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Copper-Catalyzed Intramolecular *N*-Arylation of Quinazolinones: Facile Convergent Approach to (−)-Circumdatins H and J

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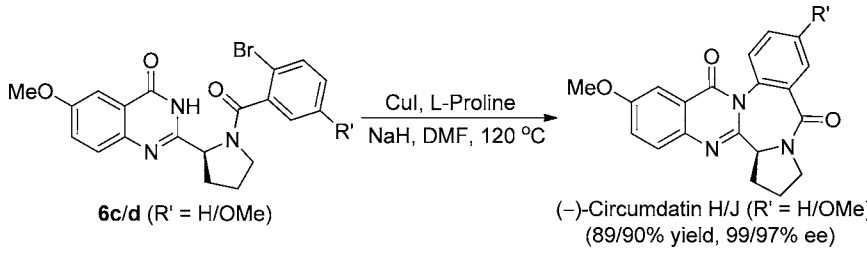
ABSTRACT



A copper-catalyzed intramolecular *N*-arylation of a quinazolinone nucleus that furnished the central benzodiazepine core unit has been demonstrated to accomplish an efficient convergent total synthesis of (−)-circumdatins H and J.

Quinazolinones are an important class of compounds, and a large number of structurally interesting and biologically important natural and synthetic quinazolinones are known in the literature.[1] Presently, some quinazolinones are in clinical use,[1,2] and on the basis of their structural architecture and promising bioactivities they have been important target compounds.[3] Circumdatins are the marine natural products from fungi of the genus *Aspergillus*, and they possess antitumor, antifungal, insecticide, and antibiotic activities (Figure 1).[4] (−)-Circumdatins H and J have been recently isolated from *Aspergillus ochraceus* and *Aspergillus ostianus*, respectively, and more specifically, the (−)-circumdatin H is an inhibitor of the mammalian mitochondrial respiratory chain, with an IC_{50} value of 1.5 μM.[5] Circumdatins are basically the quinazolinobenzodiazepines, and the provision of new efficient synthetic routes to them is the pivotal task of current interest.[6,7] Very recently, syntheses of (−)-circumdatins H and J have been reported by using an intramolecular aza-Wittig reaction and reductive cyclization as the key steps.[7] Metal-catalyzed C(aryl)−N bond-forming

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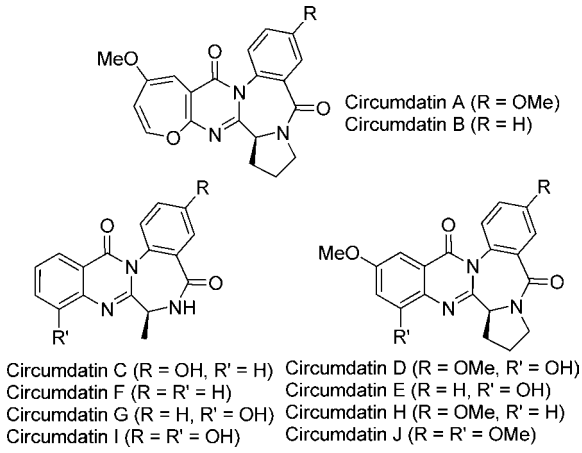

Figure 1. Naturally occurring bioactive circumdatins A−J.[4,5]

reactions under mild catalytic conditions utilizing amines, amides, and nitrogen heterocycles are imperative from a synthetic point of view to design the exotic natural products and synthetic compounds.[8−11] However, metal-catalyzed intramolecular *N*-arylation of quinazolinones has not been studied, to the best of our knowledge.[1,2] In continuation of our studies on quinazolinone chemistry,[12] we envisaged the metal-catalyzed intramolecular *N*-arylation of quinazolinones implementing the advanced Goldberg−Buchwald protocol[9,10] that would provide an efficient access to a large number of desired naturally occurring quinazolinones and their analogues and congeners. In this context, we herein report our results on copper-catalyzed intramolecular *N*-arylation of the quinazolinone nucleus and its application in the synthesis of (−)-circumdatins H and J (Schemes 1 and 2).

Careful scrutiny of circumdatin skeletons revealed that nature most likely utilizes two appropriate anthranilic acid units and L-proline/L-alanine to create them. We planned our biogenetic-type synthesis of circumdatin framework starting from anthranilamide and L-proline via the corresponding potential quinazolinone intermediate **6a** (Scheme 1). We could foresee that our major challenges would be in the metal-catalyzed intramolecular *N*-arylation of quinazolinones to form the intricate seven-membered diazepine cores and the complete conservation of enantiomeric purity throughout the synthesis. The EDCI-induced dehydrative coupling of the Boc-protected L-proline (**2**) with anthranilamide (**1**) at room temperature furnished the diamide **3** in 87% yield. The subsequent base-catalyzed intramolecular dehydrative cyclization of compound **3** provided the required quinazolinone **4** in 92% yield. The TFA deprotection of the Boc group in compound **4**, followed by the dehydrative couplings of thus-formed intermediate free amine **5** with 2-bromobenzoic acid and 2-bromo-5-methoxybenzoic acid, furnished the desired precursors **6a**/**b** in 85/83% yield but, unfortunately, with complete racemization in both the cases. Herein, the acid-catalyzed racemization of our substrate **5** took place during the TFA-induced Boc-deprotection step, plausibly because of the presence of an adjacent imine funtionality from the quinazolinone moiety. We first studied the palladium-catalyzed intramolecular *N*-arylation of quinazolinone **6a** under a variety of reaction conditions using different promising ligands (xantphos, BINAP, johnphos), bases (Cs_2CO_3/NaOBu^t), and solvents (toluene/1,4-dioxane) at elevated temperature, but unfortunately, all our attempts met

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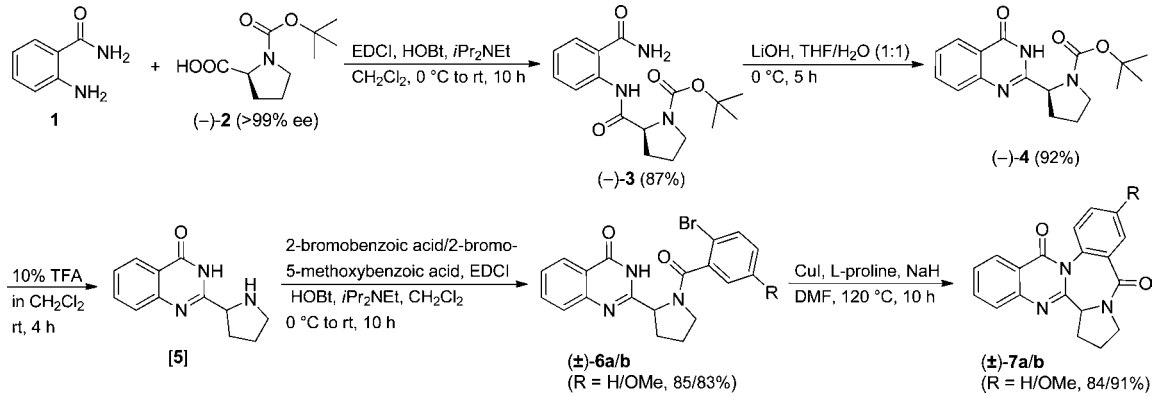
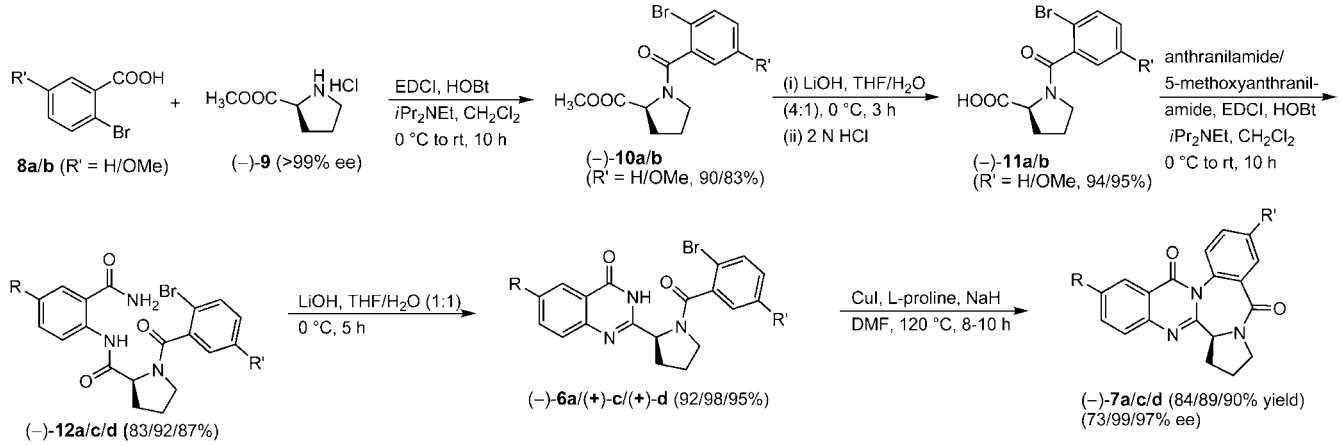
Scheme 1. Synthesis of Circumdatin Frameworks **7a/b** via the Intramolecular *N*-Arylation of Quinazolinones **6a/b**



Scheme 2. Copper-Catalyzed Intramolecular *N*-Arylation of Quinazolinones: Synthesis of Circumdatins H (**7c**) and J (**7d**)



[for **6/7/12**, **a**: R = R' = H; **c**: R = OMe, R' = H; **d**: R = R' = OMe]

with failure and we always recovered starting material, the compound **6a** (Table 1, entries 1−4). The palladium-catalyzed *N*-arylations are known to have some limitations,[9h] and hence, we decided to screen cheap and versatile copper catalysts for the intramolecular cyclization of compound **6a** to form **7a** using different ligands.[9,10] We noticed that the copper iodide catalyzed intramolecular *N*-arylation of compound **6a** using 8-hydroxyquinoline/2-oxazolidinone ligands was feasible, and we could obtain the desired product **7a**, but in low yields (Table 1, entries 5 and 6). All our attempts to further improve the yield by changing the molar ratios and reaction conditions were unsuccesful. Finally, we were delighted to learn that the copper-catalyzed regioselective intramolecular cross-coupling between the 3-position nitrogen atom in the polar quinazolinone **6a** and an adjacent aryl bromide using L-proline as the ligand and sodium hydride as the base in the solvent DMF at 120 °C exclusively furnished the desired thermodynamically more stable linear product **7a** in 84% yield (Table 1, entry 7). The circumdatin J has the methoxy group in the nonquinazolinone aromatic ring, and hence, at this stage we also studied the intramolecular *N*-arylation of compound **6b**. Similarly, the reaction

Table 1. Optimization of Reaction Conditions for the Metal-Catalyzed Intramolecular *N*-Arylation of Quinazolinones **6a/b**

entry	reaction conditions[a]	**7a/b** (% yield)
1	$Pd(OAc)_2$, xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h	**7a** (NR)[b]
2	$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 24 h	**7a** (NR)
3	$Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h	**7a** (NR)
4	$Pd_2(dba)_3$, johnphos, *t*-BuONa, toluene, 100 °C, 24 h	**7a** (NR)
5	CuI, 8-hydroxyquinoline, K_2CO_3, DMSO, 120 °C, 24 h	**7a** (11)
6	CuI, 2-oxazolidinone, MeONa, DMSO, 120 °C, 24 h	**7a** (30)
7	CuI, L-proline, NaH, DMF, 120 °C, 10 h	**7a** (84)
8	CuI, L-proline, NaH, DMF, 120 °C, 10 h	**7b** (91)

[a] 20 mol % of catalyst; 30 mol % of ligand, and 2 equiv of base were used in all the entries. [b] NR: no reaction.

of compound **6b** under the above-mentioned reaction conditions provided the desired product **7b** in 91% yield (Table 1, entry 8). Herein, mechanistically the bond formation between ligand-coordinated copper iodide and quinazolinone nitrogen atom followed by the copper-catalyzed intramolecular cross-coupling with an aryl bromide which generates the new carbon−nitrogen bond to deliver the middle diazepine ring is significant from a synthetic point of view. Thus, the racemic circumdatin frame works **7a**/**b** were obtained in five steps with 57/61% overall yields, and the obtained analytical and spectral data for the compound **7a** were in complete agreement with the reported data.[6b]

To circumvent the associated problem of racemization in our above-described Scheme 1 and also to accomplish the synthesis of enantiomerically pure natural products, the (−)-circumdatins **7c** and **7d**, we reasoned and decided to suitably alter our synthetic sequence. In our second approach, we planned to avoid the use of Boc-protected proline and its subsequent TFA-catalyzed deprotection for the conservation of enantiomeric excess. Hence, we first performed the EDCI-induced dehydrative couplings of the 2-bromobenzoic acid (**8a**) and 2-bromo-5-methoxybenzoic acid (**8b**) with the methyl ester of L-proline (**9**) and respectively obtained the corresponding products (−)-**10a**[13]/**b** in 90/83% yields (Scheme 2). The subsequent base-catalyzed ester hydrolysis of (−)-**10a**/**b** followed by the careful acidification with dilute hydrochloric acid provided the corresponding *N*-benzoylprolines (−)-**11a**/**b** in high yields. Once again, the EDCI-induced dehydrative couplings of compound (−)-**11a** with both the anthranilamide and 5-methoxyanthranilamide and (−)-**11b** with 5-methoxyanthranilamide, respectively, provided the corresponding triamides (−)-**12a**/**c**/**d** in 83−92% yields. The triamides (−)-**12a**/**c**/**d** on base-catalyzed selective intramolecular dehydrative cyclization furnished the essential quinazolinones (−)-**6a**/(+)-**c**/(+)-**d** in 92−98% yields. Thus, by altering the reaction sequence we were successful in avoiding the problem of racemization in the preparation of our potential precursors **6a**/**c**/**d**, required for the synthesis of compounds (−)-**7a**/**c**/**d**. Finally, we decided to expose the requisite quinazolinones **6a**/**c**/**d** to our previously established efficient copper-catalyzed intramolecular *N*-arylation conditions as described in entries 7 and 8 of Table 1. The copper-catalyzed intramolecular *N*-arylation of compounds **6a**/**c**/**d** using L-proline as the ligand and sodium hydride as the base in solvent DMF at 120 °C exclusively furnished the desired final products, the synthetic and natural quinazolinones (−)-**7a**/**c**/**d** in 84−90% yields. Thus, the desired products (−)-**7a**/**c**/**d** were obtained in five steps with 54/68/59% overall yields, and the obtained analytical and spectral data for the natural products (−)-circumdatins H and J (**7c**,**d**) were in complete agreement with the reported data.[5,7] Starting from the (±)-methyl ester of proline, we similarly synthesized the racemic products **7c**/**d** required for the comparison and then checked the enantiomeric purity of our final products (−)-**7a**/**c**/**d** by chiral HPLC. The chiral HPLC results revealed that we obtained the circumdatin framework product (−)-**7a** with 73% ee and the (−)-circumdatins H/J (**7c**/**d**) with 99/97% ee. These results on the conserved enantiomeric purity of (−)-**7a**/**c**/**d** clearly indicate that the compounds (−)-**6a** and/or (−)-**7a** experience ∼13% racemization under basic conditions, while the (−)-circumdatins H/J (**7c**/**d**) with the suitably placed methoxy group in ring A were not prone for such type of racemization under the set of our reaction conditions as depicted in Scheme 2. We believe the π-conjugation of methoxy group with an imine moiety from the quinazolinone ring is responsible for the preclusion of racemization at an adjacent allylic asymmetric center in the compounds (−)-**7c**/**d**. The enantiomerically pure circumdatins H and J are also the likely biosynthetic precursors of circumdatins B and A, respectively.[5b]

In summary, we have reported the concise and efficient total synthesis of (−)-circumdatins H and J by demonstrating the first copper-catalyzed intramolecular *N*-arylation of quinazolinone with the noteworthy generation of a central benzodiazepine unit. We believe our approach has broad scope and will be useful in the synthesis of a diverse range of desired natural and unnatural complex quinazolinones for SAR studies.

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Supporting Information Available: Experimental procedures for the preparation of compounds **3**, **4**, **10a**,**b**, **11a**,**b**, **12a**,**c**,**d**, **6a**−**d**, and **7a**−**d** along with their tabulated analytical and spectral data. ^{1}H NMR, ^{13}C NMR, and DEPT spectra of compounds **3**, **4**, **10a**,**b**, **11a**,**b**, **12a**,**c**,**d**, **6a**−**d**, and **7a**−**d**. HPLC data for the enantiomeric purity of the compounds **7a**,**c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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