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Total Synthesis of Caerulomycin C via the Halogen Dance Reaction

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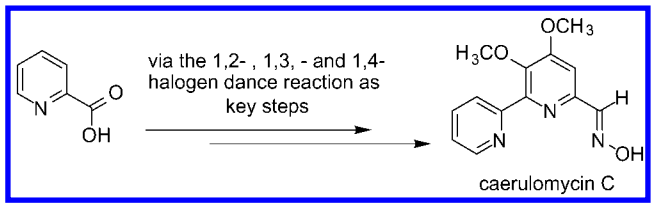
ABSTRACT

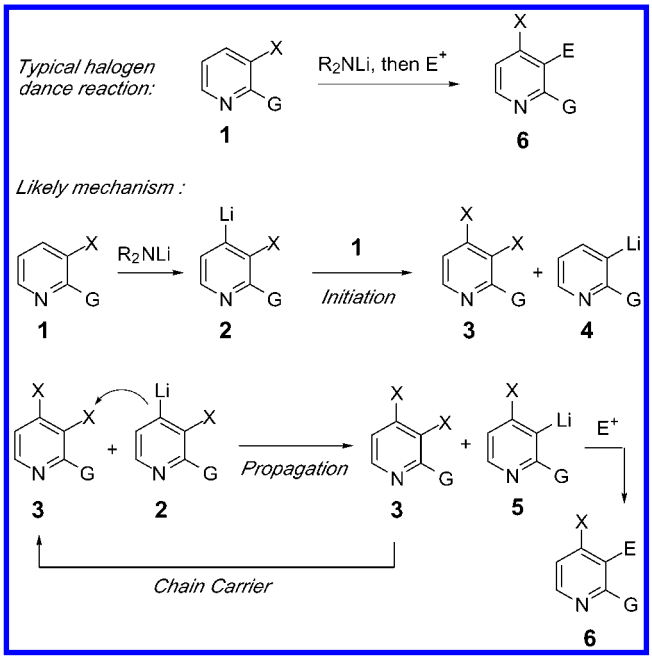


The total synthesis of caerulomycin C is described. Key steps in this synthesis utilize 1,2-, 1,3-, and 1,4-halogen dance reactions for the functionalization of the pyridine ring.

We recently described a series of pyridine-derived acyl-transfer catalysts that are effective for the selective methanolysis of hydroxy esters over ordinary esters.[1] Our interest in this class of molecules led us to explore methodology for the synthesis of substituted pyridine derivatives. One reaction that we have found particularly useful in this context is the "halogen dance" reaction,[2] a process that rearranges the position of a halogen on an arene ring. The reaction is typically performed by deprotonation of an arene that contains an exchangeable halogen (typically, Br or I) and a nonexchangeable directing group G, as illustrated with the pyridine derivative shown in Scheme 1 (compound **1**). Halogens are ortho-directing groups, and the lithiation proceeds to provide **2**.[3]

In an initiation step, compound **2** undergoes halogenation with a halogen source (e.g., another molecule of **1**) to provide the dihalo species **3** and the 3-lithio species **4**. The reaction is then propagated by a halogen−metal exchange between compounds **3** and **2**, which provides **5** and regenerates **3**.

Scheme 1



(1) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 8967. Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **1999**, *64*, 4652. Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, *65*, 974.

(2) For reviews of the halogen dance reaction, see: Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139. Frohlich, J. *Bull. Soc. Chim. Belg.* **1996**, *105*, 615. Froehlich, J. In *Progress in Heterocyclic Chemistry*; Suschitzky, H., Scriven, E. F. V., Eds.; Oxford: New York, 1994; Vol. 6, pp 1−35. For leading references to more recent work, see: Comins, D. L.; Saha, J. *Tetrahedron Lett.* **1995**, *36*, 7995. Trécourt, F.; Mallet, M.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **1994**, *59*, 6173. Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1994**, *35*, 6489. Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832. Marsais, F.; Pineau, P.; Nivolliers, F.; Mallet, M.; Turck, A.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1992**, *57*, 565.

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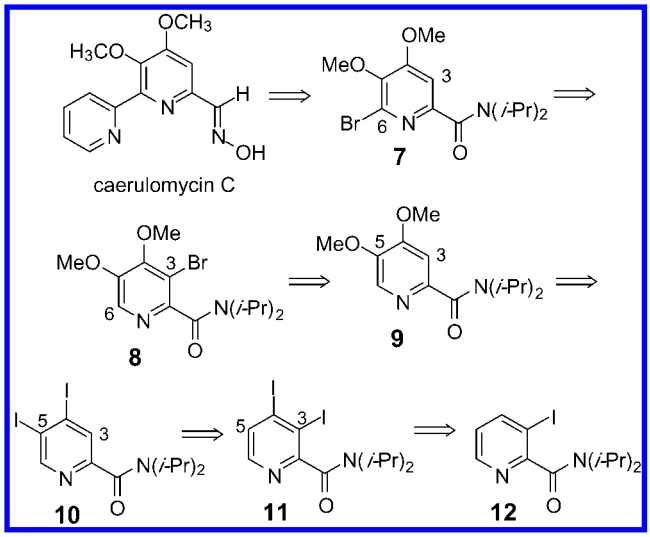
Compound **3** thereby acts as a carrier in a polar chain process for the conversion of **2** to **5**. The reaction is driven by the greater stability of compound **5**, in which the carbanion is stabilized by two ortho-directing groups (X and G), as opposed to one such group (X) in compound **2**. Treatment of **5** with an electrophile provides **6** in which the halogen has migrated by one carbon (a 1,2-shift) and the electrophile is in the position originally occupied by the halogen. Because this reaction proceeds via a series of intermolecular halogen−metal exchange reactions,[4] it is not limited to 1,2-shifts,[5] and it is an attractive method for the synthesis of functionalized pyridine and other heteroaromatic derivatives.

This paper describes the use of 1,2-, 1,3-, and 1,4-halogen dance reactions for the synthesis of caerulomycin C. Caerulomycin C is one of five caerulomycins isolated from the fermentation broth of *Streptomyces caeruleus*.[6] It has been shown to inhibit the growth of some fungi and yeasts and possesses weak antibiotic properties.[6b] Our retrosynthetic analysis begins with the disconnection of the bipyridyl moiety and replaces the oxime with a metalation directing group, simplifying our target to compound **7** (Scheme 2). After

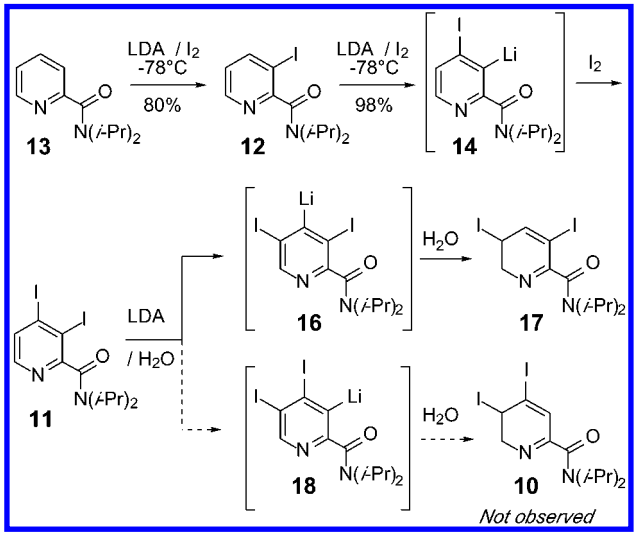
Scheme 2



considering the required properties and transformations of the directing group, we settled on the use of a tertiary amide[7] and the diisopropyl amide was chosen due to its excellent ability to direct ortho-metalations as well as its low reactivity with nucleophiles. We chose to introduce the halogen of **7** late in the synthesis using a 1,4-halogen dance via compound **8**. Compound **8** can be prepared from **9**, and introduction of the methoxy groups of **9** was envisioned via nucleophilic aromatic substitution of the diiodo derivative **10**. Compound **10** in turn can be prepared from the known compound **12** by installation of an iodide at the 4-position of **12** to provide **11**, followed by a 1,3-migration of the 3-iodide to the 5-position. This analysis takes advantage of the ease of introduction of a halogen ortho to an amide, followed by migration of the halogen to a less accessible position on the ring via the halogen dance reaction.

Our initial target for synthesis was compound **10**, and our attempted route to this compound is shown in Scheme 3.

Scheme 3



We began with the lithiation of diisopropyl amide **13** with LDA followed by trapping with iodine to provide the 3-iodo amide **12** in 80% yield. A second metalation and trapping with LDA and iodine provided the 3,4-diiodo species **11**, presumably via the 3-lithio-4-iodo compound (**14**), which is produced by a 1,2-halogen dance reaction. Compound **11** was treated with LDA and quenched with water in an attempt to prepare **10** either via a 1,3-migration of the 3-iodo substitutent or two sequential 1,2-migrations of the 4- and 3-iodo subtituents; however, under all conditions examined, the 3,5-diiodo product **17** was produced. This compound is formed by a 1,2-migration of the 4-iodide to the 5-position to provide the 4-lithio species (**16**), which is stabilized by two *o*-iodides. Apparently, compound **16** is either thermodynamically more stable than the 3-lithio species (**18**) or is kinetically unreactive and does not undergo a second halogen dance. To avoid formation of the 4-lithio species, we repeated this reaction with a nonexchangeable group at the 4-position in place of iodide and studied the 4-chloropyridine derivative **20** (Scheme 4). Our choice of chlorine was based on the fact that it does not readily undergo halogen−metal exchange, but is known to direct ortho-lithiations.[8] Chloropy-

(3) For a review of metalations of azaaromatics, see: Queguiner, G.; Marsais, F.; Sniekus, V.; Epsztajn, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Acdemic Press: San Diego, 1991; Vol. 52, pp 187−304.

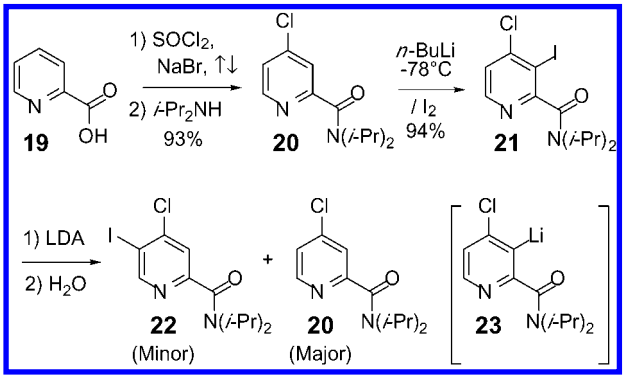
(4) The intermediacy of an aryne can be ruled out since the expected products (addition of the amine base to the aryne) are not observed.

(5) For examples, see: Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron Lett.* **1998**, *39*, 6465. Bury, P.; Hareau, G.; Kocienisky, P.; Dhanak, D. *Tetrahedron* **1994**, *29*, 8793. Sauter, F.; Froehlich, H.; Kalt, W. *Synthesis* **1989**, 771.

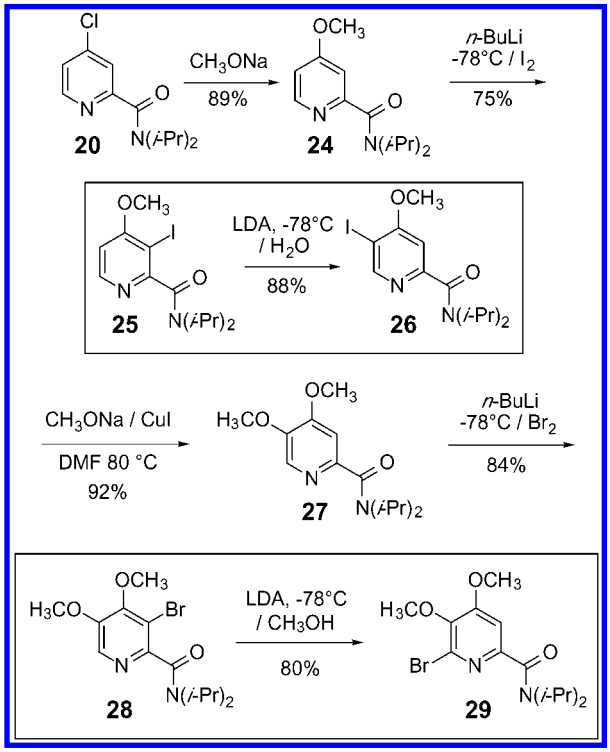
(6) (a) Isolation: Funk, A.; Divekar, P. *Can. J. Microbiol.* **1959**, *5*, 317. (b) Structure determination and biological activity: McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4159. (c) Synthesis: Trécourt, F.; Gervais, B.; Mallet, M.; Quéguiner, G. *J. Org. Chem.* **1996**, *61*, 1673.

(7) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

Scheme 4



Scheme 5



ridines are also susceptible to nucleophilic aromatic substitution with alkoxides, and as such the chlorine provides a handle for the introduction of the methoxy group at the 4-position of the pyridine. Compound **21** was prepared in three steps from 2-picolinic acid by oxidation to 4-chloropicolinyl chloride using Sundberg's procedure,[9] condensation of the acid chloride with diisopropylamine to provide the diisopropyl amide, and ortho-lithiation of the amide with LDA followed by trapping with iodine. Unfortunately, treatment of **21** with either LDA or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at −78 °C followed by an aqueous workup provided variable yields of products. While some of the desired product (**22**) was observed, the deiodinated product **20** was always the major product, and at times it was the sole product. We were unable to discover conditions that reliably provided **22**, and we speculate that deiodination occurs due to the enhanced stability of the 3-lithio species **23**, rendering **21** unusually susceptible to nucleophilic de-iodination. We therefore decided to examine a different non-exchangeable group at the 4-position, one that is less effective as a carbanion stabilizing group so that de-iodination would not be a problem, and chose a methoxy group (Scheme 5).[10]

The 4-methoxypyridine derivative **24** was prepared in 89% yield from **20** by nucleophilic aromatic substitution using sodium methoxide. Metalation of **24** with *n*-BuLi and trapping with iodine provided **25** in 75% yield. Treatment of **25** with LDA smoothly induced a 1,3-migration of the iodide from the 3- to the 5-position and provided the more stable 3-lithiopyridine, which upon aqueous workup provided compound **26** in 88% yield and none of the deiodinated compound (**24**). Nucleophilic aromatic substitution of the iodide at the 5-position proved to be more difficult than at the 4-position.[11] We therefore utilized a modified Ullmann coupling procedure that consisted of treating **26** with sodium methoxide in dimethylformamide containing CuI at 80 °C to provide **27** in 92% yield.[12,13] In the absence of Cu(I) salts, or in less polar solvents, significant quantities of the reduced byproduct **24** were observed. With **27** in hand, we required the installation of our coupling substituent at the 6-position of the pyridine. This was accomplished as planned by introduction of a bromine at the 3-position of **27** (*n*-BuLi, Br_2, 84%), followed by a 1,4-dance of the bromine from the 3-position to the 6-position (LDA −78 °C, CH_3OH, 80%). Thus, the 1,4-dance proceeded cleanly and in high yield to provide **29** ready for coupling with a pyridine derivative.

Completion of the synthesis of caerulomycin C required a cross-coupling with a suitably functionalized pyridine, followed by functional group manipulations to convert the amide to an oxime. We found that the best procedure for this cross-coupling was a Negishi coupling,[14] using $Pd_2(dba)_3$/Ph_3P as the catalyst, and obtained an 80% yield of bipyridyl

(8) Gschwend, H. w.; Rodriguez, H. R. Heteroatom Facilitated Lithiations. *Org. React. (N.Y.)* **1979**, *26*, 1−30. Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059.

(9) Sundberg, R. J.; Jiang, S. *Org. Prep. Proced. Int.* **1997**, *29*, 117.

(10) A methoxy group can be a better kinetic ortho-directing group than a chlorine atom; however, chlorine can be a better thermodynamic carbanion stabilizing group. For a discussion, see: Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622. For a related competition experiment, see: Slocum, D. W.; Dietzel, P. *Tetrahedron Lett.* **1999**, *40*, 1823. Iwao ascribed the kinetic preference for deprotonation ortho- to a methoxy group to complexation to the alkyllithium base; however, Collum has recently provided evidence that complexation-induced proximity effects are not important in the lithiation of anisole. See: Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640.

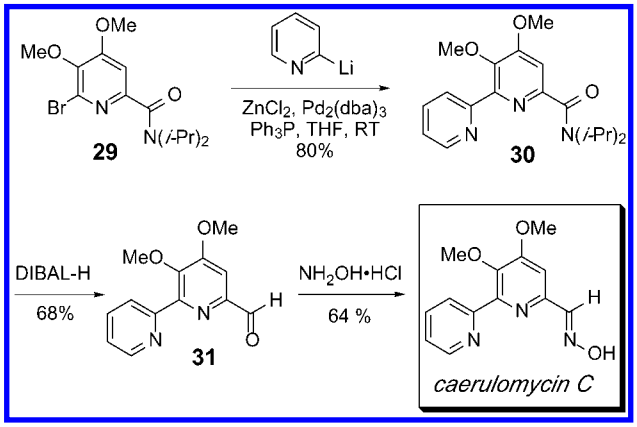
(11) Nucleophilic aromatic substitution at the 3- or 5-position of pyridines is known to be more difficult than at the 2- or 4-position. See: Schofield, K. *Hetero-Aromatic Nitrogen Compounds Pyrroles and Pyridines*; Plenum: New York, 1967; p 244.

(12) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633.

(13) This product is contaminated with about 5% of the reduced compound **27**, which is difficult to separate at this stage, but is readily removed in the next step.

(14) For a review, see: Negishi, E.-i. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 1. The corresponding Stille reaction using 2-tributlystannyl pyridine was less efficient and provided the desired product in 50% yield under optimized conditions ($Pd_2(dba)_3$, P(2-furyl)$_3$, CuI, DMF, 80 °C). See: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.

Scheme 6



30 (Scheme 6). Conversion of the amide of **30** to the oxime was accomplished in two steps in 44% overall yield by reduction of the amide to the aldehyde with diisobutylaluminum hydride to provide **31** followed by condensation with hydroxylamine. Material prepared in this way displayed ^{1}H and ^{13}C NMR spectra identical to those reported for caerulomycin C.[6]

This synthesis illustrates the utility as well as some limitations of the halogen dance reaction. It is interesting to note that the substrates that have the potential to provide unusually stable carbanions (i.e., **11** and **21**) were problematic. However, with appropriately functionalized systems, both the 1,3- and 1,4-halogen dance reactions can provide high yields of compounds that are difficult to access by other methods. Studies to further extend the scope of this process are currently in progress.[15]

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Supporting Information Available: Spectroscopic and analytical data as well as experimental procedures for the synthesis of all compounds shown in Schemes 5 and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **Note Added in Proof:** While this manuscript was undergoing review, a new synthesis of caerulomycin C appeared. See: Mongin, F.; Trecourt, F.; Gervais, B.; Mongin, O.; Queguiner, G. *J. Org. Chem.* **2002**, *67*, 3272.