Natural Product Synthesis

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Total Synthesis and Stereochemical Reassignment of (±)-Indoxamycin B**

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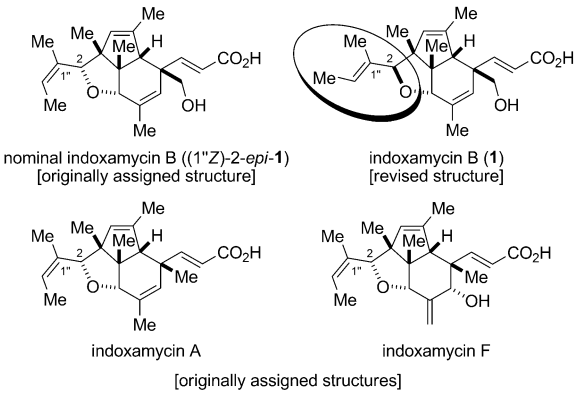
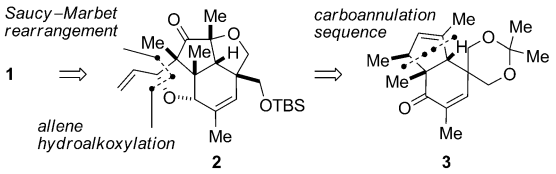
The order Actinomycetales includes Gram-positive microorganisms that have been a rich source of biologically active compounds, yielding more than 50% of all microbial antibiotics discovered to date.[1] Over the last five decades most small-molecule discovery efforts have focused on bacteria of terrestrial origin. However, microbes from aquatic environments have recently gained in importance as a source of structurally diverse natural products.[2] In 2009 a research group in Japan isolated a novel class of polyketides, subsequently named indoxamycins, from saline cultures of marine-derived actinomycetes (Scheme 1). Within this



Scheme 1. Originally assigned structures of indoxamycins A, B, and F. Revised structure of indoxamycin B.

family, indoxamycins A and F have been shown to display growth inhibition against HT-29 tumor cell lines (IC_{50} = 0.59 μM and 0.31 μM, respectively).[3] Their biological activity in conjunction with the highly congested and stereochemically dense core render the indoxamycins notable as targets for synthetic studies. Herein, we report a total synthesis of (±)-indoxamycin B (**1**), which is not only the first synthesis of a member of this unprecedented structural class, but has also led to the stereochemical reassignment of the natural product.

The unique tricyclic carbon skeleton common to the indoxamycins bears six contiguous asymmetric centers, an α,β-unsaturated carboxylic acid side chain, and a trisubstituted alkene appendage. Three of the six stereogenic centers are quaternary, of which two are vicinal. As outlined in Scheme 2, the synthetic strategy envisioned relies on the



Scheme 2. Retrosynthetic analysis of indoxamycin B.

implementation of a number of key transformations, including a Saucy–Marbet (propargyl Claisen) rearrangement, which is followed by an allene hydroalkoxylation to install the embedded tetrahydrofuran. Furthermore, an oxidative carboannulation sequence would be employed to construct the key dihydroindenone core in **3** from a C_{2v}-symmetric cyclohexa-2,5-dienone precursor.

The synthesis commenced with commercially available methyl 3,5-dimethylbenzoate (**4**), which was converted to cyclohexa-2,5-dienone **5** in four steps and 59% overall yield (Scheme 3). In preliminary investigations, **5** proved reluctant to undergo conjugate addition, which led to the examination of alternatives, such as ketone crotylation followed by anionic oxy-Cope rearrangement. The conditions identified for ketone addition involved treatment of **5** with a 1,3-dimethylallyltitanocene reagent generated in situ from (*E*)-4-methoxypent-2-ene (**6**) and $[Cp_2TiCl_2]$/*n*BuLi.[4] Tertiary alcohol **7** was thus isolated in 62% yield as a 3.8:1 mixture of olefin diastereomers, as determined by ^{1}H NMR spectroscopy. Exposure of **7** to *t*BuOK/[18]crown-6 led to its participation in a [3,3]-sigmatropic rearrangement to furnish the corresponding ketone enolate, which was trapped with Et_3SiCl to afford **8** (70%). Enolsilane **8** readily underwent oxidative cyclization to give dihydroindenone **3** in 74% yield upon exposure to $Pd(OAc)_2$ (10 mol%) in DMSO with O_2 as a terminal oxidant.[5]

With a reliable route to dihydroindenone **3** established, the full elaboration of the highly congested core could be addressed (Scheme 4). Following hydrolysis of acetonide **3** (aq HCl, THF), the 1,3-diol produced was subjected to vanadium-catalyzed epoxidation conditions. In the experiment, a tandem reaction was observed wherein the intermediate epoxide underwent a group-selective intramolecular

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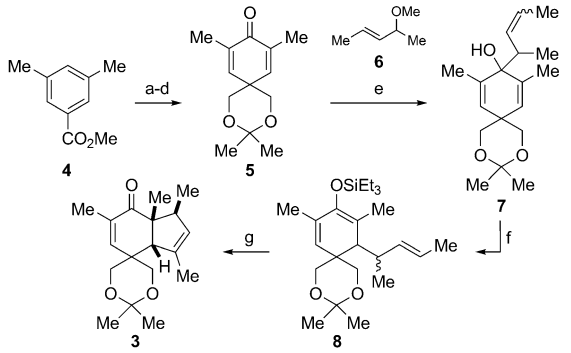
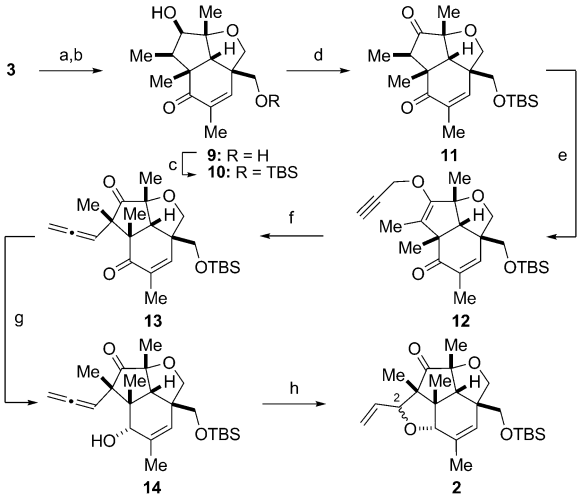


Scheme 3. Reagents and conditions: a) Li (2.2 equiv), *t*BuOH (1.05 equiv), NH_3/THF, −78 °C; then $ICH_2OC(O)tBu$ (1.0 equiv), −78 °C; b) $LiAlH_4$ (1.5 equiv), THF, 0 °C; c) TsOH (10 mol %), $Me_2C(OMe)_2$, RT, 96% over 3 steps; d) Pd/C (10 wt %, 2.5 mol %), *t*BuOOH (2.5 equiv), K_2CO_3 (0.25 equiv), CH_2Cl_2, 0 °C, 61 %; e) $[Cp_2TiCl_2]$ (3.0 equiv), *n*BuLi (6.0 equiv), (*E*)-4-methoxypent-2-ene (**6**) (1.5 equiv), THF, −78 °C to RT; then **5**, −40 °C to 10 °C, 3.8:1 ratio of olefin diasteromers, 62 %; f) *t*BuOK (3.0 equiv), [18]crown-6 (3.0 equiv), THF, −78 °C to −40 °C, then Et_3SiCl (3.0 equiv), −78 °C, d.r. = 3.6:1, 70 %; g) $Pd(OAc)_2$ (10 mol %), O_2 atmosphere, Me_2SO, 45 °C, 74 %. Cp = cyclopentadienyl, TsOH = *p*-toluenesulfonic acid.

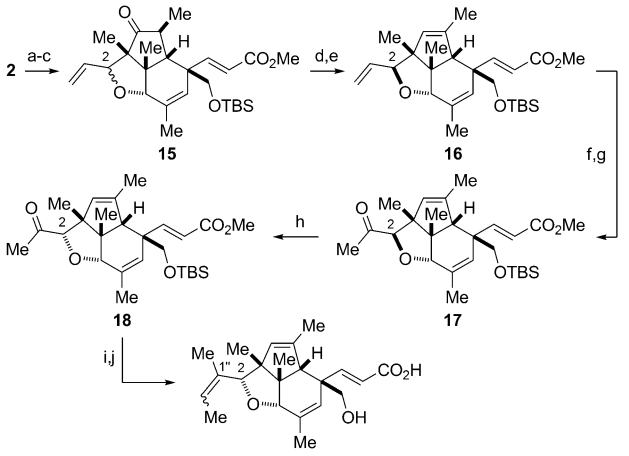


Scheme 4. Reagents and conditions: a) HCl (aq, 1.0 M, 2.9 equiv), THF, RT, quant; b) $[VO(acac)_2]$ (5 mol %), *t*BuOOH (3.0 equiv), 4,4′-thiobis(2-*tert*-butyl-5-methylphenol) (2.5 mol %), 4 Å M.S., CH_2Cl_2, 40 °C, 75 %; c) $tBuMe_2SiCl$ (1.2 equiv), NEt_3 (2.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C to RT, 88 %; d) DMP (1.5 equiv), CH_2Cl_2, 0 °C to RT, 95 %; e) KH (1.1 equiv), THF, RT; then [18]crown-6 (1.5 equiv), propargyl bromide (1.2 equiv), 0 °C, 87 %; f) $[(Ph_3PAu)_3O]BF_4$ (1 mol %), 1,2-dichloroethane, 75 °C, 84 %; g) $LiBHEt_3$ (1.1 equiv), THF, −78 °C, 80 %; h) chloro[2-(di-*tert*-butylphosphino)biphenyl]gold(I) (10 mol %), AgOTs (10 mol %), PhMe, 60 °C, d.r. = 3.2:1, 72 %. acac = acetylacetonato, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, M.S. = molecular sieves.

ring opening, affording **9** in 75 % yield.[6–8] The primary hydroxy group in **9** was then selectively protected as a silyl ether ($tBuMe_2SiCl$, NEt_3, DMAP, 88 %), and the remaining secondary alcohol in **10** was oxidized to afford ketone **11** (DMP, 95 %).[9] O-alkylation of the potassium enolate of **11** with propargyl bromide in the presence of [18]crown-6 furnished propargyl vinyl ether **12** in 87 % yield. Attempts at conducting the Saucy–Marbet rearrangement at elevated temperatures (160 °C, *o*-xylene) failed to give the desired product. Gratifyingly, the rearrangement was observed to proceed through the use of the trinuclear Au^I-oxo complex $[(Ph_3PAu)_3O]BF_4$ as catalyst (1 mol %), yielding allene **13** as the only detectable diastereomer (84 %) by ^1H NMR spectroscopy.[10] Chemo- and diastereoselective reduction of the cyclohexenone carbonyl in **13** was accomplished with $LiBEt_3H$, giving alcohol **14** in 80 % yield. The formation of the tetrahydrofuran ring of the indoxamycin framework was then achieved through an intramolecular Au^I-catalyzed hydroalkoxylation of allene **14**, to form tetracyclic intermediate **2** as a 3.2:1 mixture of inseparable diastereomers at C(2) (72 %).[11]

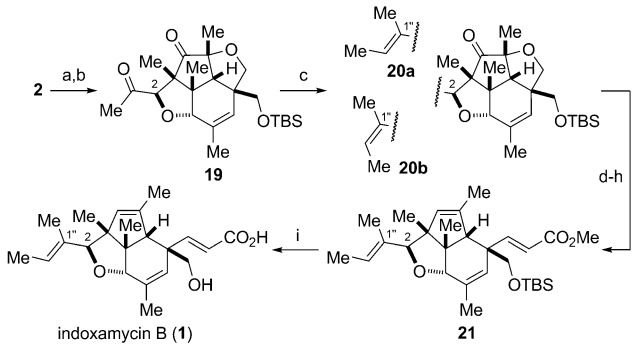
Reductive cleavage of the α-keto ether (SmI_2, THF/MeOH) in cyclopentanone **2** released a primary alcohol, which was oxidized to the corresponding aldehyde (DMP, 97 %; Scheme 5). The latter was subjected to Horner–Wadsworth–Emmons olefination delivering the α,β-unsaturated ester **15** in 92 % yield. Chemoselective reduction of the ketone in **15** ($BH_3{\cdot}NH_2tBu$, CH_2Cl_2, reflux) furnished the corresponding secondary alcohol (88 %),[12] which was exposed to Burgess' reagent, yielding cyclopentene **16** in 44 % yield.[13] It was envisioned that the conversion of the terminal olefin in **16** to the corresponding methyl ketone **17** would not only set the stage for the introduction of the trisubstituted (*Z*)-olefin side chain but also provide the opportunity for C(2) epimerization to arrive at the reported structure of indoxamycin B ((1″*Z*)-2-*epi*-**1**). Accordingly, **16** was taken forward in a two-step sequence involving regioselective hydration ($[Mn(dpm)_3]$ (10 mol %), $PhSiH_3$, O_2, d.r. = 1:1, 49 %),[14,15] followed by oxidation of the intermediate secondary alcohols (DMP, 85 %). The resulting methyl ketone **17** was exposed to equilibration conditions (DBU, toluene, 100 °C) to obtain a 6:1 mixture of C(2) epimers, favoring **18**. Separation by chromatography on silica gel furnished **18** in 58 % yield. When **18** was subjected to Wittig olefination, a 1.6:1 mixture of olefin isomers was obtained (70 %), which could not be separated. Sequential deprotection of this mixture was effected by ester saponification (aq LiOH) followed by addition of aq HCl to attain removal of the silyl protective group. Surprisingly, neither olefin isomer obtained displayed spectral properties (^1H and ^{13}C NMR) that matched those reported for the natural product. Careful reexamination of the published NMR data (including NOESY spectra) of several members of the indoxamycin family of natural products led to the conclusion that the relative configuration at C(2) had been misassigned.[3a] Furthermore, there was considerable ambiguity regarding the geometry of the trisubstituted olefin side chain. We subsequently targeted the revised structures (1″*E*/*Z*)-**1** for synthesis.

In contrast to the route previously discussed for the conversion of **2** to (1″*E*/*Z*)-2-*epi*-**1** (Scheme 5), it seemed prudent to install the side chain at C(2) prior to manipulation of the cyclopentane ring in order to compare the spectroscopic properties of olefins **20a** and **20b** with those of the natural product. Accordingly, tetracycle **2** was subjected to



Scheme 5. Reagents and conditions: a) SmI_2 (1.0 equiv), THF/MeOH, RT, d.r. = 3.2:1, quant; b) DMP (1.25 equiv), CH_2Cl_2, 0 °C to RT, d.r. = 3.8:1, 97%; c) methyl diethylphosphonoacetate (5.0 equiv), NaH (5.0 equiv), THF, RT, d.r. = 3.6:1, 92%; d) $BH_3{\cdot}t$BuNH$_2$ (2.0 equiv), CH_2Cl_2, 40 °C, d.r. = 9:1, 88%; e) Burgess' reagent (2.0 equiv), PhMe, 110 °C, 44%; f) Mn(dpm)$_3$ (10 mol%), $PhSiH_3$ (2.5 equiv), O_2 atmosphere, EtOH, RT, d.r. = 1:1, 49%; g) DMP (2.0 equiv), CH_2Cl_2; 0 °C to RT, 85%. h) DBU (5.0 equiv), PhMe, 100 °C, 58%; i) Ph_3PEtBr (6.0 equiv), KN(SiMe$_3$)$_2$ (5.0 equiv), THF/DMPU, RT, −78 °C to 0 °C, 1:1.6 ratio of olefin isomers, 70%; j) LiOH (18 equiv); then HCl (aq, 1.0 M, 53 equiv), THF/MeOH/H_2O, RT, 73%. dpm = 2,2,6,6-tetramethyl-3,5-heptanedionato, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

the hydration–oxidation protocol disclosed earlier to provide methyl ketone **19** as a single diastereomer at C(2) (53% over 2 steps; Scheme 6).[16] Wittig olefination of **19** under the conditions disclosed by Still proved capricious, giving **20a** and **20b** in a wide range of selectivity (2.5:1 to 15:1),[17,18] with the olefin configuration unambiguously secured by NMR spectroscopic experiments after separation by chromatography on silica gel (NOESY analysis: see the Supporting Information). The similarity of the ^{1}H NMR resonances of diastereomer **20a** to those reported for natural indoxamycin B led to the hypothesis that the natural product has the structure shown for **1** in Scheme 1.



Scheme 6. Reagents and conditions: a) [Mn(dpm)$_3$] (10 mol%), $PhSiH_3$ (2.5 equiv), O_2 atmosphere, EtOH, RT, d.r. = 1:1, 73%; b) DMP (1.5 equiv), CH_2Cl_2; 0 °C to RT, 72%; c) Ph_3PEtBr (6.0 equiv), KN(SiMe$_3$)$_2$ (5.0 equiv), THF/HMPA (10:1), RT, −78 °C to −30 °C, 2.5:1–15:1 ratio of olefin isomers, 80%; d) SmI_2 (1.0 equiv), THF/MeOH (7:3); RT, 99%; e) DMP (1.25 equiv), CH_2Cl_2; 0 °C to RT, quant; f) methyl diethylphosphonoacetate (5.0 equiv), NaH (5.0 equiv), THF, RT, 99%; g) $BH_3{\cdot}t$BuNH$_2$ (2.0 equiv), CH_2Cl_2, 40 °C, 79%; h) Burgess' reagent (2.0 equiv), PhMe, 110 °C, 69%; i) LiOH (10 equiv), then HCl (aq, 1.0 M, 29 equiv), THF/MeOH/H_2O, RT, 96%. HMPA = $(Me_2N)_3PO$.

Olefin **20a** was advanced by employing the sequence described for the conversion of **2** to **15** (steps a–c; Scheme 5) to furnish the corresponding enoate in 98% overall yield. The introduction of the unsaturation in the five-membered ring proceeded in 55% yield over two steps, following the analogous reduction–dehydration protocol (steps d and e; Scheme 5). Deprotection of **21** afforded carboxylic acid **1** in 96% yield, which, after conversion to the corresponding potassium salt, exhibited ^{1}H and ^{13}C NMR spectra identical in all respects to those reported for natural indoxamycin B.[19]

In conclusion we have described the first total synthesis (±)-indoxamycin B (**1**), which has culminated in the structural reassignment of the natural product. The synthetic strategy is based on the use of a highly symmetric cyclohexa-2,5-dienone precursor and relies on a series of modern metal-catalyzed reactions to construct the tricyclic core framework. The salient features of the route include an efficient carboannulation sequence involving a Ti-mediated ketone crotylation and anionic oxy-Cope rearrangement, as well as a Pd-catalyzed oxidative cycloalkenylation reaction to rapidly access the key dihydroindenone intermediate. Moreover, a highly diastereoselective vanadium-catalyzed tandem reaction and a series of Au^I-catalyzed transformations (Saucy–Marbet rearrangement and allene hydroalkoxylation) allow for elaboration of the sterically congested scaffold. We propose that the structural revision for indoxamycin B ((1″*Z*)-2-*epi*-**1** to **1**) described herein is also valid for the other members of the natural product family, but validation of this hypothesis awaits additional experimentation. Efforts to expand the described strategy to the synthesis of other indoxamycins are subject of current research in our laboratories and will be reported in due course.

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[16] After hydration of **2**, the pair of alcohols C(1″)-*R**/C(2)-*R** and C(1″)-*S**/C(2)-*R** was separated from diastereomers C(1″)-*R**/C(2)-*S** and C(1″)-*S**/C(2)-*S** by chromatography on silica gel to furnish an inconsequential 1:1 mixture of C(1″) epimers that were subsequently oxidized to the corresponding ketone (see the Supporting Information).

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[18] Preferential formation of diastereomer **20a** stands in contrast to the expected product on the basis of the substrates examined by Still. However, the presence of a bishomoallylic ketone in the substrates in this study may be responsible for the observed outcome.

[19] We note that the ^{1}H and ^{13}C NMR spectra for synthetic **1** obtained from purification by preparative TLC (as previously described for the natural product) did not match those reported, albeit the observed differences in the resonances were minor (^{1}H: $|\Delta\delta| \leq 0.33$ ppm; ^{13}C: $|\Delta\delta| \leq 6.5$ ppm). However, incremental addition of 1.0 equiv of CD_3OK to a solution of **1** in CD_3OD led to a new set of signals in the ^{1}H and ^{13}C NMR spectra that were in full accordance with the reported data for the natural product (see the Supporting Information).

