

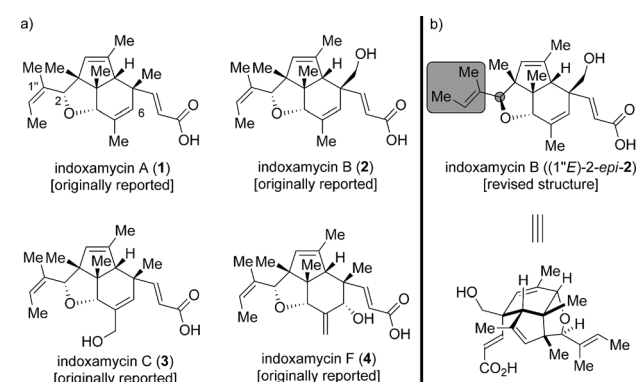
Divergent Total Synthesis of Indoxamycins A, C, and F**

Chi He, Chenlong Zhu, Zhifeng Dai, Chih-Chung Tseng, and Hanfeng Ding*

As a novel class of polyketides, indoxamycins A–F were isolated in 2009 by Sato et al. from saline cultures of marine-derived actinomycetes.^[1a] Within this family, indoxamycins A and F have exhibited promising growth-inhibition activity against HT-29 tumor cell lines (IC_{50} = 0.59 μ M and 0.31 μ M, respectively), thus achieving levels of activity similar to that of mitomycin (IC_{50} = 0.66 μ M). The absolute and relative stereochemistry of indoxamycins was originally assigned based on a combination of one- and two-dimensional NMR experiments and CD studies (Scheme 1 a).^[1b] The indoxamy-

the side chain (Scheme 1 b).^[2] Based on this result, the structural revision was also proposed to be required for the other members of this family. However, apart from these significant achievements by Carreira and co-workers, no synthetic approach towards indoxamycins has been disclosed to date. Herein, we report a divergent approach for the total synthesis of indoxamycins A, C, and F, which culminated in the elucidation of the stereochemistry of these natural products.

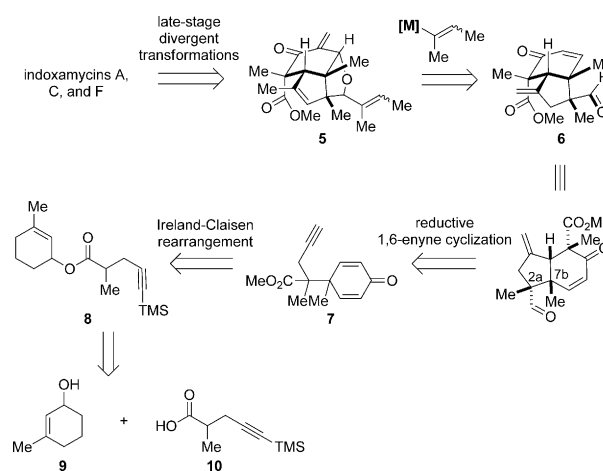
Our retrosynthetic analysis is shown in Scheme 2. We rationalized that indoxamycins A, C, and F might be synthesized from a common late-stage intermediate **5**. For its construction, we envisaged a substrate-controlled tandem



Scheme 1. a) Structures of indoxamycins A–C and F originally reported by Sato;^[1] b) structure of indoxamycin B revised by Carreira.^[2]

cin skeleton consists of an unprecedented [5,5,6] tricyclic cage-like carbon framework and two side chains having a trisubstituted olefin and an unsaturated carboxylic acid, respectively. The core structure features six contiguous stereogenic centers, of which three are quaternary, including two vicinal carbon atoms embedded in a sterically congested tetrahydrofuran subunit (Scheme 1 a).

In 2012, Carreira and co-workers reported an elegant total synthesis of *rac*-indoxamycin B ((1'*E*)-2-*epi*-2), which led to a structural reassignment of the relative configuration at the C2 position and the geometry of the trisubstituted alkene in



Scheme 2. Retrosynthetic analysis of indoxamycins A, C, and F.

reaction,^[3] involving a 1,2-addition/oxa-Michael/methylenation sequence, to forge the [5,5,6] tricyclic framework of the molecule. The essential enone–aldehyde precursor **6** could be obtained through a transition-metal-catalyzed^[4] reductive cyclization of 1,6-dienyne **7** with concomitant installation of the two challenging vicinal quaternary centers at the C2a and C7b positions with the desired stereochemical outcome. Dienyne **7** could be prepared through an Ireland–Claisen rearrangement^[5] from allyl ester **8**, which may in turn be obtained from the readily available building blocks **9** and **10**.^[6]

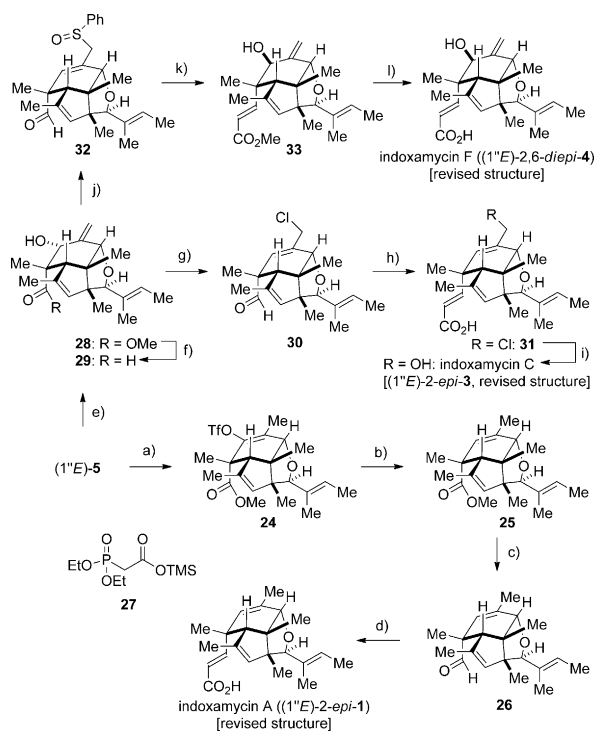
The realization of our synthetic strategy commenced with the construction of the required [5,6] bicyclic enone–aldehyde precursor **6** (Scheme 3). Esterification of **9** and **10** proceeded smoothly to give the ester **8** in 90% yield as a mixture of diastereomers. The introduction of the two vicinal quaternary centers at the C2a and C7b positions by an Ireland–Claisen rearrangement is one of the critical steps of the synthesis. Pleasingly, under optimized conditions, these two centers were successfully constructed by direct heating of the silyl

[*] C. He,^[+] C. Zhu,^[+] Z. Dai, Dr. C.-C. Tseng, Prof. Dr. H. Ding
Department of Chemistry, Zhejiang University
148 Tianmushan Road, Hangzhou 310028 (China)
E-mail: hfding@zju.edu.cn

[†] These authors contributed equally to this work.

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Scheme 5. Divergent total synthesis leading to the revised structures of indoxamycins A, C, and F. Reagents and conditions: a) PhNTf₂, L-Selectride (1.0 M in THF), THF, −78→25°C, 79%; b) Pd(OAc)₂, PPh₃, Et₃N, HCO₂H, THF, 65°C, 85%; c) Dibal-H (1.5 M in toluene), pentane, −105°C, 81%; d) **27**, *n*BuLi, THF, 25°C, 95%; e) NaBH₄, CeCl₃·7H₂O, −20°C; f) Dibal-H (1.5 M in toluene), CH₂Cl₂, −50°C, 84% over two steps; g) SOCl₂, pyridine, Et₃O, 0°C, 97%; h) **27**, *n*BuLi, THF, 25°C; i) AgNO₃, acetone/H₂O (4:1), 25°C, 78% over two steps; j) PhSCl, Et₃N, Et₂O, 0°C, 92%; k) (EtO)₂P(O)CH₂CO₂Me, NaH (60% wt/wt in mineral oil), THF, 25°C, 95%; l) LiOH (1.0 M, aq.), MeOH/THF (3:1), 25°C, 92%. L-Selectride = lithium tri-*sec*-butylborohydride, Tf = trifluoromethanesulfonyl.

acid-catalyzed isomerization of the *exo* double bond^[17] in **23** provided the desired product (1''E)-5 in 82% yield.

The final stages of the synthesis are summarized in Scheme 5. Conjugate reduction of (1''E)-5 with L-Selectride followed by trapping with PhNTf₂ gave enol triflate **24** (79% yield). Reductive detriflation delivered alkene **25** in 85% yield, which was then converted into aldehyde **26** on careful treatment with Dibal-H (81% yield). Horner–Wadsworth–Emmons (HWE) olefination of **26** with phosphonate **27** efficiently furnished (1''E)-2-*epi*-1 in 95% yield. On the other hand, sequential reduction of enone ester (1''E)-5 generated allylic alcohol **29** as a single diastereomer (84% yield over two steps), which underwent nucleophilic chlorination to give allylic chloride **30** in 97% yield. Subsequent olefination followed by hydrolysis of the resulting enoic acid **31** in the presence of AgNO₃^[18] afforded (1''E)-2-*epi*-3 in 78% yield over two steps.

For the synthesis of indoxamycins F, we utilized the well-established sulfoxide/sulfenate rearrangement^[19e–i] to invert the configuration at the C6 position of allylic alcohol **29**.^[20,21] Thus, **29** was first treated with benzenesulfonyl chloride to give sulfoxide **32** in 92% yield. Pleasingly, a Mislow–Evans

rearrangement occurred during the HWE olefination, presumably induced by the phosphate generated in situ,^[19] and afforded the desired allylic alcohol **33** in one step in 95% yield. Saponification of **33** then delivered (1''E)-2,6-di-*epi*-4 in 92% yield.

After conversion into the corresponding potassium salts,^[2] all of the spectroscopic (¹H and ¹³C NMR) and mass spectrometric data of synthetic (1''E)-2-*epi*-1, (1''E)-2-*epi*-3, and (1''E)-2,6-di-*epi*-4 were consistent with those reported for the natural indoxamycins A, C, and F, respectively.^[1]

Having established the relative configuration of indoxamycins A, C, and F by racemic total synthesis, an asymmetric approach was pursued. In our initial synthetic design, we planned to take advantage of a diastereoselective Ireland–Claisen rearrangement that had been developed by Zakarian and co-workers.^[5g,22] Disappointingly, individual treatment of both diastereomers of the enantiopure ester **8** with chiral Koga-type bases only led to moderate improvements in diastereoselectivity (1.7:1–2.6:1 d.r., see the Supporting Information for details). Therefore, we turned our attention to the development of an enantioselective version of the reductive 1,6-enyne cyclization.

Although enantioselective variants of the Alder–ene reaction have been described by the groups of Trost,^[23a] Ito,^[23b] Mikami, and Hatano,^[23c–h] palladium-catalyzed enantioselective reductive cyclizations of 1,*n*-enyne have not been investigated thus far.^[24] Inspired by Ito and Mikami et al., we employed a chiral C₂-symmetric bidentate phosphorus ligand. A preliminary screen revealed Pd(tfa)₂/segphos to be an effective catalyst system (Table 1, entry 2) for the stereo-

Table 1: Stereodivergent reductive 1,6-enyne cyclization.^[a]

Entry	[Pd]	<i>t</i> [h]	(+)-13, 2a- <i>epi</i> -13 Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1 ^[d]	[Pd ₂ (dba) ₃]	24	15, n.d.	65, –
2 ^[d]	Pd(tfa) ₂	10	40, 32	72, 64
3	[Pd(MeCN) ₄](BF ₄) ₂	0.5	42, 33	84, 71
4 ^[e]	[Pd(MeCN) ₄](BF ₄) ₂	0.5	46, 43	93, 80

[a] Reaction conditions: **7** (0.1 mmol), [Pd] (0.025 equiv), (R)-segphos (0.05 equiv), AcOH (2.0 equiv), and Et₃SiH (1.5 equiv) in DMSO at 25°C. [b] Yields of isolated products. [c] Determined by HPLC analysis. [d] Benzene was used as the solvent. [e] HCO₂H (2.0 equiv) was used instead of AcOH. n.d. = not determined, (R)-segphos = (R)-(4,4'-bi-1,3-benzodioxole)-5,5'-diylbis(diphenylphosphine), tfa = trifluoroacetate.

divergent formation^[25] of the enantioenriched bicyclic products (+)-13 (40% yield, 72% *ee*) and 2a-*epi*-13 (32% yield, 64% *ee*). Accelerating the reaction by using a cationic Pd^{II} catalyst, [Pd(MeCN)₄](BF₄)₂, afforded (+)-13 in 42% yield and 84% *ee* (entry 3). However, replacing segphos with other ligands led to decreased yields and *ee* values (see the Supporting Information for details). Gratifyingly, by using [Pd(MeCN)₄](BF₄)₂ in combination with formic acid,^[4d,e]

(+)-**13** was obtained with excellent enantioselectivity (93 % *ee*) and yield (46 %), with concomitant formation of 2a-*epi*-**13** in 43 % yield and 80 % *ee* (entry 4).

Following the route described for the racemic compounds, (+)-**13** was transformed into tricyclic enone (+)-**23**; the enantiomeric purity of (+)-**23** could be increased to 96 % *ee* through recrystallization. Further elaboration of (+)-**23** led to (–)-indoxamycins A ((1′′*E*)-2-*epi*-**1**), C ((1′′*E*)-2-*epi*-**3**), and F ((1′′*E*)-2,6-di-*epi*-**4**), which exhibited satisfactory optical rotations and identical CD spectra (see the Supporting Information for details).

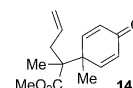
In conclusion, we have developed a concise and efficient route for the divergent total synthesis of indoxamycins A, C, and F in their racemic and enantiomerically pure forms. This first total synthesis unambiguously determined the stereochemistry of these natural products, thus validating the hypothesis by Carreira and co-workers. The key steps of the strategy entail an Ireland–Claisen rearrangement, a stereo-divergent reductive 1,6-enyne cyclization, and a tandem 1,2-addition/oxa-Michael/methylenation reaction. The described strategy and methods are currently applied to the synthesis of other members and analogues of the indoxamycin family in our laboratory to enable further biological evaluation of these compounds.

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