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Tackling the Spiro Tetracyclic Skeleton of Cyanogramide: Incorporation of a Hydantoin Moiety

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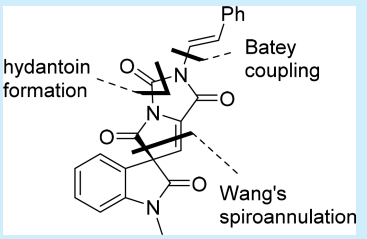
Supporting Information

ABSTRACT: Wang's enantioselective thiourea-catalyzed spiro-annulation paved the way to the first tetracyclic analog of the marine natural product cyanogramide from the actinobacterium *Actinoalloteichus cyanogriseus*. The synthesis comprises seven steps starting from an alkylidene indolinone. Installation of the (*E*)-styryl side chain faced a regiochemistry problem, circumvented by prior conversion to the hydantoin and employing Batey's conditions. Comparison of the ECD spectra of the spiro indoline pyrrolo[1,2-*c*]imidazole and cyanogramide confirmed the absolute configuration of the natural product.

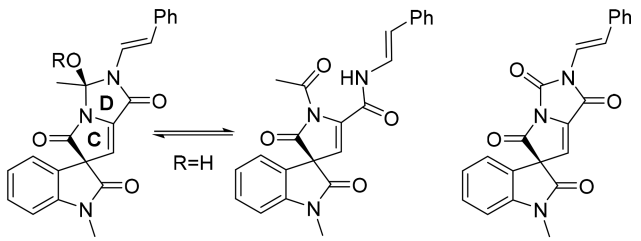


The marine indole alkaloid cyanogramide (**1**, Scheme 1) was isolated from the marine-derived actinobacterium *Actinoalloteichus cyanogriseus* by Weiming Zhu et al. in 2014.[1] The molecule features a pyrrolo[1,2-*c*]imidazole system, which is spiro-fused to an oxindole. Cyanogramide (**1**) is the only natural product exhibiting that tetracyclic partial structure. Besides, only a few tetracyclic structures are known that share the tricyclic spiro[indoline-3,3′-pyrrole]dione moiety with compound **1**. In all cases, an oxazolidine ring is annulated instead of the imidazolinone of cyanogramide (**1**).[2−4] Only one molecule has been described that contains the double bond present in ring C of cyanogramide.[5] While cyanogramide (**1**) showed only weak cytotoxicity against the adriamycin- and vincristine-resistant cancer cell lines, it reversed their resistance against adriamycin and vincristine at 5 μM concentration. This effect was attributed to inhibition of the P-glycoprotein, an ATP dependent drug efflux pump highly expressed in the tested cell lines, by cyanogramide (**1**).[1]

Initially, we expected that the pyrrolo[1,2-*c*]imidazole-1,5-dione system of cyanogramide (**1**, rings C and D, Scheme 1) could be accessed by cyclization of an *N*-acetylated, pyrrolone carboxamide-based precursor **3**, being in equilibrium with aminal ester **2**. We also included the related tetracyclic compound **4**, where the C_2 unit of cyanogramide is replaced by a carbonyl group. The resulting hydantoin moiety of **4** could be more stable than ring D of the putative, demethylated cyanogramide derivative **2**. The styryl side chain was to be introduced by Cu-mediated N−C coupling.

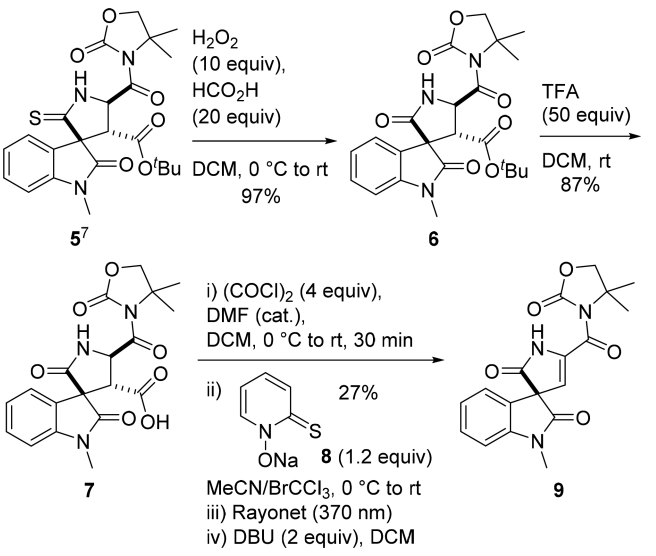
For studies toward **3**, we chose racemic 3,3′-thiopyrrolidonyl spiro-oxindole **5**, the ethyl ester analog of which had been obtained by Jiangtao Sun et al.[6] and by Rui Wang et al.[7] by Michael addition/cyclization of α-isothiocyanato imides to 2-oxoindolin-3-ylidene acetates in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, Scheme 2; see the Supporting

Scheme 1. Spiro-indolone Alkaloid Cyanogramide (1) from the Marine-Derived Bacterium *Actinoalloteichus cyanogriseus*, Putative Synthetic Precursors



1: cyanogramide (R=CH_3)
2: R=H
3
4

Scheme 2. Synthesis of Spiro-indolone Pyrrolone 9 from Spiro-thiolactam 5



5[7]
6
7
9

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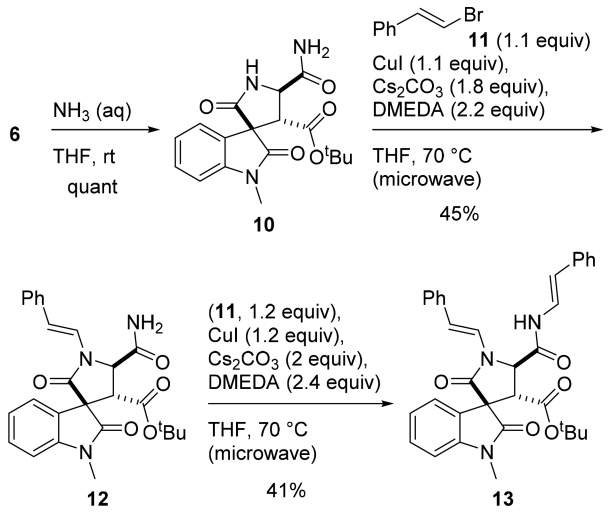
Information). It was possible to convert spiro-pyrrolidine-2-thione **5** to the corresponding lactam **6** by treatment with H_2O_2/HCO_2H (97%), followed by conversion to carboxylic acid **7** with TFA (trifluoroacetic acid). For the subsequent Barton decarboxylation we were inspired by Williams' synthesis of spirotryprostatin B and derivatives.[8] Decarboxylation of **7** by formation of the acid chloride, in situ conversion to the Barton ester, reaction with $BrCCl_3$ under irradiation conditions,[8] and reaction with DBU afforded the α,β-unsaturated spiro-indolone pyrrolone **9** in modest yield (27%), which was difficult to purify. All our attempts to subject **9** to ammonolysis led to decomposition, which led us to abandon that pathway.

As long as the ester moiety was in place, ammonolysis of **6** was facile and afforded pyrrolidinone carboxamide **10** (Scheme 3). Buchwald coupling of **10** with (*E*)-β-bromostyrene (**11**)

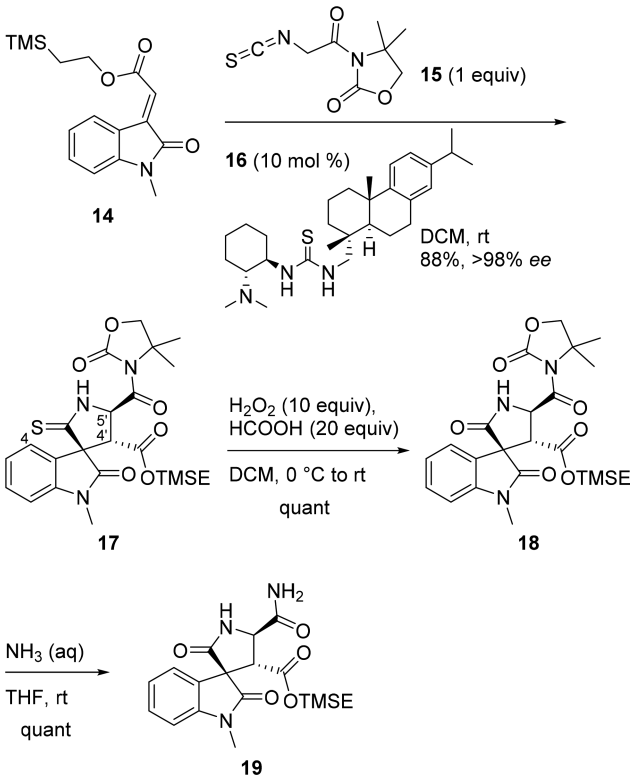
Scheme 3. Study on the Relative Reactivity of the Lactam and Primary Amide Nitrogen Atoms towards Buchwald Coupling, Starting from Spiro-indolone 6



under microwave conditions with elevated amounts of CuI (1.1 equiv)/DMEDA (*N*,*N*′-dimethylethylenediamine, 2.2 equiv), as applied in our synthesis of parazoanthine F,[9] resulted in the formation of the undesired *N*-styryllactam **12** (45%). The primary amide moiety had remained in place. To check the general availability of the primary amide moiety for Buchwald coupling, we reacted **12** again and obtained bis-styryl product **13** in moderate yield (41%). Thus, both functional groups did react, but not in the desired order, and the lactam nitrogen had to be functionalized before Buchwald coupling.

For further experiments, we replaced the *tert.*-butyl ester by a TMSE ((trimethylsilyl)ethyl) ester function, because the *tert*-butyl group had shown some instability. We also switched to the optically active series. TMSE ester **14** (Scheme 4) was obtained by Wittig reaction of *N*-methylisatin and the corresponding acetic acid based phosphorane (see the Supporting Information). Reaction of **14** with isothiocyanato compound **15**[10] in the presence of chiral organocatalyst **16**[7] afforded spiro-indolinone **17** in high yield (88%) and perfect *ee* (Scheme 4, >98%, as judged by analytical HPLC; see the Supporting Information). The relative configuration of product **17** was derived from an intense NOESY correlation between 5′-H and 4-H of the indolone.

Scheme 4. Synthesis of TMSE-Protected Spiro-pyrrolidinone Carboxamide 19 via Thiourea-Catalyzed Michael Addition/Cyclization



The optical rotatory power of **17** ($[\alpha]_D^{20} = -33.6$, $c = 1.0$) corresponds well to values reported by Wang et al. for similar compounds. Oxidative hydrolysis of **17** afforded lactam **18**, followed by ammonolysis to TMSE ester **19**.

As concluded from the behavior of spiro-pyrrolone carboxamide **10** (Scheme 3), regioselective *N*-styrylation would require protection of the lactam nitrogen, ideally by acetylation. Thus, we attempted the acetylation of lactam **19** (Scheme 5). Acetylated product **20** was obtained regioselectively in quantitative yield. The constitution of **20** was secured by an HMBC correlation of the α-hydrogen 5′-H and the acetyl carbonyl carbon. Heating of **19** under reflux with 10 equiv of Ac_2O led to double *N*-acetylation affording **24** (82%). However, there was no tendency of **20** or **24** to undergo cyclization to a 2-hydroxy-2-methylimidazolidin-4-one, which would correspond to the core structure of cyanogramide (**1**).

Surprisingly, Buchwald coupling of *N*-acetylated lactam **20** with bromostyrene **11** did not occur at the free primary amide moiety. Instead, we isolated compound **21** (Scheme 5), where the acetyl was replaced by the styryl group. Apparently, the acetyl group was cleaved off by Cs_2CO_3 that preceded the N–C coupling. Even under Batey's conditions[11] employing potassium styryl trifluoroborate (**22**)/$Cu(OAc)_2/O_2$ we observed undesired styrylation of the lactam nitrogen. Differing from **21**, the acetyl group had migrated to the neighboring primary amide resulting in compound **23**. All attempts to install a styryl unit at the diacetylated tricycle **24** under either Buchwald's or Batey's conditions failed.

We concluded that the fourth ring of the cyanogramide skeleton had to be formed prior to styrylation and, given our observation with the acetyl group, introduced a C_1 instead of a C_2 unit. While treatment of lactam-carboxamide **19** with

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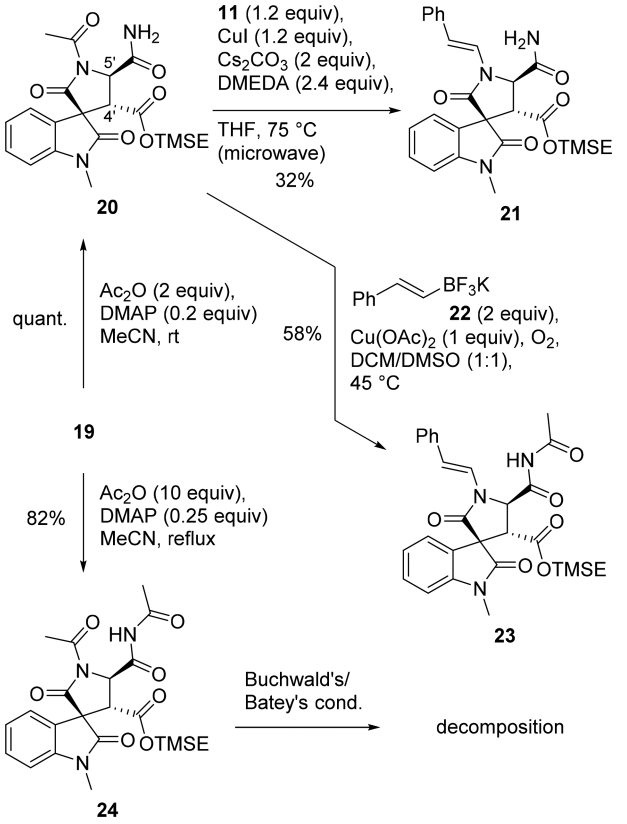
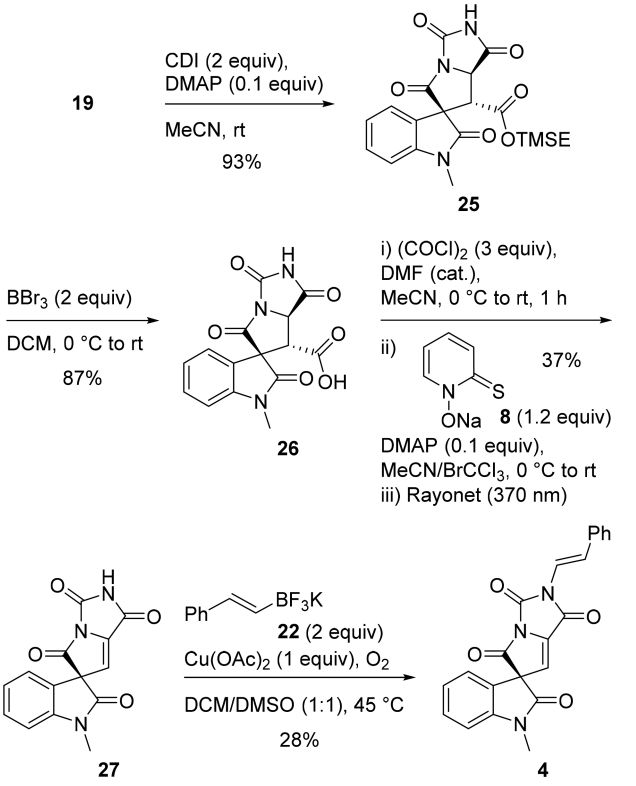
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Reaction of Mono- or Diacetylated Spiro-indoles 20 and 24 under Buchwald's and Batey's Conditions, Leading to Deacetylation or Acetyl Shift, Respectively, and Styrylation at the Lactam Nitrogen



Scheme 6. Synthesis of Cyanogramide Analog 4 Containing a Hydantoin Partial Structure



trimethylorthoacetate was unsuccessful, CDI (carbonyldiimidazole)/DMAP (*N*,*N*-dimethylaminopyridine) afforded tetracyclic hydantoin **25** in very good yield (93%) without epimerization (Scheme 6). With thiocarbonyldiimidazole we obtained a smaller yield (72%) and observed partial epimerization at C5′. The TMSE protecting group of **25** was removed by treatment with BBr_3/DCM affording carboxylic acid **26** that could be purified conveniently by precipitation from MeCN. Fluoride sources such as TBAF (tetra-*n*-butylammonium fluoride), HF-pyridine, or NH_4F failed. Carboxylic acid **26** was activated with oxalyl chloride, followed by addition of sodium pyrithione (**8**)/DMAP. We were able to observe the resulting, labile Barton ester on the TLC, as analyzed by TLC/MS. On prolonged standing, the Barton ester decomposed. We added $BrCCl_3$ in MeCN, irradiated at 370 nm (Rayonet, 1 h),[8] and obtained a rather complex mixture of reaction products, from which tetracycle **27** containing the desired spiro-pyrrolidone ring was isolated (37% after chromatography, $[\alpha]_D^{20}$ − 41.6, *c* = 1.5). Differing from precursor **26**, alkylidene hydantoin **27** proved to be unstable and very difficult to purify.

On applying Buchwald's conditions to **27** we did not observe any product. However, we were pleased to find that under Batey's conditions (stoichiometric $Cu(OAc)_2$, oxygen) target compound **4** could be obtained on reaction with potassium styryl trifluoroborate (**22**, 28%).[11] As in the case of **27**, alkylidene hydantoin **4** proved to be very sensitive under chromatography conditions and was accompanied by small amounts (12%) of a methylester derived from a degraded hydantoin moiety (see the Supporting Information). To our knowledge, hydantoins have not been subject to copper-mediated N−C coupling.

Several attempts were made to transform the hydantoin moiety of analog **4** into ring D of cyanogramide (**1**) by treatment with organometallic methylation reagents (MeMgCl, MeLi) or Cp_2TiMe_2 (Petasis reagent). Unfortunately, none of these attempts were successful and only led to decomposition of tetracycle **4**.

The ECD spectrum of **4** (MeOH, *c* = 0.01 mg/mL) proved to be almost identical to that of the natural product cyanogramide (**1**) [λ_{max} ($\Delta\varepsilon$) 276 (3.0), 258 (−4.9), 237 (6.1), 220 (−9.5) nm for **2**, compared to λ_{max} ($\Delta\varepsilon$) 310 (−1.4), 277 (1.1), 258 (−5.3), 238 (2.2), 222 (−2.6) nm for **1**] providing independent evidence for the correct assignment of the absolute configuration of **1**. The ECD spectra are clearly dominated by the rigid tetracyclic cores. The optical rotation of cyanogramide analog **4** is negative ($[\alpha]_D^{20}$ = −21.0, *c* = 1.0), as is the reported value of cyanogramide (**1**, $[\alpha]_D^{23}$ = −96.0, *c* = 0.1).[1]

Even if the cyclic ester aminal moiety of cyanogramide (**1**) has still to be assembled, we consider the enantioselective synthesis of the close structural analog **4** as an important step forward. As the ester aminal moiety of cyanogramide (**1**, ring D) suggests, facile methanolysis of the alkylidene hydantoin moieties of **27** and **4** could start at the urea moiety. We performed orienting quantum chemical calculations (DFT, ωB97X-D, 6-31G*; see the Supporting Information) that indicate that cyanogramide (**1**) indeed prefers the observed methoxyimidazolidinone ring, whereas the hydroxy analog **2** should prefer (19 kJ/mol in the gas phase, 15 kJ/mol in DMF, continuum model) an open state with the lactam nitrogen being acetylated. This may also be true for compound **20**

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(Scheme 5) that did not cyclize to the ester aminal. The methoxy group of cyanogramide could originate from methanol, which was used as solvent during extraction and chromatography.[1]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03540.

All relevant experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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