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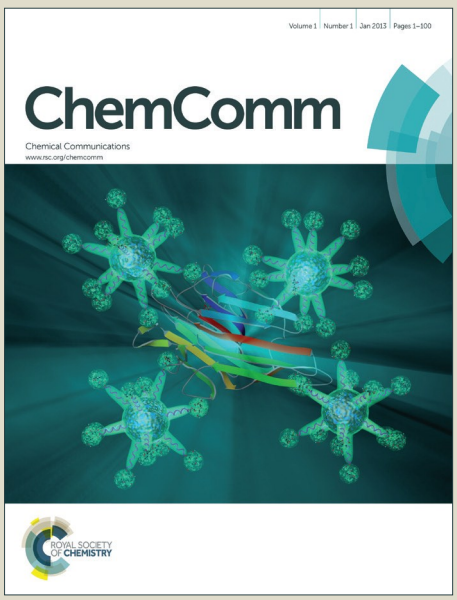

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Total Syntheses of (±)-Spiroindimicins B and C Enabled by a Late-Stage Schöllkopf-Magnus-Barton-Zard (SMBZ) Reaction

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The spiroindimicins are a family of structurally unprecedented alkaloids isolated from the deep-sea-derived marine actinomycete *Streptomyces* sp. SCSIO 03032. The total syntheses of (±)-spiroindimicins B and C are disclosed, the first of any member of this family. Central to the successful strategy was installing the spirocentre using a mild intramolecular Heck reaction, the assembly of a pentacyclic spirobisindole by Fischer indolization and a late-stage Schöllkopf-Magnus-Barton-Zard (SMBZ) reaction to construct the trisubstituted pyrrole.

Deep-sea organisms have evolved to survive under their extreme environment by adapting a wide range of their biochemical processes and metabolic pathways, often assembling secondary metabolites that are structurally distinct to those produced by organisms dwelling in shallow waters.[1] A pertinent example is the deep-sea-derived marine actinomycete *Streptomyces* sp. SCSIO 03032, which produces a range of structurally unprecedented natural products[2] including spiroindimicins A-D (**1**-**4**),[3] dichlorinated bisindole alkaloids possessing unique heteroaromatic frameworks featuring [5,6] (**1**) or [5,5] (**2**-**4**) spiro-rings (Fig. 1). Biological evaluation revealed **2**-**4** are moderately cytotoxic to various cancer cell lines (IC_{50} ranging from 4 to 12 μg/mL), with **1** showing no activity.

The combination of an ongoing interest in bisindole alkaloids[4] and the unprecedented molecular architecture present in the the spiroindimicins led us to instigate a program pursuing their syntheses, initially geared towards the [5,5]-spiroindimicins B (**2**) and C (**3**) (Scheme 1). Spiroindimicin B (**2**) will be available by methylation of spiroindimicin C (**3**), itself secured by the late-stage construction of the pyrrole ring from heteroannulation[5] of vinylsulfone **5** with methyl isocyanoacetate according to Magnus,[5a] a mechanistically identical procedure to the Schöllkopf-Barton-Zard reaction.[6,7] The vinylsulfone **5** will be obtained by oxidation of the vinylsulfide resulting from subjecting ketone **6** to Mukaiyama's protocol,[8] which in turn is available from the Yonemitsu oxidation[9] of spirobisindole **7**. A Fischer indolization is to be used to construct the spirobisindole **7** from spiroindolinyl pentanone **8**, the all-carbon spirocentre in which will be installed by an intramolecular reductive Heck cyclization[10] of **9**, itself acquired by alkylation of iodoaniline **10** with bromide **11**.

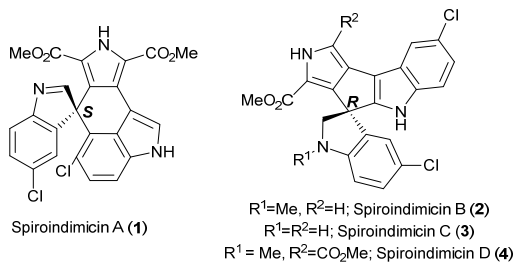
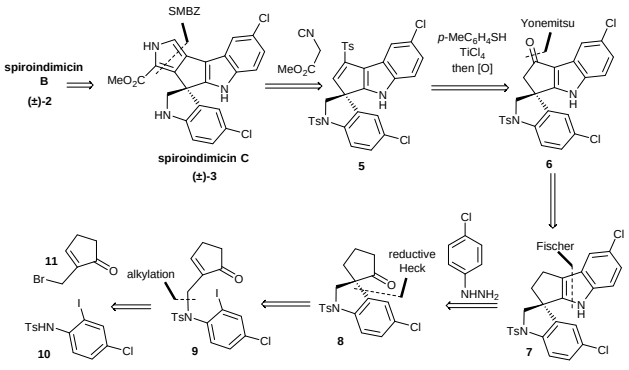


Fig. 1 Spiroindimicins A-D (**1**-**4**).



Scheme 1. Retrosynthesis of spiroindimicins B (±)-**2** and C (±)-**3**; Ts = *p*-toluenesulfonyl.

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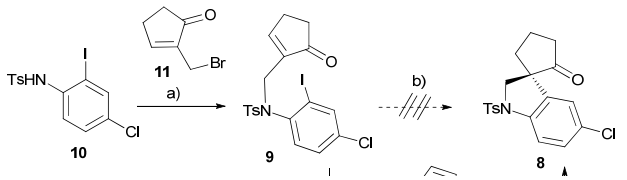
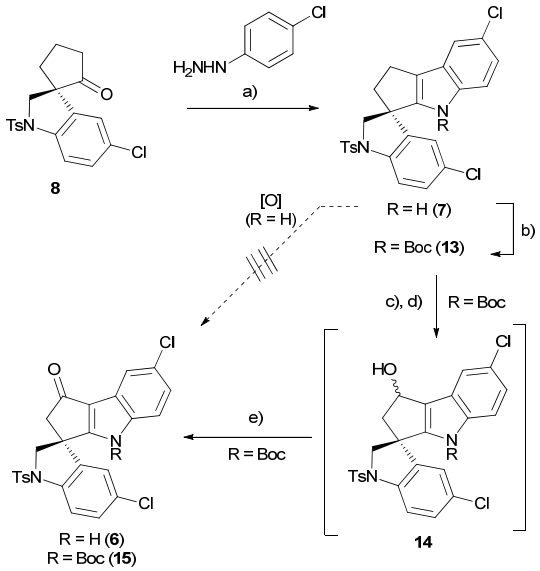
The first task was to assemble the intramolecular Heck precursor **9** (Scheme 2). The alkylation of iodoaniline **10**[11] with bromide **11**[12] proceeded through the S_N2 pathway[13] to give the desired product **9**. Upon subjecting **9** to reductive Heck conditions (HCO_2Na as the hydride source), the spiroindolinyl pentenone **(±)-12** was formed, the result of a 'normal' Heck reaction and migration of the double bond. The formation of 'normal' Heck products under reductive conditions is due to rapid *syn*-β-hydride elimination occurring before the reduction step,[4d,14] with isomerization of the double bond resulting from reinsertion of the hydridopalladium species into the alkene and subsequent migration.[15,16] Interestingly, silver nitrate[17] could be added to the reductive conditions to increase the yield of **(±)-12** (63% vs 93%). In this case, the double bond was not required and **(±)-12** was readily hydrogenated to **8** in excellent yield.

With the spiroindolinyl pentanone **8** in hand, the stage was set for the critical Fischer indolization (Scheme 3). Upon heating a solution of **8** and 4-chlorophenylhydrazine in acetic acid to reflux, the spirobisindole **7** was obtained in excellent yield, demonstrating the timeless utility of this classic reaction in complex natural product synthesis.[18] The spirobisindole **7** resisted conversion to ketone **6** under classic Yonemitsu oxidation conditions[9] (DDQ, THF-H_2O, RT to reflux), leaving the substrate **7** untouched and an alternative bromination-hydrolysis strategy was performed accordingly.[19] *N*-Protection of **7** gave **13** which upon radical bromination followed by immediate hydrolysis gave alcohol **14** (inconsequential mixture of diastereomers) that was oxidized to ketone **15** (69% over 3 steps from **13**).

Attention then turned to the conversion of ketone **15** to the SMBZ precursor, with the initial plan to convert ketone **15** to the vinylsulfide[8] that upon oxidation would deliver the vinylsulfone **16** (Scheme 4). Although the conditions from the initial report[8] (1 equiv. $TiCl_4$, 2 equiv. Et_3N, 1.1 equiv. thiol) failed to effect any reaction on ketone **15**, when an excess of each reagent was employed the thioketal **17** was formed, which underwent oxidation-elimination[20] to give a mixture of vinylsulfone **16** and vinylsulfoxide **18** (1.3:1), with extended reaction times and additional oxidant failing to drive the reaction to completion. The critical SMBZ reaction[5] of **16** with methyl isocyanoacetate proceeded smoothly to give **19**, securing the complete heteroaromatic framework of the [5,5]-spiroindimicins, as confirmed by X-ray analysis.[21] Although the



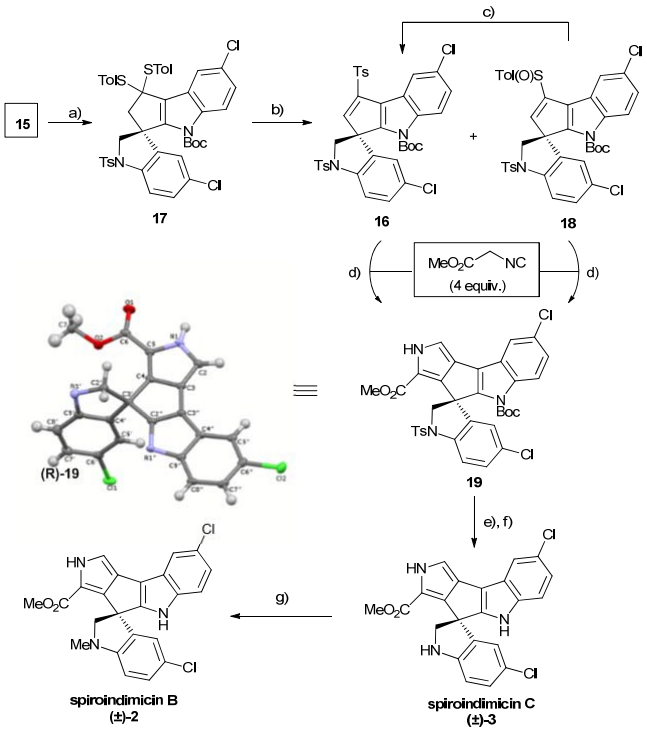
Scheme 2. Constructing the spirocentre; Reagents and conditions: a) NaH, TBAI, THF, 0 °C to RT, 3 h; 81%; b) $Pd(OAc)_2$ (20 mol %), HCO_2Na, TBAC, $AgNO_3$, NMP, RT, 3 h; 93%; c) Pd/C (10 mol %), H_2 (balloon), EtOAc, RT, 1 h; 99%. TBAI = tetra-*n*-butylammonium iodide, TBAC = tetra-*n*-butylammonium chloride hydrate, Ts = *p*-toluenesulfonyl.



Scheme 3. Fischer indolization and ketone formation; Reagents and conditions: a) AcOH, 110 °C, 40 h; 75% of **7**; b) Boc_2O, DMAP, THF, RT, 1 h; 96%; c) NBS, AIBN (5 mol %), CCl_4, 65 °C, 2 h; d) THF-aq. $NaHCO_3$ (3:1), RT, 1 h; e) MnO_2, CH_2Cl_2, RT, 16 h; 69% over 3 steps. Boc_2O = di-*tert*-butyl dicarbonate, DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, AIBN = azobisisobutyronitrile, Ts = *p*-toluenesulfonyl.

vinylsulfoxide **18** could be oxidized to the vinylsulfone **16**, it was itself a viable substrate[22] for the SMBZ reaction (31% of **19**). Removal of the protecting groups from **19** proceeded without incident to give spiroindimicin C **(±)-3**, which upon reductive amination delivered spiroindimicin B **(±)-2**. The spectroscopic data for the synthetic samples of spiroindimicins B and C were in agreement with the literature data[3,23] and with authentic samples of the natural products.[23]

In summary, the first total syntheses of spiroindimicins B and C have been achieved, which serve to confirm the unique heteroaromatic structure of these deep-sea derived natural products. Some observations with implications beyond this synthetic study include: 1) construction of all carbon spirocentre using an intramolecular Heck reaction under mild, reductive conditions promoted by silver(I); 2) successful application of the Fischer indolization to construct a pentacyclic spirobisindole; 3) a late-stage SMBZ reaction using both a vinyl sulfoxide and a vinyl sulfone to form a trisubstituted pyrrole.



Scheme 4. Total syntheses of spiroindimicins B and C by late-stage SMBZ reaction, with X-ray crystal structure of **19** (*N*-protecting groups omitted for clarity); Reagents and conditions: a) $TiCl_4$ (3 equiv.), Et_3N (10 equiv.), 4-methylbenzenethiol (3.7 equiv), RT, 2 h; 78%; b) *m*-chloroperbenzoic acid (5 equiv.), K_2CO_3 (excess), CH_2Cl_2, 0 °C to reflux, 24 h; 70% (**16**:**18** = 1.3:1); c) *m*-chloroperbenzoic acid (1.1 equiv), K_2CO_3 (1.5 equiv), CH_2Cl_2, RT, 3 h; 70%; d) potassium *tert*-butoxide (4 equiv.), THF, 0 °C to RT; 62% from **16**, 31% from **18**; e) sodium naphthalenide, THF, -78 °C, 15 min; f) $AlCl_3$, CH_2Cl_2, RT, 30 min; 67% over 2 steps; g) 37% aq. formaldehyde, $NaBH_3CN$, AcOH, MeOH, RT, 15 min; 92%. STol = *p*-toluenesulfenyl, S(O)Tol = *p*-toluenesulfinyl, Ts = *p*-toluenesulfonyl.

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