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Total Synthesis of Citridone A

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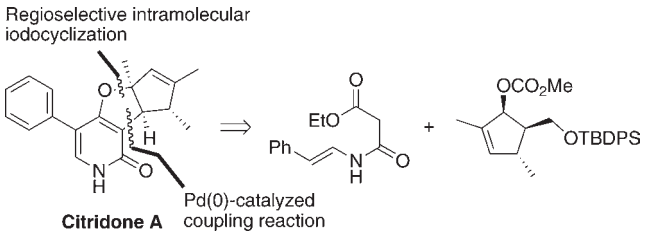
ABSTRACT

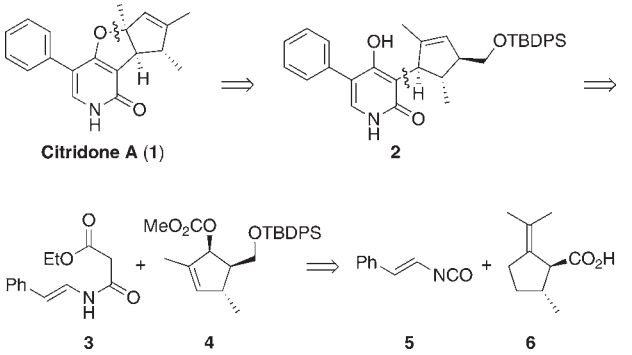


The first total synthesis of citridone A has been achieved through regioselective intramolecular iodocyclization and regio- and stereoselective Pd(0)-catalyzed coupling as key reactions.

Patients with compromised immune systems, e.g. those receiving organ transplants, undergoing cancer chemotherapy, or those infected by the human immunodeficiency virus (HIV) are particularly prone to opportunistic infections caused by *Candida albicans*,[1] a problematic fungi. Unfortunately, azole antifungals have become increasingly ineffective, thus prompting the development of various inhibitors that can overcome the resistance mechanisms of azole-resistant *C. albicans*. Continuous screening for such inhibitors has resulted in the discovery of a novel natural product, citridone A (**1**), which was isolated from the fermentation broth of *Penicillium* sp. FKI-1938.[2] Although **1** itself does not possess antimicrobial activity, it has exhibited reinforcement effects toward miconazole activity against *C. albicans*. However, a detailed mode of action has yet to be defined. Although natural products that possess a phenyl-α-furopyridone subunit have been reported, we believe that this is the first incidence of a novel 6-6/5/5 ring system. Due to its biological properties and the uniqueness of the structure, we decided to undertake its synthesis. Herein we report the total synthesis of **1**, along with the determination of its absolute configuration.

As shown in a retrosynthetic analysis of **1** (Scheme 1), the dihydrofuran unit of **1** was envisioned to arise via iodocyclization of the 4-hydroxy-2-pyridone **2**. In turn, precursor **2** would be constructed via a coupling reaction between enamide **3** and allylic carbonate **4**, followed by the formation of the pyridine ring. Enamide **3** and allylic carbonate **4** would be obtained from known isocyanate **5**[3] and carboxylic acid **6**,[4] respectively.

Scheme 1. Retrosynthetic Analysis of Citridone A (**1**)



Our synthesis began with the preparation of *trans*-isopropylidenecyclopentane **7** via a known carboxylic acid **6**[4] derived from (+)-pulegone (Scheme 2). The carboxylic acid moiety of **6** was reduced with $LiAlH_4$, followed by

(1) Nishiyama, Y.; Yamaguchi, H. *Antibiot. Chemother.* **2000**, *16*, 19–26.

(2) (a) Fukuda, T.; Yamaguchi, Y.; Masuma, R.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2005**, *58*, 309–314. (b) Fukuda, T.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2005**, *58*, 315–321 and references for other natural products including the phenyl-α-furopyridone unit are cited therein.

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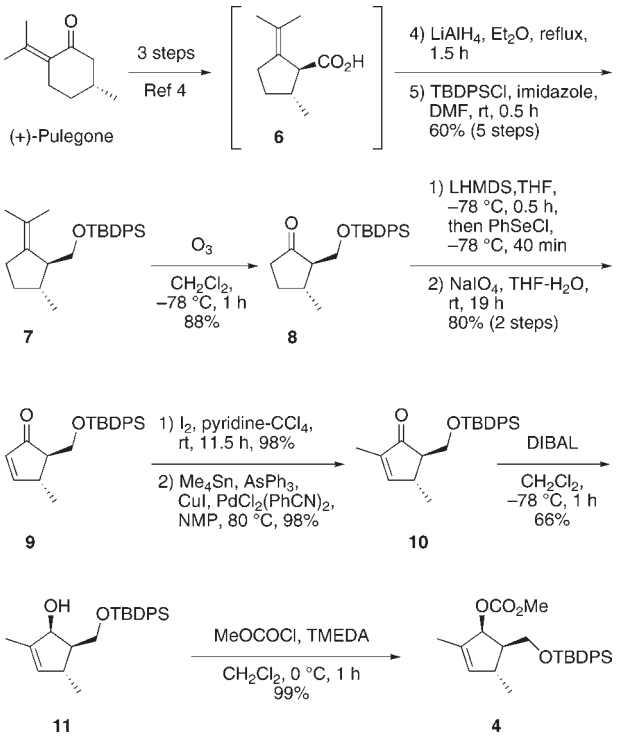
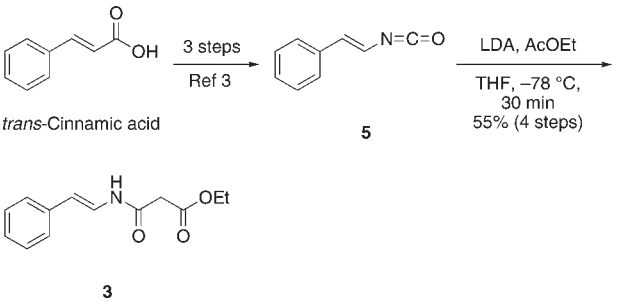
Scheme 2. Synthesis of Key Intermediate **4**



protection as the TBDPS ether to afford **7**. Overall, the conversion of (+)-pulegone to **7** was carried out in 60% yield over five steps, with purification only required in the final step. Ozonolysis of **7** furnished *trans*-cyclopentanone **8** (88% yield) which was converted to **9** by α-selenenylation/oxidation/elimination (80% yield, two steps). The derived enone **9** underwent iodination/dehydrohalogenation to provide the vinyl iodide, which was subsequently employed in a Stille coupling with Me_4Sn, affording *trans*-cyclopentenone **10** in quantitative yield. After screening several reductants, DIBAL was selected for the subsequent stereoselective 1,2-reduction to produce the desired *β*-allyl alcohol **11** in 66% yield. As a note, the undesired α-allyl alcohol was also obtained (30% yield) and could be recycled to **11** via Dess–Martin oxidation followed by DIBAL reduction. Treatment of **11** with methyl chloroformate provided the key intermediate for the allylic alkylation **4**,[5] in quantitative yield.

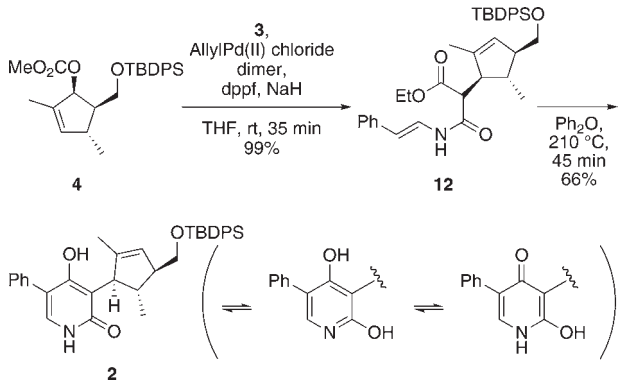
Scheme 3. Synthesis of the Allylic Alkylation Nucleophile **3**



As shown in Scheme 3, the allylic alkylation nucleophile **3** was prepared from known isocyanate **5** which was obtained from *trans*-cinnamic acid via Curtius rearrangement.[3] In the critical coupling step, **5** was exposed to the lithium enolate derived from ethyl acetate at −78 °C to afford **3** in 55% yield (four steps).

Next, the Pd(0)-catalyzed coupling reaction between **3** and **4** was investigated using various palladium catalysts and phosphine ligands. After considerable experimentation, the optimal conditions for accessing **12**[5] with high efficiency and excellent regio- and stereocontrol were determined to be a combination of an allylpalladium(II) chloride dimer and dppf.[6] Gratifyingly, heating of **12** led to pyridine ring formation[7] and afforded the advanced intermediate **2** in 66% yield.

Scheme 4. Synthesis of 4-Hydroxy-2-pyridone **2**



With **2** in hand, the stage was set for the intramolecular iodocyclization. A C-4 regioselective cyclization was required for the total synthesis of **1**; however, undesired iodocyclization at the C-2 position as a concomitant reaction was also considered due to the 4-hydroxy-2-pyridone **2** tautomeric equilibrium as depicted in Scheme 4. To the best of our knowledge, only a few regioselective reactions of 4-hydroxy-5-phenyl-2-pyridones have been reported[8] in which C-4 position-selective cyclization proceeds preferentially, but the respective reaction mechanisms are not clear. At the outset, treatment of **2** with I_2 in CH_2Cl_2 at rt furnished the undesired iodocyclized

(3) (a) Jones, L. W.; Mason, J. P. *J. Am. Chem. Soc.* **1927**, *49*, 2528–2536. (b) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224–228.

(4) (a) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *11*, 1602–1606. (b) Wolinsky, J.; Chan, D. *J. Org. Chem.* **1965**, *30*, 41–43.

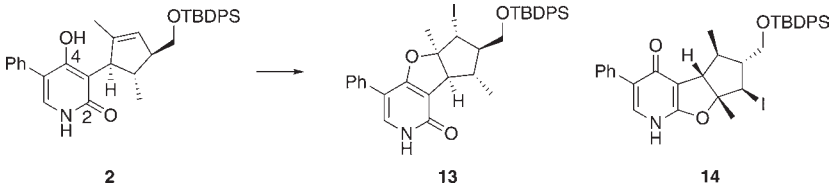
(5) The relative stereochemical configurations were confirmed by NOE experiments on each compound; also see the Supporting Information.

(6) (a) Acharya, H. P.; Kobayashi, Y. *Tetrahedron* **2006**, *62*, 3329–3343. (b) Hoke, M. E.; Brescia, M. R.; Bogaczyk, S.; Deshong, P. *J. Org. Chem.* **2002**, *67*, 327–335.

(7) (a) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852–5853. (b) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774–5781.

(8) (a) Intramolecular 1,4-addition: Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5361–5364. (b) Intramolecular lactonization and nonregioselective intramolecular cyclization: Snider, B. B.; Che, Q. *Org. Lett.* **2004**, *6*, 2877–2880.

Table 1. Regioselective Intramolecular Iodocyclization of **2**



2 **13** **14**

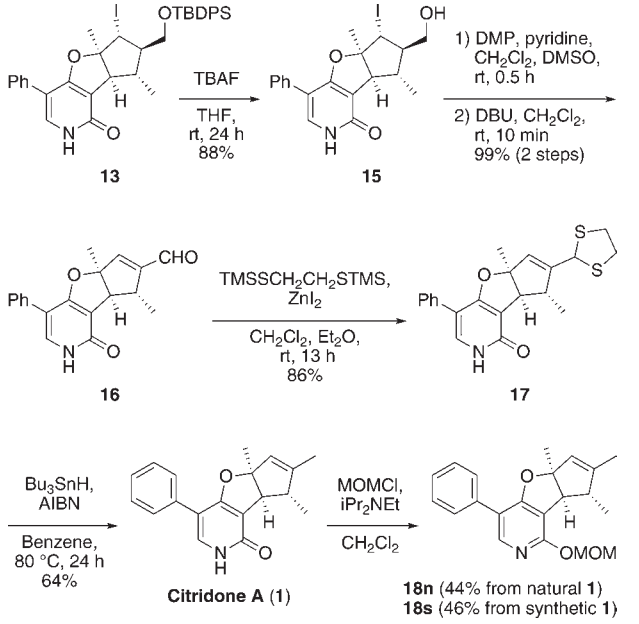
entry	reagent	solvent	temp (°C)	product (%)[a]
1	I_2	CH_2Cl_2	rt	**14** (66)
2	NIS	CH_2Cl_2	0	**14** (63)
3	NIS	CH_2Cl_2/DBU = 10:1	0	**13** (67)
4	NIS	CH_2Cl_2/Et_3N = 10:1	0	**13** (67)
5	NIS	CH_2Cl_2/pyridine = 10:1	0	**13** (70)
6	NIS	MeCN/pyridine = 10:1	0	**13** (70)
7	NIS	MeOH/pyridine = 10:1	0	**13** (61)
8	NIS	THF/pyridine = 10:1	0	**13** (68)
9	(1) BuLi (2 equiv) (2) NIS	THF	0	**13** (67)

[a] Isolated yield.

compound **14** as the major product (66% yield); merely a trace amount of desired product **13** was observed (Table 1, entry 1). Similar results were obtained using *N*-iodosuccinimide (NIS) in place of I_2 at 0 °C (entry 2). Interestingly, the addition of DBU as a cosolvent in CH_2Cl_2 (entry 3) shifted the regioselectivity of the reaction to give the desired intramolecular iodocyclization product **13** in 67% yield with a trace amount of undesired product **14**. Similar effects were observed using bases such as Et_3N and pyridine (entries 4 and 5, respectively). Changing solvents also did not affect the regioselectivity (entries 6−8). Moreover, iodocyclization with NIS after stoichiometric deprotonation of **2** by treatment with 2 equiv of *n*-butyllithium afforded similar results (entry 9). The structures of **13** and **14** were determined by NMR and UV spectra,[9] and their stereochemical configurations were confirmed by NOE experiments.[5] Mechanistically, the regioselective intramolecular iodocyclization in the presence of only I_2 or NIS (without added base) can be rationalized as proceeding via reaction at the least hindered C-2 oxygen. On the other hand, in the presence of added base, the anion of **2** could form an ion-pair aggregate with the corresponding cationic species at the least hindered C-2 position. However, the similar formation at the C-4 position could be prevented by steric hindrance of the two *ortho*-substituents. Therefore, the nucleophilicity of the C-4 alkoxide could be higher than that of the C-2 alkoxide, leading to C-4 regioselective intramolecular iodocyclization under basic conditions.

TBDPS ether **13** was deprotected by treatment with TBAF to give alcohol **15** in 88% yield (Scheme 5).

Scheme 5. Completion of the Total Synthesis of Citridone A (**1**)



Dess−Martin oxidation of **15** followed by β-elimination promoted by DBU furnished α,β-unsaturated aldehyde **16** in 99% yield (two steps). Dithioacetalization of **16** gave **17** (86% yield) which was subjected to radical reduction using Bu_3SnH to provide **1** in 64% yield. Although synthetic **1** exhibited biological activity and spectra (^1H and ^{13}C NMR, IR, and FAB-MS) that were comparable to those of the natural compound, the values of their optical rotation were not comparable. Upon remeasurement, the optical rotation of natural **1** was found to be

(9) Sakemi, S.; Border, J.; Decosta, D. L.; Dekker, K. A.; Hirai, H.; Inagaki, T.; Kim, Y. J.; Kojima, N.; Sims, J. C.; Sugie, Y.; Sugiura, A.; Sutcliffe, J. A.; Tachikawa, K.; Truesdell, S. J.; Wong, J. W.; Toshikawa, N.; Kozima, Y. *J. Antibiot*. **2002**, *55*, 6–18.

variable,[10] which can be attributed to the tautomerization of the 2-pyridone moiety of **1**. Consequently, to prevent the tautomerization of the 2-pyridone moiety, *O*-MOM-protected **1** (**18s** and **18n**) were prepared from natural and synthetic **1**, respectively. Importantly, optical rotation data obtained for *O*-MOM protected **18s** and **18n** were comparable [**18n**: +3.3 (*c* 1.0, CH_3OH), **18s**: +3.5 (*c* 1.0, CH_3OH)]. Given the known absolute stereochemistry of the starting material (+)-pulegone, this result establishes the absolute configuration of **1** to be as depicted.

In conclusion, we have achieved the first total synthesis of citridone A (**1**) in 3.2% overall yield over 24 steps from *trans*-cinnamic acid and (+)-pulegone via a regioselective intramolecular iodocyclization that was developed as a key step. Furthermore, our synthetic scheme allowed for the determination of the absolute configuration of **1**. Applications of the regioselective intramolecular iodocyclization of 3-allyl-5-phenyl-2,4-dihydroxypyridine derivatives toward the syntheses of other natural products and efficient synthesis of di- and tricyclic compounds including pyridine and dihydroxyfuran and pyran rings are currently underway in our laboratory.

(10) Lit. −1.6 (*c* 1.0, CH_3OH),[2b] observed: −4.7 to +10.0 (*c* 1.0, CH_3OH).

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