steps and 0.25% overall yield from 6-methoxyindole. A more efficient approach towards **1** was subsequently developed by *Hino* and co-workers,[10] which was based on the oxidative elaboration of *N*-methoxycarbonyl-L-tryptophan methyl ester into 6-methoxy-L-tryptophan methyl ester[19–21] and subsequent *C*-ring construction through *Pictet–Spengler* reaction. *Hino*'s synthesis delivered **1** in 11 chemical steps and 11% overall yield from *N*-methoxycarbonyl-L-tryptophan methyl ester. A similar overall approach was followed by *Li* and co-workers in their synthesis of Ko143 (**2**),[18] which is summarized in *Scheme 1*. In addition to following *Hino*'s route for the synthesis of 6-methoxy-L-tryptophan methyl ester (**6**), the latter was also obtained, and more efficiently so, by *Lewis* acid-catalyzed ring opening of aziridine **5** with 6-methoxyindole (**4**); *Pictet–Spengler* reaction with isovaleraldehyde (**7**) then gave a separable mixture of C(12)-diastereomeric tetrahydro-β-carbolines (reported *dr*'s (*cis*/*trans* ratios) are 37:63 and 45:55),[3] of which the desired *cis*-isomer **8** (obtained in 34% or 40% yield) was elaborated into **1** by acylation with Fmoc-glutamic acid-γ-*tert*-butyl ester followed by Fmoc-cleavage and concomitant diketopiperazine formation. The overall yield of Ko143 (**2**) for the longest linear sequence of 11 steps (for the more efficient approach, proceeding through aziridine **5**) was 3.2% (from D-serine methyl ester, as the precursor of aziridine **5**[22]).

While we have successfully followed *Li*'s approach for the synthesis of Ko143 analogs for SAR studies,[9] we still felt that the distinct lack of selectivity in the *Pictet–Spengler* reaction and the moderate yield for the acylation of **8** with Fmoc-Glu(O^{t}Bu)-OH (54% and 38%) called for optimization of this route. In this article, we report on a selective approach towards the construction of the C(12) stereocenter in Ko143 (**2**) and fumitremorgin C (**1**) through a *Bischler–Napier-*

[3] Ref. [18] describes two syntheses of Ko143 (**2**), which differ in the synthesis of intermediate **6**, while they are identical for the elaboration of **6** into **2**. However, two different yields are reported for each step leading from **6** to **2** in the two separate syntheses.



Scheme 2. Retrosynthesis of Ko143 (**2**).

alski/reduction sequence and the high-yielding conversion of the resulting tetrahydro-β-carbolines into **2** and **1**, respectively. In addition, we also describe an alternative approach towards the synthesis of 6-methoxy-L-tryptophan methyl ester (**6**) from Cbz-L-aspartic acid α-methyl ester.

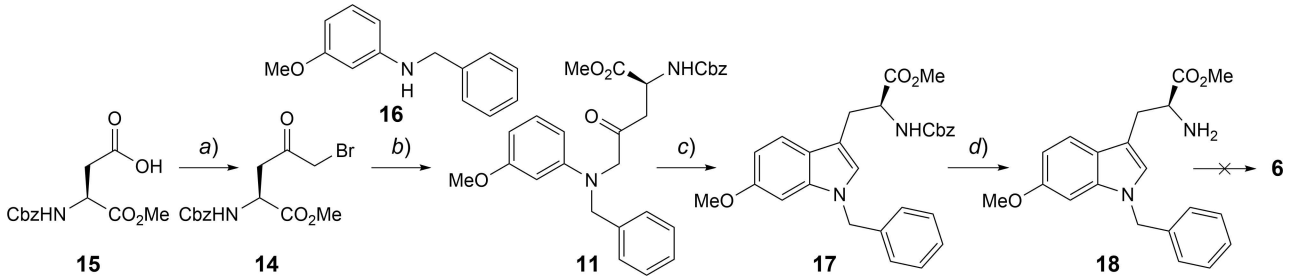
Results and Discussion

As depicted in *Scheme 2*, our approach towards Ko143 (**2**), as in *Li*'s syntheses of **2**[18] and *Hino*'s synthesis of fumitremorgin C (**1**),[10] was to rely on spontaneous formation of the diketopiperazine ring after Fmoc-removal from glutamylated tetrahydro-β-carboline **8**. The stereoselective construction of the C(12) stereocenter was envisioned to be achieved by a substrate-controlled, stereoselective reduction of the imine derived from amide **10** through *Bischler–Napieralski* cyclization.[23] Amide **10** was to be formed by the reaction of isovaleryl chloride with 6-methoxy-L-tryptophan methyl ester (**6**; see *Scheme 1*), which, in turn, was to be derived from amino ketone **11** by *Lewis* acid-mediated indole formation in a *Friedel–Crafts*-type reaction followed by (ideally simultaneous) removal of the N_α-Cbz and N(11)-benzyl groups. Intermediate **11** can be traced back to *m*-anisidine (**12**), benzaldehyde (**13**) and α-keto bromide **14**. The latter has been reported in the literature to be accessible from Cbz-L-aspartic acid α-methyl ester in 3 chemical steps and 87% overall yield in a one-pot procedure.[24]

Compared to the synthesis of **6** from L-serine methyl ester by *Li*,[18] our projected synthesis of **6** from Cbz-L-aspartic acid α-methyl ester comprised the same number of actual transformations (*i.e.*, seven for the longest linear sequence), while the number of operational steps would be either the same of slightly higher (four or five *vs.* four, depending on whether the removal of the N-protecting groups could be carried out as a one-pot procedure).[4] At the same time, our approach requires three steps from **6** to tetrahydro-β-carboline **8** compared to only a single step for *Li*'s *Pictet–Spengler* approach; however, the reaction of **6** with isovaleraldehyde (**7**) gave **8** only in 34% or 40% yield (*Scheme 1*), which we surmised could be surpassed even with a three-step sequence if the imine reduction would be sufficiently selective.

As shown in *Scheme 3*, Cbz-L-aspartic acid α-methyl ester (**15**) could be converted into α-bromo ketone **14** according to *Shibata*'s protocol[24] in high yield (80%). Reaction of **14** with secondary amine **16** (obtained by

[4] By 'operational step' we mean any number of successive transformations combined that are all carried out in the same reaction vessel.



Scheme 3. Reagents and conditions: *a*) 1. $SOCl_2$, 40 °C, 30 min; 2. $TMSCHN_2$, CH_2Cl_2, −78 °C to −40 °C, 14 h; 3. aq. HBr (48%), $CHCl_3$/Et_2O 1:1, 0 °C, 3 h 45 min, 80%. *b*) DIEA (2×5.0 equiv.), MeCN, 75 °C, 17 h, 78%. *c*) $ZnCl_2$, toluene, 100 °C, 2 h, 87%. *d*) Pd/C, H_2, MeOH, r.t., 2 h, 77%.

reductive amination of benzaldehyde with *m*-anisidine (**12**)) gave β-amino ketone **11** as the precursor for indole formation.[5] Cyclization of **11** occurred readily upon treatment with $ZnCl_2$ in toluene at 100 °C,[25,26] to deliver protected indole **17** in 87% yield. Exposure of **17** to hydrogen over Pd/C at room temperature and ambient pressure smoothly furnished N(1)-benzyl-6-methoxy-L-tryptophan methyl ester (**18**) in 77% yield (*i.e.*, cleavage of the N(11)-benzyl group did not occur under these conditions to any significant extent).

While the persistence of the N(11)-benzyl group under mild hydrogenation conditions was not surprising, unfortunately, we were unable to achieve clean removal of the benzyl group from **18** under any other conditions investigated (see the *Supporting Information*), in spite of the fact that there is ample literature precedent for the N-debenzylation of indole derivatives.[27–29] In the absence of a plausible explanation for these observations, subsequent experimental work was focused on the exploration of other N(11)-protecting groups on the indole nucleus. The corresponding variants of **17** bearing a PMB (**19**), a DMB (**20**), or an *o*-nitrobenzyl (ONB) group (**21**) on N(11) (*Scheme 4*) could be efficiently prepared through $ZnCl_2$-mediated indole formation from the corresponding β-amino ketone precursors (see the *Supporting Information*).

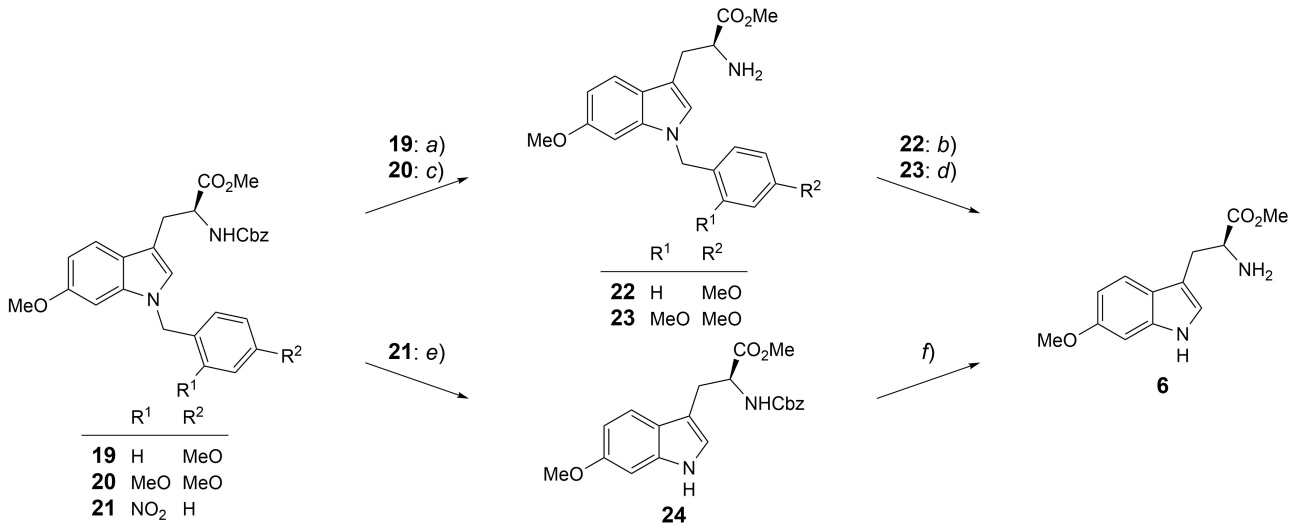
Hydrogenolytic removal of the Cbz group from **19** and **20** gave **22** and **23** in 87% and quantitative yield, respectively; for **21**, we chose to remove the *o*-nitrobenzyl group prior to hydrogenation, in order to avoid problems with reduction of the nitro group (*Scheme 4*).

Attempts to remove the PMB group from **22** under standard oxidative cleavage conditions either with DDQ[30] or CAN[31] resulted in the formation of a multitude of unidentified products (based on TLC analysis). Likewise, treatment of **22** with TFA/TfOH/PhSH at room temperature gave a complex product mixture, while TFA/PhSH or TFA/H_2SO_4/anisole, both at 60 °C, did not give any conversion. In contrast, TFA/anisole under MW irradiation at 110 °C for 4 h gave **6** in 42% yield; however, these conditions still led to slow formation of decomposition products.

As for PMB-protected **22**, attempts to remove the DMB group from **23** with DDQ[30] produced a complex mixture of products (according to TLC; see *Supporting Information*). However, the increased acid-lability of the DMB group allowed deprotection of the indole nitrogen in **23** under somewhat milder conditions than for **22** (TFA/anisole, 70 °C) and with improved yield (52%; *Scheme 4*).

Finally, the cleavage of the ONB group from **21** could be achieved photolytically (at 350 nm)[32,33] in 61% yield; subsequent hydrogenolytic removal of the Cbz group from **24** then proceeded quantitatively (*Scheme 4*). Thus, the route from Cbz-L-Asp-OMe (**15**) to **6** through ONB derivative **21** proved to be the most efficient, furnishing **6** in 20.5% overall yield compared to *ca.* 12% through both intermediates **19** or **20** (although yields in most cases are unoptimized). At the same time, we note that, unfortunately, even with intermediate **21**, the overall yield of **6** from **15** is significantly lower than from L-serine methyl ester, which essentially reflects the high efficiency of the conversion of this starting material into aziridine **5** (five chemical steps, two operational steps, 70% overall yield).[22] No further attempts were made at this point to identify N(11)-substituents that could lead to an

[5] *Shibata* and co-workers[24] have also used bromo ketone **14** as an intermediate for indole synthesis, but their cyclization method (and the structure of their target indole) was different from the ones described here.



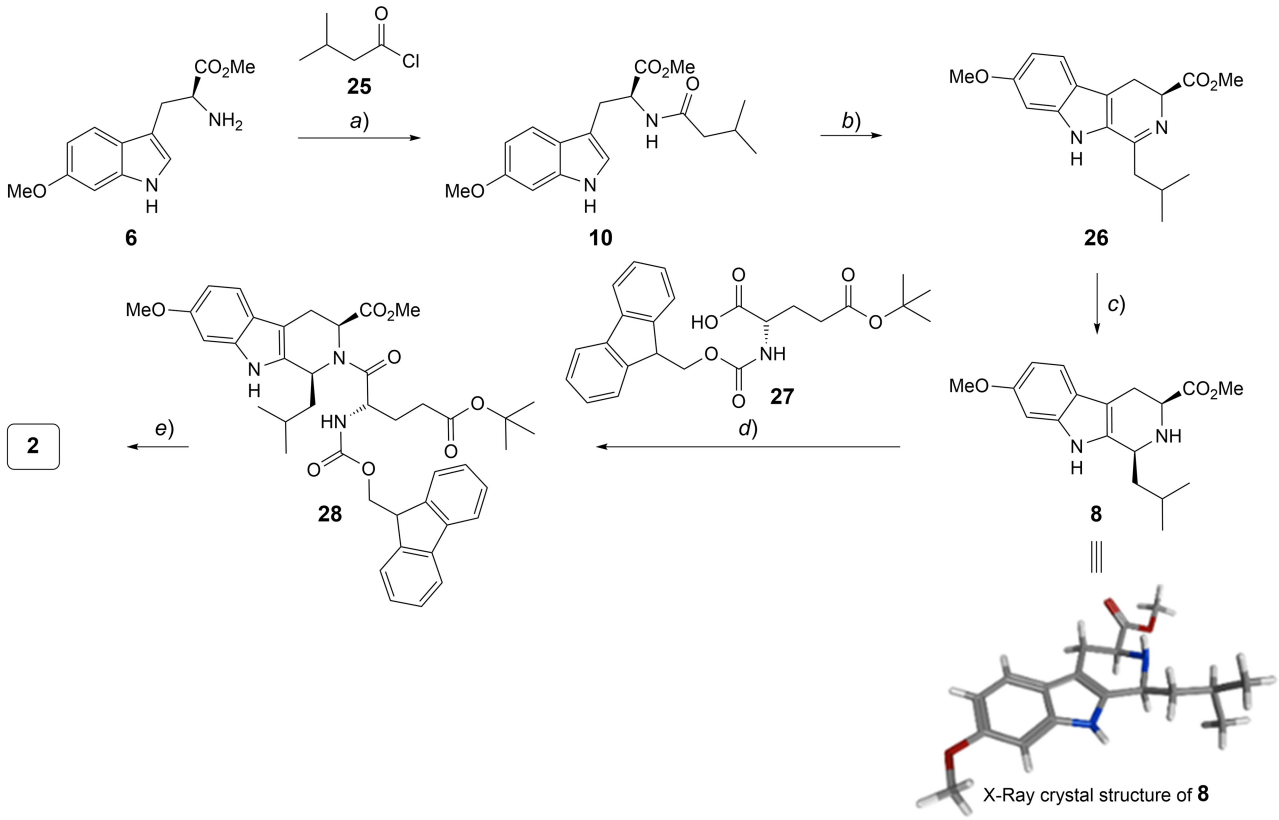
Scheme 4. Reagents and conditions: *a*) Pd/C, H_2, MeOH, r.t., 2 h, 87%. *b*) TFA, anisole, 110 °C, MW irradiation, 4 h, 42%. *c*) Pd/C, H_2, MeOH, r.t., 2 h, quant. *d*) TFA, anisole, 70 °C, 22 h, 52%. *e*) UV light (350 nm), MeOH, r.t., 24 h, 61%. *f*) Pd/C, H_2, MeOH, r.t., 2 h, quant.

improved yield of **6** from **15**. Rather, we shifted our focus to the possible stereoselective elaboration of **6** into Ko143 (**2**) through the projected *Bischler–Napieralski*/reduction approach.

As depicted in *Scheme 5*, amino ester **6** could be readily acylated with isovaleryl chloride (**25**), to furnish amide **10** in 85% yield. Treatment of this amide with $POCl_3$ in benzene (5 °C to reflux, 5 h)[23] gave imine **26**, which was not purified but directly treated with 10 equiv. of $NaBH_4$ in MeOH at 0 °C. The reaction proceeded with a *dr* of 15:1 and gave **8** as a single isomer in 64% isolated yield, thus validating our original hypothesis that the C(7) substituent would efficiently control the stereochemical course of the reduction. Tetrahydrocarboline **8** was obtained from **6** in 54% overall yield, which compares favorably with the yield reported by *Li* for the *Pictet–Spengler* reaction of **6** with isovaleraldehyde (**7**) (*vide supra*).[18] The relative and absolute configuration of **8** was unequivocally established by X-ray crystallography.[6]

Amide bond formation between **8** and Fmoc-Glu(O*t*Bu)-OH (**27**) has been reported by *Li* and co-workers[18] to proceed in only moderate yields (54% or 38%) with 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate (ClP)[34] as the coupling agent. In our hands, the ClP-mediated coupling between **8** and **27** gave **28** in 28% yield, but no attempts were made to optimize the reaction. Instead, we investigated if the use of other coupling reagents would lead to higher yields of amide bond formation. Reagents screened[35,36] included DCC/HOBt, EDC/HOAt, HATU, *iso*-butylchloroformate,[37] COMU,[38] TCFH,[39] and Cl_3CCN/PPh_3.[40] With the exception of Cl_3CCN/PPh_3, which we had previously employed in the synthesis of a series of Ko143 analogs with moderate to good success,[9] all of these reagents produced only traces of **28** at best (TCFH, HATU); Cl_3CCN/PPh_3 gave variable yields of **28** ranging from 10% to 40%. After extensive experimentation, a substantial improvement in the efficiency of the coupling reaction could finally be realized by the use of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[41] as an activating agent, which gave amide **28** reproducibly in yields of 74% to 88%. The conversion of **28** into Ko143 (**2**) with piperidine/CH_2Cl_2 was then uneventful and furnished

[6]The X-ray crystal structure of **8** was obtained with material that had been prepared by *Pictet–Spengler* reaction of **6** with isovaleraldehyde. The spectral data of this material were identical (within error) with those of **8** prepared through the *Bischler–Napieralski*/reduction sequence (*i.e.*, through imine **26**) and distinctly different from those of its C(12)-(*R*) isomer **8A**, which was the major product in the reaction of **6** with isovaleraldehyde (see the *Supporting Information*). CCDC-2220396 contains the supplementary crystallographic data for this article, including structure factors and refinement instructions. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk), or through https://www.ccdc.cam.ac.uk/structures.



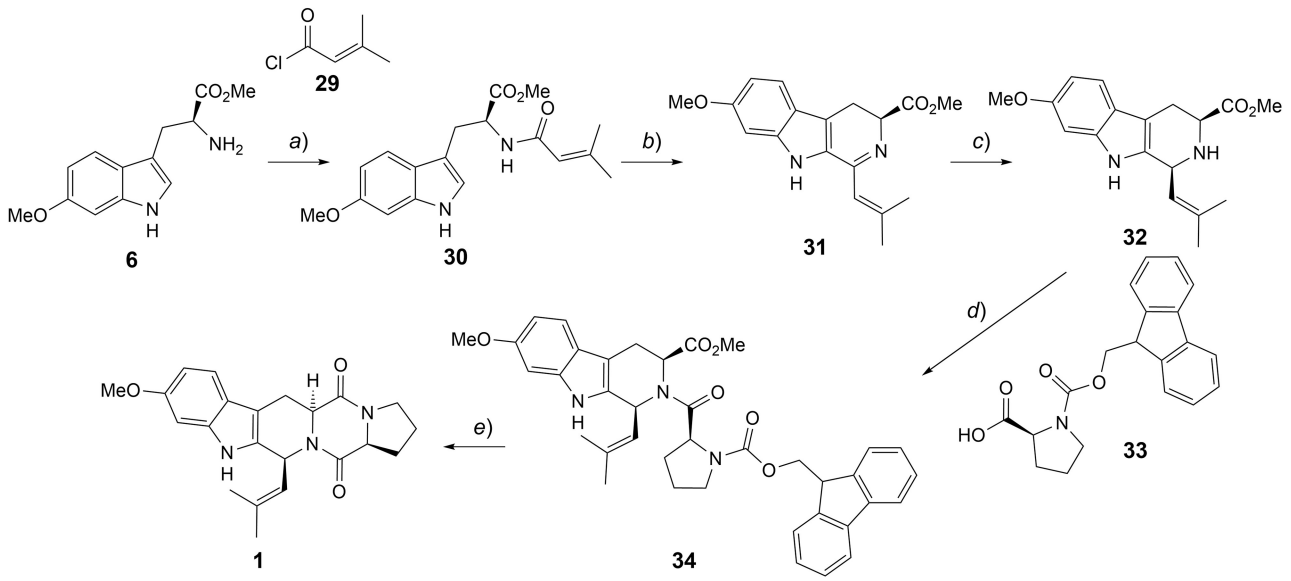
Scheme 5. Reagents and conditions: *a*) Isovaleryl chloride (**25**), Et_3N, THF, 0 °C to r.t., 10 min, 85 %. *b*) $POCl_3$, benzene, 5 °C to reflux, 3 h, quant., crude. *c*) $NaBH_4$ (10 equiv.), MeOH, 0 °C, 5 min, 64 % over two steps. *d*) Fmoc-Glu(O^{t}Bu)-OH (**27**), DMTMM, THF, r.t., 2 d, 74–88 %. *e*) Piperidine, CH_2Cl_2, r.t., 1 h, 85 %.

Ko143 (**2**) in 85 % yield through the free amino ester, which spontaneously cyclizes to the diketopiperazine under the reaction conditions.[10,18] Quite notably, the use of CH_2Cl_2 as the solvent in the final deprotection/cyclization step seems to have a profound effect on the yield of the reaction, as the use of piperidine/THF by *Li* and co-workers furnished **2** in only 54 %/60 % yield.[18] The overall yield of **2** from **6** was between 34 % and 40 % *vs.* 10 %/11 % in *Li*'s syntheses.

Given the selective formation of tetrahydro-β-carboline **8** through the above *Bischler–Napieralski*/reduction sequence, we felt enticed to investigate if the method could also come to bear on the total synthesis of the natural product fumitremorgin C (**1**). In the event, treatment of **6** with 3-dimethylacryloyl chloride (**29**) furnished amide **30** in excellent yield (94 %; *Scheme 6*). Treatment of **30** with $POCl_3$ then furnished dihydro-β-carboline **31**,[23] which was not purified but directly submitted to reduction with $NaBH_4$. Gratifyingly, using the optimized conditions previously established for the stereoselective reduction of **26** (10 equiv. of $NaBH_4$, MeOH, 0 °C) gave the desired *cis*-tetrahydro-β-carboline **32** as a single isomer in 45 % yield (from **6**; the *dr* of crude **32** was 20 : 1).

Unexpectedly, the DMTMM[41]-mediated coupling of **32** with Fmoc-Pro-OH (**33**) under the same conditions that had provided access to amide **28** from **8** and Fmoc-Glu(O^{t}Bu)-OH (**27**) in high yield, led to epimerization at the C(11) stereocenter. The resulting amide was thus obtained as a 1 : 1.2 mixture of the desired **34** and its C(12)-(*R*) (*trans*) epimer. This problem could be overcome, however, by the addition of 6 equiv. of DIEA to the mixture; under these modified conditions, the reaction proceeded with a *dr* of *ca.* 22 : 1 and **34** was finally obtained as a single isomer in 70 % yield.

Removal of the Fmoc group with piperidine in CH_2Cl_2 followed by spontaneous diketopiperazine formation then furnished fumitremorgin C (**1**), which was obtained from **6** in six chemical steps (five operational steps) and 27 % overall yield. In comparison, *Hino*'s synthesis required five chemical steps (four operational steps) for the same overall transformation and gave **1**



Scheme 6. Reagents and conditions: *a*) 3,3-Dimethylacryloyl chloride (**29**), Et_3N, THF, 0 °C to r.t., 10 min, quant. *b*) $POCl_3$, benzene, 5 °C to reflux, 3 h, quant. crude. *c*) $NaBH_4$, MeOH, 0 °C, 1 min, 45% over two steps, *dr* of the crude = 20:1. *d*) Fmoc-Pro-OH (**33**), DMTMM, DIEA (6 equiv.), THF, r.t., 60 h, 70% (*dr* of the crude = 23:1). *e*) Piperidine, CH_2Cl_2, r.t., 1 h, 87%.

in 34% overall yield (from **6**). While the two reaction sequences cannot be compared directly, the difference in overall yield is largely due to the higher-yielding acylation of a slightly different variant of **32** with Troc-Pro-Cl (92% *vs.* 70% with Fmoc-Pro-OH/DMTMM) and a higher yield in the final deprotection/cyclization step (96% *vs.* 86% in our case).

Conclusions

We have established a new stereoselective approach towards the potent multidrug reversal agent Ko143 (**2**) and the natural product fumitremorgin C (**1**), based on the construction of the C(12) stereocenter through a *Bischler–Napieralski*/reduction sequence from 6-methoxy-L-tryptophan methyl ester (**6**). The selectivity of this approach more than compensates for the three-step sequence from **6** to **8** compared to the direct formation of **8** through a *Pictet–Spengler* reaction. We have also elaborated a new route to **6** from Cbz-L-aspartic acid methyl ester (**15**), which should also be applicable to the synthesis of other modified tryptophans. However, while this route gave **6** in 20% overall yield from **15**, it does not reach the efficiency of the synthesis of **6** from L-serine methyl ester.

Experimental Section

Details on synthetic procedures, analytical data for new compounds, copies of ^{1}H- and ^{13}C-NMR spectra, as well as details on the X-ray structure determination of **8** are all described in the *Supporting Information*.

Acknowledgements

This work supported by the *Swiss National Science Foundation* through the National Centre of Competence in Research (NCCR) TransCure. Institutional support by the ETH Zurich is also gratefully acknowledged (*K.-H. A.*). We are indebted to Dr. *Bernhard Pfeiffer* and Dr. *Philipp Waser* (ETHZ) for NMR support, to *Kurt Hauenstein* (ETHZ) for technical advice and to *Oswald Greter*, *Louis Bertschi*, *Michael Meier*, and *Daniel Wirz* (ETHZ) for HR-MS spectra acquisition. We are grateful to Dr. *Nils Trapp* (ETHZ) for solving the X-ray crystal structure of compound **8**.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Author Contribution Statement

M. Z. and *K.-H. A.* designed the research; *M. Z.* and *K.-H. A.* designed experiments; *M. Z.* carried out experiments; *K.-H. A.* provided supervision. *K.-H. A.* wrote the paper.

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Received November 22, 2022
Accepted December 23, 2022

