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Total Synthesis of Lodopyridone

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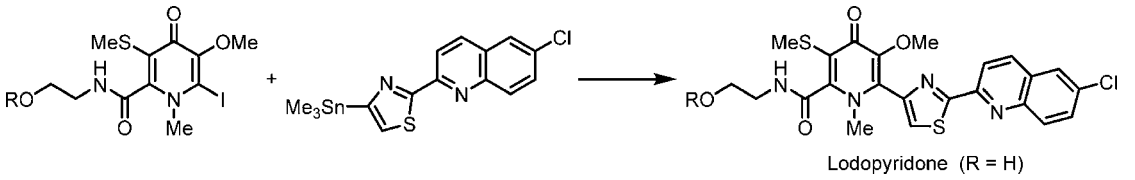
ABSTRACT



A convergent total synthesis of the structurally unprecedented alkaloid lodopyridone was achieved using a cross-coupling of an iodopyridone fragment with a quinolinethiazolylstannane. Key features of the syntheses of the pentasubstituted 4-pyridone were a regioselective bromination of a 4-pyridone derived from kojic acid, a subsequent Cu-mediated introduction of the thioether, and a directed lithiation/iodination step. A chemoselective Negishi cross-coupling of a dibromothiazole and a quinolinylzinc reagent was used to assemble the chloroquinolinethiazol moiety.

4-Pyridones are important heterocyclic substructures occurring in a variety of organic compounds.[1] They are found inter alia in natural products (mimosine/leucenol,[2] piericidin A1[3]), antibiotics (cefazedone[4] and cefpiramid[5]), and contrast media (propyliodone).

Lodopyridone (**1**) was isolated by Fenical's group from the marine bacterial strain CNQ490 which was collected near the mouth of the La Jolla Canyon.[6] The name was derived from the Spanish *Lodo* (mud) because of the muddy marine sediments the bacterial sample was isolated from. Lodopyridone exhibits cytotoxic activity against HCT-116 human colon cancer cells with $IC_{50} = 3.6\ \mu M$.[6]

The structure of lodopyridone (**1**) (Figure 1) was elucidated by X-ray crystallography.[6] The unprecedented skeleton of the new alkaloid natural product contains a pentasubstituted 4-pyridone with a rare methyl thioether at C3. C6 is linked to a thiazole which itself is connected at C9 to a chloroquinoline moiety. A short ethanolamine side chain is attached to C1.

Figure 1. Structure of lodopyridone (**1**).

The unprecedented structure of lodopyridone, in particular the pentasubstituted 4-pyridone substructure, makes it an attractive synthetic target. Here, we present a total synthesis of lodopyridone (**1**). Our synthetic strategy was based on a late cross-coupling of an iodopyridone **2** with an chloroquinoline–thiazolyl metal compound **3** (Scheme 1).

The synthesis of the pyridone fragment **9** started with kojic acid (**4**) (Scheme 2). The methyl ether at C2 was introduced by treatment of compound **4** with dimethyl sulfate to give pyrone **5**.[7]

Jones oxidation of the primary alcohol **5** yielded the carboxylic acid **6**.[8] The acid could be converted via EDC

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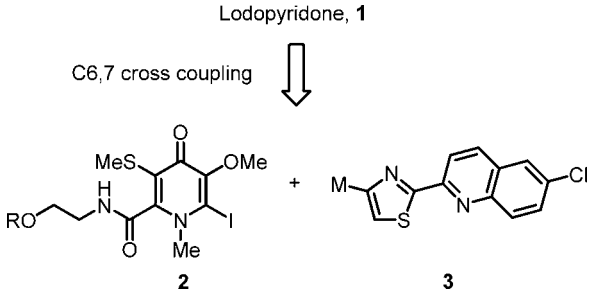
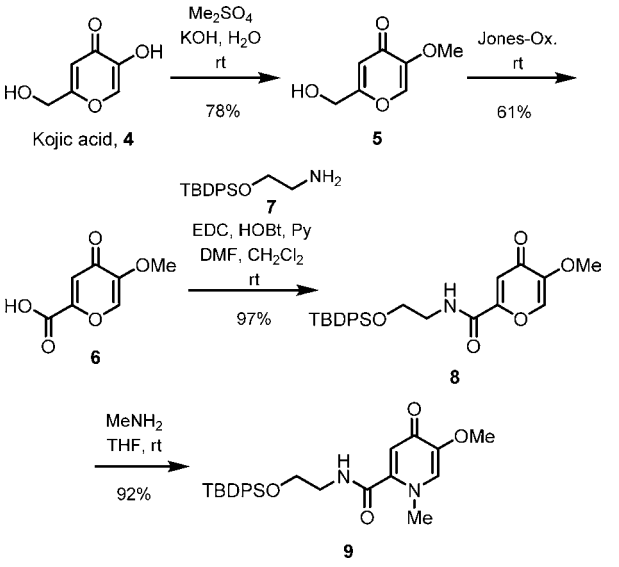
Scheme 1. Retrosynthesis of Lodopyridone (**1**)



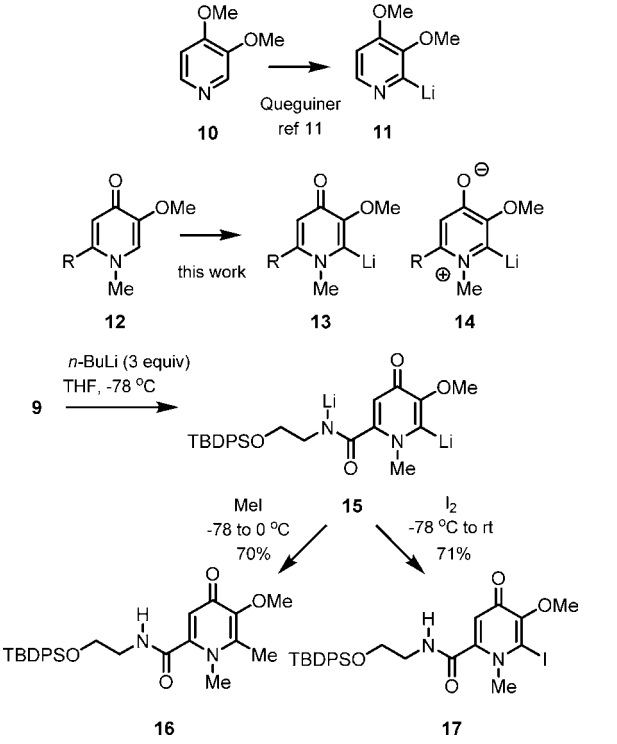
Scheme 2. Synthesis of the Pyridone Fragment **9**



coupling with the amine **7**[9] into the amide **8**. The subsequent pyrone–pyridone transformation[10] proceeded smoothly. Treatment of the 4-pyrone **8** with methylamine gave the 4-pyridone **9** in excellent yield.

Introduction of the C3 and C6 substituents at the 4-pyridone ring were addressed next. First, the possibility of a regioselective lithiation of compound **9** was examined (Scheme 3). The *ortho*-lithiation of 3-methoxy pyridines is a reliable tool for the introduction of a substituent in the C2-pyridine position (**10** → **11**).[11] For the present case, it was found that the *ortho*-lithiation of a 3-methoxy-4-pyridone **12** results in the formation of the lithiated pyridone **13**. The zwitterionic structure **14** indicates the stabilization of this reactive intermediate.[12] Treatment of 4-pyridone **9** with 3 equiv of *n*-BuLi gave the double-lithiated intermediate **15**, which could be cleanly methylated to **16** or iodinated to **17**.

Scheme 3. *Ortho*-Lithiation of the Pyridone **9**



Next, the regioselective functionalization of the C3 position was investigated (Scheme 4). NBS-bromination of pyridone **9** provided the C3-bromination product **18** exclusively. The carboxamide at C2 has no deactivating effect on the C2–C3 double bond. As indicated by X-ray of the pyridone **20** (vide infra), the carboxamide adopts an orthogonal conformation with respect to the pyridone ring, due to steric interference. Thus, bromination at C3 is strongly favored over bromination at C6. Having installed a bromine at C3 in **18**, different conditions for its conversion into a methyl thioether **19** were tested. NaSMe addition alone gave a very low yield (<25%) even at elevated temperature. Considerable side reactions including cleavage of the methyl ether and TBDPS deprotection were observed. Optimal was the combination of NaSMe and CuI in dioxane, which led to the desired thioether **19** in very good yield. The lithiation/iodination protocol developed for **9** (Scheme 3) could be applied successfully to the introduction of the iodo substituent at C6 (**19** → **20**), even in the presence of the thioether. An X-ray structure of the iodopyridone **20** proved the correct position of all five substituents at the 4-pyridone.

The synthesis of the chloroquinolinethiazolyl fragment started with amide **21** (Scheme 5). Conversion into 6-chloroquinol-2-one following Turner's route[13] and subsequent

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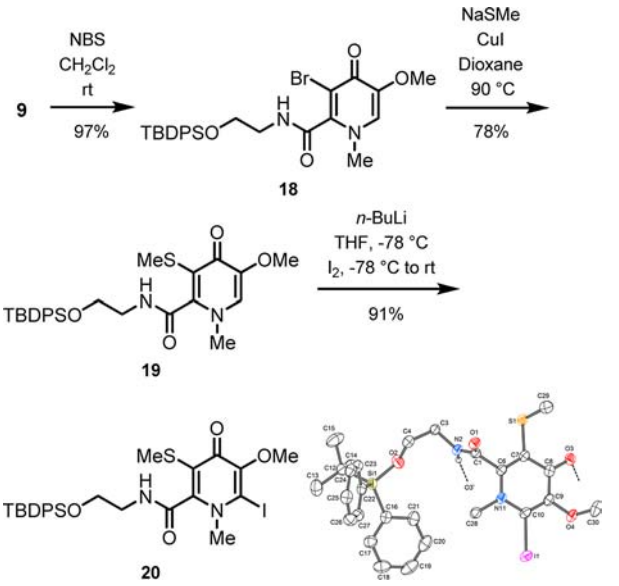
Scheme 4. Regioselective Synthesis of the Pentasubstitued Iodopyridone **20** and X-ray Structure of **20**

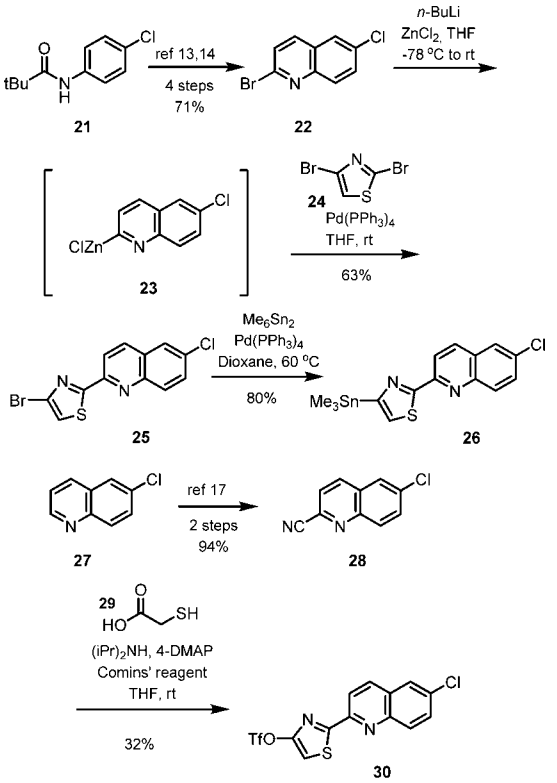


treatment with $POBr_3$ yielded 2-bromo-6-chloroquinoline (**22**).[14] Different cross-coupling scenarios were investigated for the linkage between the quinoline and the thiazole. Initially, a longer Stille route that required the transformation of bromide **22** into the corresponding 2-stannylquinoline was used. Later, a shorter, more efficient Negishi coupling was applied. Bromide **22** was converted via bromine−lithium exchange and subsequent transmetalation into the quinolinyl zinc reagent **23**. Reaction of the quinolinylzinc **23** with 2,3-dibromothiazole **24** using $Pd(PPh_3)_4$ gave the coupling product **25** in good yield. The chemoselectivity observed for this step matches Bach's observation[15] for related cases. After Pd-mediated conversion of bromide **25** into a trimethylstannyl[16] group, the desired chloroquinoline−thiazolylstannane **26** was obtained.

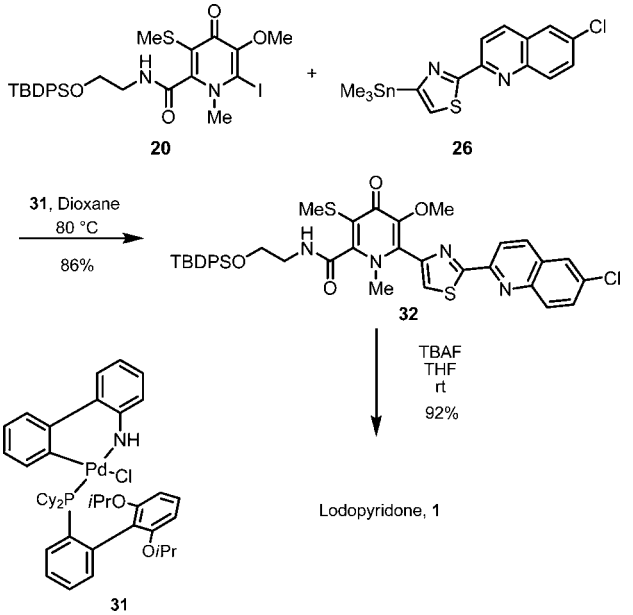
The chloroquinoline−thiazolyl substructure could also be obtained starting from 6-chloroquinoline (**27**) via the nitrile **28**.[17] Reaction with mercaptoacetic acid and subsequent conversion of the hydroxythiazole into the corresponding triflate using *N*-(5-chloro-2-pyridyl)triflimide (Comins' reagent) gave compound **30**, however, in low yield.[18]

With both fragments **20** and **26** in hand, we turned our attention to the final coupling (Scheme 6). A priori, a Pd-catalyzed Stille reaction[16] or a Cu-mediated Liebeskind

Scheme 5. Synthesis of the Chloroquinolinethiazolylstannane **26**



Scheme 6. Final Part of the Lodopyridone Synthesis



coupling[19] are suitable to link an alkenyl iodide with an alkenylstannane.

Stille coupling of the α-*N*-alkylated, *ortho*-substituted iodopyridone **20** with $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ was successful, but only gave yields lower than 30%. Purification

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of the desired product **32** required HPLC to remove traces of ligand and iodopyridone **20**. Similar results were achieved under Liebeskind conditions using copper(I) thiophene carboxylate. Even though product **32** could be obtained, yields did not exceed 24%. Considering these results, we decided to focus on Stille coupling. Second-generation Buchwald Pd precatalyst **31**[20] provided access to coupling product **32** in very good yield.

After removal of the TBDPS group, lodopyridone (**1**) was obtained. The spectra and analytical data of the synthetic sample were identical to those reported for the natural material.[6]

In conclusion, we have reported the first total synthesis of lodopyridone in nine linear steps and 23% overall yield (longest linear sequence). Salient features of our convergent synthesis include a regioselective construction of the pentasubstitued 4-pyridone and a cross-coupling of this highly hindered system utilizing a second-generation Buchwald Pd precatalyst. A Cu-mediated protocol was established to introduce the thioether moiety. Our observations concerning the regioselectivity will allow the efficient sythesis of analogous, highly substituted 4-pyridones.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.