Natural Product Synthesis

DOI: 10.1002/ange.201307426

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

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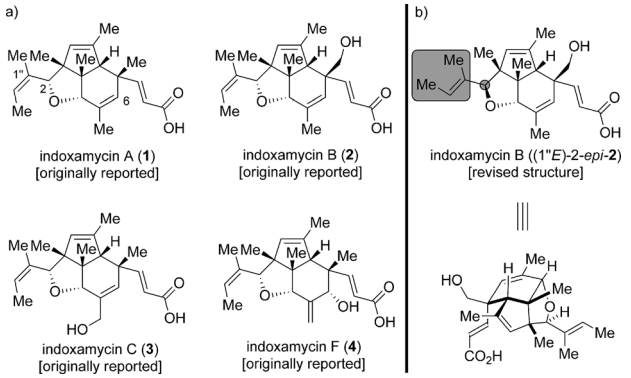
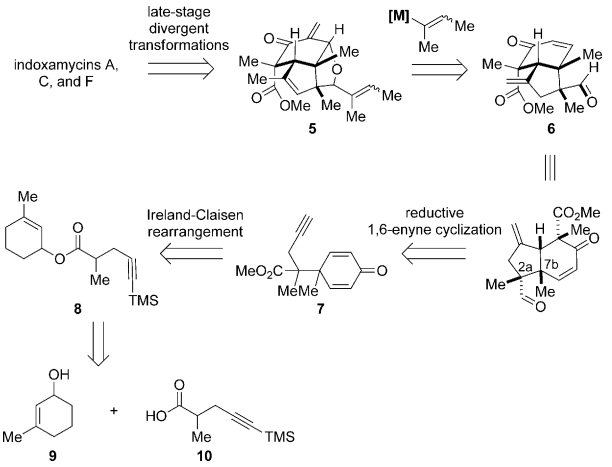
As a novel class of polyketides, indoxamycins A–F were isolated in 2009 by Sato et al. from saline cultures of marine-derived actinomycetes.[1a] Within this family, indoxamycins A and F have exhibited promising growth-inhibition activity against HT-29 tumor cell lines ($IC_{50} = 0.59$ μM and 0.31 μM, respectively), thus achieving levels of activity similar to that of mitomycin ($IC_{50} = 0.66$ μM). 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 1a).[1b] The indoxamycin 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 1a).



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

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 the side chain (Scheme 1b).[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 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]



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

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

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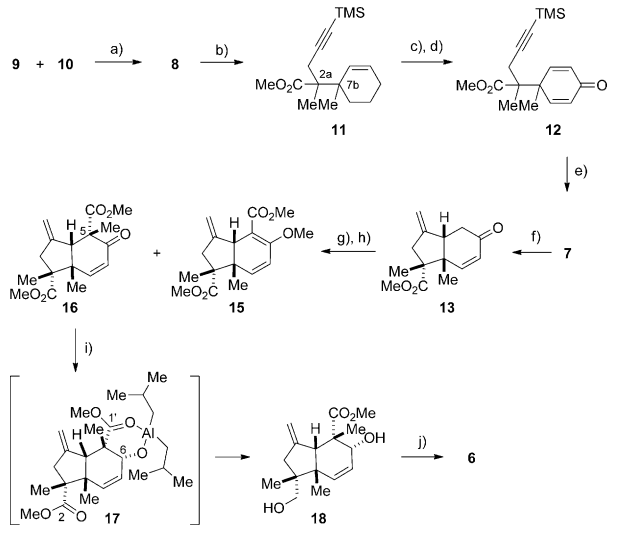
[**] This work was supported by the NSFC (21202144), the Fundamental Research Funds for the Central Universities (2011QNA3010, 2013QNA3021), the Zhejiang Provincial NSFC (LQ12B02003), and the New Teacher's Fund for Doctor Stations, Ministry of Education (20120101120087).

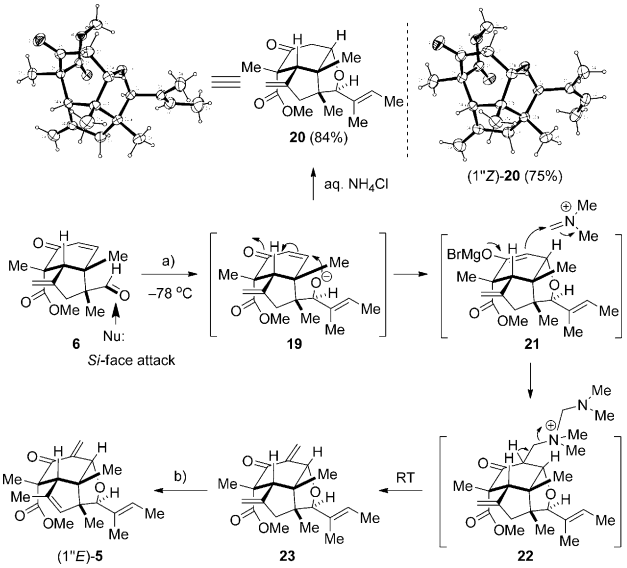
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307426.



Scheme 3. Synthesis of enone–aldehyde **6**. Reagents and conditions: a) EDC·HCl, 4-DMAP, CH_2Cl_2, 0→25 °C, 90%; b) KHMDS (1.0 M in THF), TMSCl, Et_3N, toluene, −78→70 °C; then $TMSCHN_2$, CH_2Cl_2, 25 °C, 85% (mixture of diastereomers, ca. 1.5:1 d.r. by ^1H NMR spectroscopy); c) CrO_3, 3,5-DMP, CH_2Cl_2, −20→25 °C, 86% (mixture of diastereomers, ca. 1.5:1 d.r. by ^1H NMR spectroscopy); d) DDQ, 1,4-dioxane, 100 °C, 83%; e) K_2CO_3, MeOH, 25 °C, 85%; f) $[Pd_2(dba)_3]$, $P(o\text{-tol})_3$, Et_3SiH, AcOH, benzene, 25 °C, 87%; g) LiHMDS (1.0 M in THF), Mander's reagent, THF, −78 °C; h) NaH (60% wt/wt in mineral oil), CH_3I, DME, 25 °C, 78% over two steps (together with 15% of **15**); i) Dibal-H (1.5 M in toluene), CH_2Cl_2, −78 °C; j) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0→25 °C, 76% over two steps. dba = dibenzylideneacetone, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Dibal-H = diisobutylaluminium hydride, DME = 1,2-dimethoxyethane, 3,5-DMP = 3,5-dimethylpyrazole, EDC·HCl = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, KHMDS = potassium bis(trimethylsilyl)amide, LiHMDS = lithium bis(trimethylsilyl)amide, THF = tetrahydrofuran.

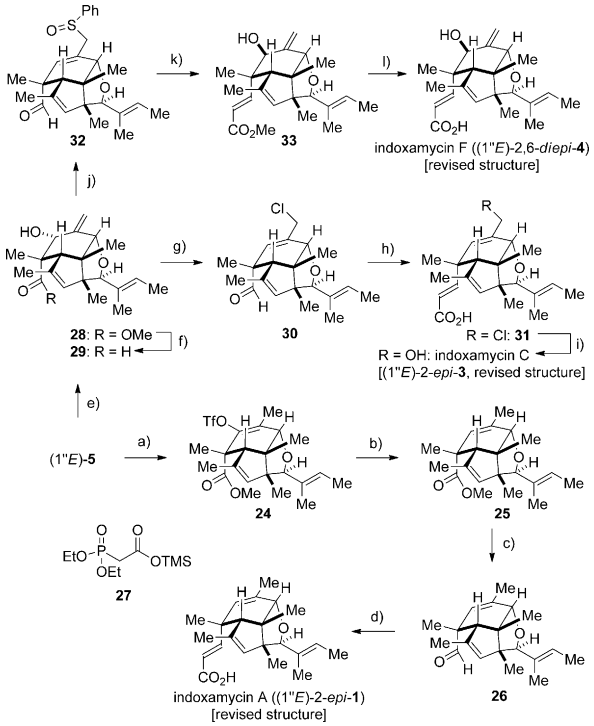
ketene acetal formed in situ, which afforded **11** in 85% yield as an inseparable but inconsequential mixture of diastereomers (ca. 1.5:1 d.r.). Subsequent allylic oxidation[7] followed by DDQ dehydrogenation[8] yielded dienone **12**, which was converted into dienyne **7** upon removal of the trimethylsilyl (TMS) group (61% overall yield from **11**), setting the stage for enyne cyclization. An initial exploration of reaction conditions[9] suitable for radical pathways proved fruitless, we therefore focused on transition-metal-catalyzed reductive cyclizations.[4] Although Alder–ene cyclizations of 1,*n*-enynes have been widely applied for the construction of carbon frameworks, the reductive cyclization of cyclohexadienone-containing terminal alkynes has hardly been studied.[10] Fortunately, the desired bicyclic product **13** was obtained as a single diastereomer in 87% yield simply by subjecting **7** to $[Pd_2(dba)_3]/P(o\text{-tol})_3$ in the presence of Et_3SiH and AcOH.[11] The reasons for the stereochemical outcome, namely a *syn* relationship between the two vicinal methyl groups at the C2a and C7b positions of **13**, are unknown at this point. More detailed mechanistic studies of this transformation are currently underway in our laboratory. After rapid construction of **13**, a two-step procedure led to the installation of the quaternary center at the C5 position and delivered the bicyclic product **16** in 78% yield; this was accompanied by the formation of O-methylated **15** (15%). The latter can be recycled through hydrolysis under acidic conditions (*p*-TsOH·H_2O, see the Supporting Information). Treatment of the enone–diester **16** with Dibal-H at −78 °C resulted in regioselective reduction of the ester at the C2 position, presumably via the chelated alkoxyaluminium intermediate **17**.[12] Exposure of the resulting diol **18** to Dess–Martin periodinane afforded **6** in 76% yield over two steps.

With precursor **6** in hand, we then set out to synthesize the common intermediate **5** (Scheme 4). As expected, a Grignard reagent promoted the tandem 1,2-addition/oxa-Michael[13a,b]/



Scheme 4. Synthesis of the common intermediate (1″*E*)-**5** and ORTEP drawings of **20** and (1″*Z*)-**20**. Ellipsoids set at 40%. Reagents and conditions: a) (*E*)-2-butenyl-2-magnesium bromide, THF, −78 °C; then *N*,*N*-dimethylmethyleneiminium chloride, −78→25 °C, 80%; b) *p*-TsOH·H_2O, toluene, 60 °C, 82%. Ts = tosyl.

methylenation reaction, which proceeded smoothly to furnish tricyclic enone **23**. To the best of our knowledge, oxa-Michael reactions have seldom been developed for domino reactions, presumably because of the inherent instability of the generated enolates towards elimination or retro-Michael processes.[13c] The instability of intermediate **22** might be the driving force of the spontaneous elimination, which results in an excellent yield (80%) of **23** in the absence of any additional base.[14] The relative configuration at the C2 position was initially predicted based on a *Si*-face attack of the Grignard reagent on the aldehyde moiety of **6**. When the reaction was quenched by the addition of aqueous NH_4Cl prior to methylenation, **20** was isolated in 84% yield; the relative stereochemistry of **20** was unambiguously assigned by X-ray crystallographic analysis[15] (ORTEP drawing, Scheme 4). When the organolithium reagent derived from lithium–halogen exchange between *n*BuLi and (*E*)-2-bromobut-2-ene was employed, a mixture of the C2 epimers of **20** (42% yield, ca. 1:1 d.r.) was observed. Moreover, (1″*Z*)-**20**[15] was also synthesized using the corresponding (*Z*)-Grignard reagent in 75% yield (ORTEP drawing, Scheme 4).[16] Finally,



Scheme 5. Divergent total synthesis leading to the revised structures of indoxamycins A, C, and F. Reagents and conditions: a) $PhNTf_2$, L-Selectride (1.0 M in THF), THF, −78→25 °C, 79%; b) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, 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) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, −20 °C; f) Dibal-H (1.5 M in toluene), CH_2Cl_2, −50 °C, 84% over two steps; g) $SOCl_2$, pyridine, Et_2O, 0 °C, 97%; h) **27**, *n*BuLi, THF, 25 °C; i) $AgNO_3$, acetone/H_2O (4:1), 25 °C, 78% over two steps; j) PhSCl, Et_3N, Et_2O, 0 °C, 92%; k) $(EtO)_2P(O)CH_2CO_2Me$, 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 $PhNTf_2$ 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 $AgNO_3$[18] afforded (1″*E*)-2-*epi*-**3** in 78% yield over two steps.

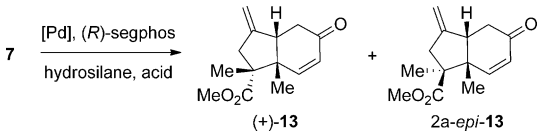
For the synthesis of indoxamycins F, we utilized the well-established sulfoxide/sulfenate rearrangement[19e–i] to invert the configuration at the C6 position of allylic alcohol **29**.[20,21] Thus, **29** was first treated with benzenesulfenyl chloride to give sulfoxide **32** in 92% yield. Pleasingly, 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 ^{13}C 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*-enynes have not been investigated thus far.[24] Inspired by Ito and Mikami et al., we employed a chiral C_2-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]	*t* [h]	(+)-**13**, 2a-*epi*-**13** Yield[b] [%]	*ee*[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 Et_3SiH (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] HCO_2H (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, $[Pd(MeCN)_4](BF_4)_2$, 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 $[Pd(MeCN)_4](BF_4)_2$ 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 stereodivergent 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.

Received: August 23, 2013
Revised: October 1, 2013
Published online: October 31, 2013

Keywords: enynes · sigmatropic rearrangement · structural elucidation · tandem reactions · total synthesis

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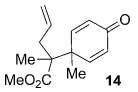
[11] By contrast, employing the classical method described in Ref. [4a], which entails the addition of AcOH over a period of hours, gave predominantly **14** by alkyne reduction.



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[12] The relative configuration of the C6 position was confirmed by detailed NOESY analysis of diol **18**.

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[15] CCDC 953500 (**20**) and 953501 [(1″*Z*)-**20**] contain 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/data_request/cif.

[16] In our earlier work, (1″*Z*)-**20** was transformed into indoxamycin A; the spectra recorded for this product did not match those reported for natural indoxamycin A.

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[20] Olefination and saponification of **29** afforded products with spectroscopic data that are inconsistent with those reported for natural indoxamycin F. Careful reexamination of the NMR data revealed that the configuration at the C6 carbon atom had been assigned incorrectly. The revised structure was confirmed by detailed NOESY analysis of both compound **29** and synthetic indoxamycin F ((1″*E*)-2,6-di-*epi*-**4**).

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