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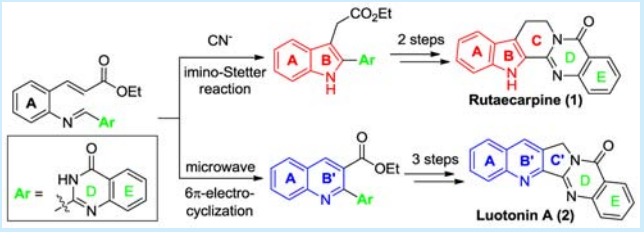
Total Synthesis of Luotonin A and Rutaecarpine from an Aldimine via the Designed Cyclization

Se Hyun Kwon, Hong-Ahn Seo, and Cheol-Hong Cheon*

Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea

Supporting Information

ABSTRACT: The total synthesis of rutaecarpine (**1**) and luotonin A (**2**) is described through controlled cyclization of a common aldimine intermediate **5** derived from ethyl-2-aminocinnamate and quinazolinone-2-carbaldehyde. The cyanide-mediated imino-Stetter reaction of aldimine **5** provided the corresponding indole derivative **3**, from which the total synthesis of rutaecarpine (**1**) was completed via the formation of a 6-membered C-ring. On the other hand, microwave-assisted thermal 6π-electrocyclization of the common intermediate **5**, followed by the formation of a 5-membered C′-ring, allowed the completion of the total synthesis of luotonin A (**2**).

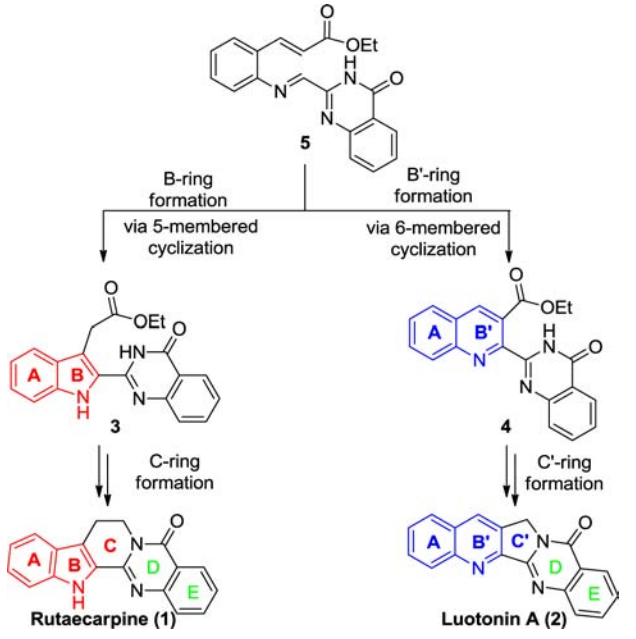


A conventional strategy for the total synthesis of natural products is the design of a specific target molecule via an independent synthetic pathway. However, recently, a divergent strategy for total synthesis, in which several natural products can be prepared from the same intermediate, has been receiving much attention as a complementary method to the conventional target-oriented total synthesis.[1−3] Despite the considerable number of divergent total syntheses of natural products that have been reported to date,[4,5] most of the previous approaches have focused on the total synthesis of natural products that bear a common skeleton with either different appendages on the same skeleton (appendage divergent total synthesis)[4] or the same substituents with different stereochemistry (stereochemical divergent total synthesis).[5] However, skeleton-divergent total syntheses, where natural products bearing different skeletons are prepared from the same intermediate, have been far less investigated.[6]

Since rutaecarpine (**1**) and luotonin A (**2**) (Scheme 1) display a wide range of interesting biological activities, not surprisingly, numerous synthetic endeavors have been made toward the total syntheses of these natural products.[7−10] Despite the fact that these two natural products belong to the same family of quinazolinone alkaloids, most of the previous syntheses of these natural products have been accomplished via independent synthetic routes that utilize starting materials bearing different skeletal frameworks. The synthesis of these two quinazolinone alkaloids from a common intermediate has not been reported to date.[11] This is presumably due to the lack of efficient methods to construct a divergent skeleton (i.e., both indole and quinoline scaffolds) from the same intermediate.

Both alkaloids possess heterofused pentacyclic structures bearing a quinazolinone moiety as the common building block. The major structural difference is that rutaecarpine (**1**) has a 5,6-membered fused B,C-ring structure, while luotonin A (**2**) has a 6,5-membered fused B′,C′-ring system. Based on their structural similarity, we envisaged that rutaecarpine (**1**) and luotonin A (**2**) could be prepared from the same intermediate **5** wherein the formation of the heterofused polycyclic B,C- and B′,C′-ring systems in each respective natural product could be controlled selectively (Scheme 1).[12,13] Herein, we describe the total synthesis of rutaecarpine (**1**) and luotonin A (**2**) from a

Scheme 1. Synthetic Strategy for the Total Synthesis of Rutaecarpine (1) and Luotonin A (2) via Controlled Cyclization



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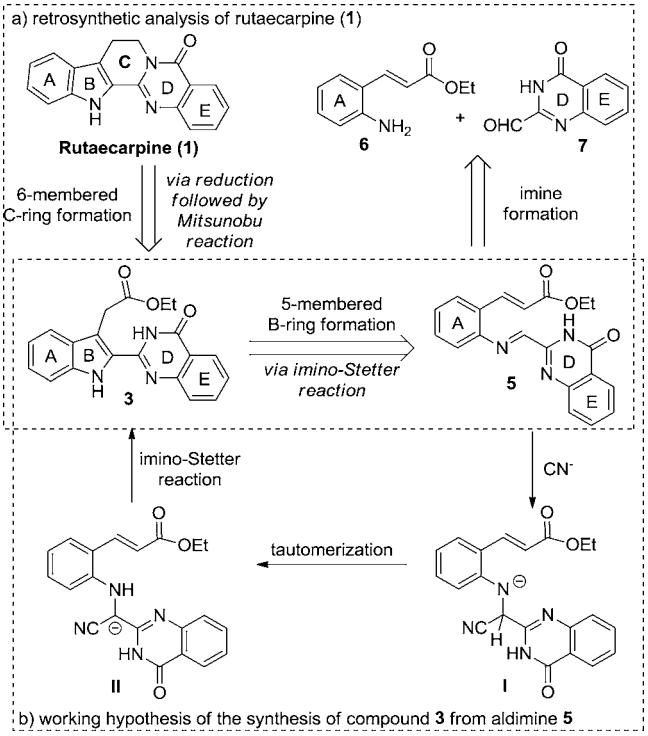
common aldimine **5**, derived from ethyl-2-aminocinnamate **6** and quinazolinone-2-carbaldehyde **7**.

The retrosynthetic analysis of rutaecarpine (**1**) (Scheme 2a) is based on our synthetic plan illustrated in Scheme 1. In this

Scheme 2. (a) Retrosynthetic Analysis of Rutaecarpine (1) and (b) Working Hypothesis of the Imino-Stetter Reaction as a Key Step in the Synthesis of Indole 3

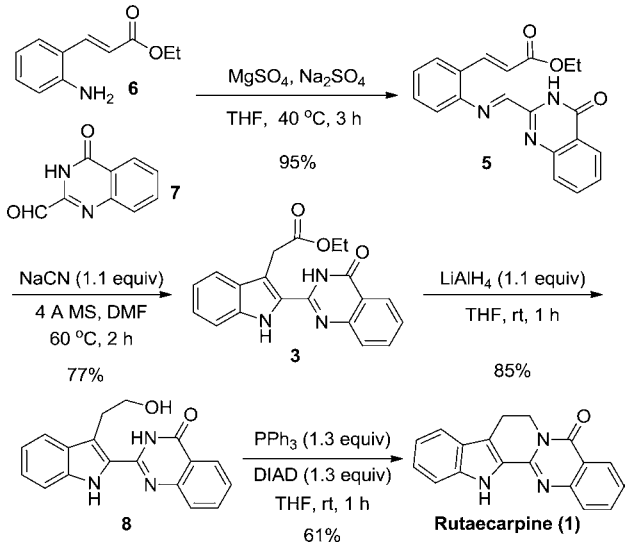


pathway, the 6-membered C-ring in rutaecarpine (**1**) could possibly be prepared via intramolecular cyclization from ethyl 2-quinazolinonylindole-3-acetate **3**. Indole compound **3** was anticipated to be prepared from aldimine **5** that in turn is formed from ethyl 2-aminocinnamate **6** and quinazolinone-2-carbaldehyde **7**.[14] The success of this approach depends on the choice of a proper transformation reaction in which aldimine **5** could be converted into indole compound **3**.

Very recently, our group developed a novel protocol for the synthesis of 2-arylindole-3-acetic acid derivatives from aldimines obtained from 2-aminocinnamic acid derivatives and aromatic aldehydes via a cyanide-catalyzed imino-Stetter reaction.[15,16] Based on this methodology, we envisaged that if a similar transformation were performed with **5** this reaction would provide the corresponding indole-3-acetic acid derivative **3** carrying the quinazolinone moiety present in the 5-membered B-ring of rutaecarpine (**1**) (Scheme 2b). For example, cyanide adduct **I** of aldimine **5** would undergo tautomerization, generating umpolung **II** of aldimine **5**,[17] and the subsequent imino-Stetter reaction of umpolung **II** to the adjacent α,β-unsaturated ester moiety would afford indole compound **3**.

With this working hypothesis in mind, we first explored the imino-Stetter reaction of aldimine **5** in the presence of cyanide (Scheme 3). When **5** was subjected to the reaction conditions used in our previous work[15] in the presence of a catalytic amount of cyanide, the desired indole product **3** was obtained in only low yield. Since our previous studies suggested that

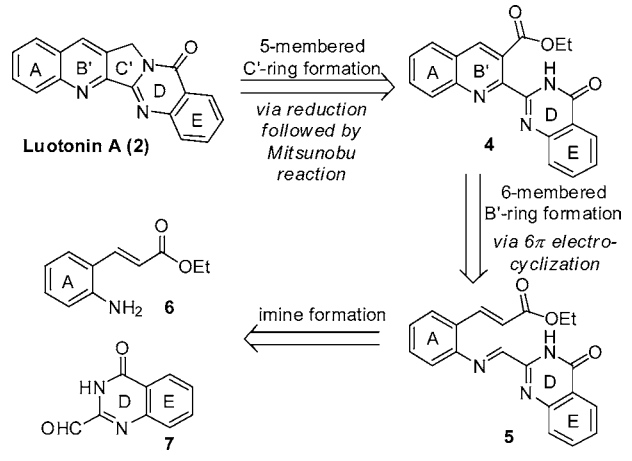
Scheme 3. Total Synthesis of Rutaecarpine (1)



aldimines possessing an acidic proton generally require a stoichiometric amount of cyanide to promote the imino-Stetter reaction[15,16] and **5** possesses an acidic proton on the quinazolinone ring, we performed the same transformation with a stoichiometric amount of cyanide. Delightfully, aldimine **5** was completely consumed, and the desired product **3** was obtained in 77% yield. Reduction of the ester moiety in **3** with $LiAlH_4$ provided the corresponding alcohol **8** with 85% yield, and subsequent formation of the 6-membered C-ring via the intramolecular Mitsunobu reaction afforded rutaecarpine (**1**) in 61% yield. Overall, we completed the total synthesis of rutaecarpine (**1**) from known starting materials in only four steps with an overall yield of 38%.

With the successful application of **5** to the synthesis of rutaecarpine (**1**), we further attempted to develop a new synthetic route for luotonin A (**2**) from the same intermediate (Scheme 4). We postulated that luotonin A (**2**) could be prepared by 5-membered C′-ring formation in ethyl 2-quinazolinonylquinoline-3-carboxylate **4** via reduction of an ester moiety followed by an intramolecular Mitsunobu reaction.[18] In turn, **4** could be prepared through 6-membered B′-ring formation of aldimine **5**, which was used as a key intermediate in the synthesis of rutaecarpine(**1**).

Scheme 4. Retrosynthetic Analysis of Luotonin A (2)



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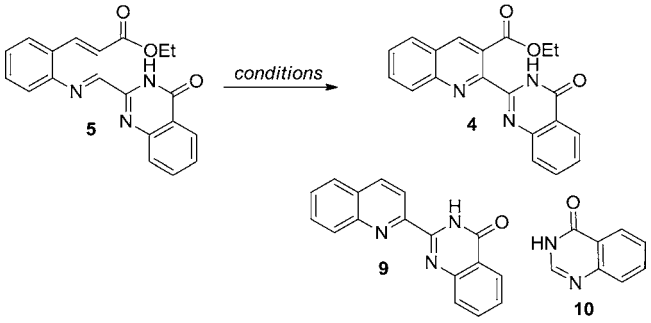
We next needed to determine the proper protocol required to construct the quinoline scaffold (B′-ring) in luotonin A (**2**) from aldimine **5**. Among several choices of the 6-membered B′-ring formation reactions, thermal 6π-electrocyclization was chosen to construct the quinoline scaffold in luotonin A (**2**).[19] With this synthetic plan in mind, we investigated the thermal 6π-electrocyclization of **5** (Table 1). When **5** was treated at 200 °C in 1,2,4-trichlorobenzene for 24 h, the desired product **4** was afforded with low yield (~20% yield). This was accompanied by the formation of several unexpected side-products (entry 1). The careful structural analysis of these side products determined that decarboxylated compound **9** and quinazolinone **10** (12% and 15% yields, respectively) formed via unexpected carbon−carbon bond cleavage. Despite numerous efforts to improve the yield of compound **4** in this reaction, we were unable to suppress the formation of the side products. In order to improve the yield of the desired product, electrocyclization was carried out under microwave irradiation.[20] The reaction temperature played a crucial role in the efficiency of this transformation. The desired product was not afforded when electrocyclization was carried out at temperatures <150 °C, and the aldimine remained unreacted (entry 2). On the other hand, at higher temperatures, there was a considerable increase in the amount of side-products, without any improvement in the yield of the desired product **4** (entries 3−5). After further investigation of the electrocyclization, **4** was finally obtained in 42% yield (entry 3).

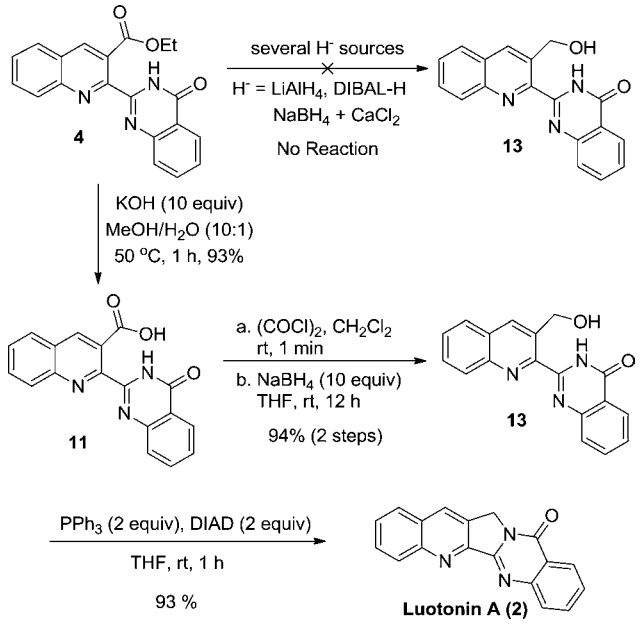
Table 1. Thermal Electrocyclization of Aldimine 5



entry	conditions	result
1	1,2,4-$C_6H_3Cl_3$ air, 200 °C, 24 h	**4** (23%) + **9** (27%) + **10** (26%) + unidentifiable mixture
2	1,2,4-$C_6H_3Cl_3$ MW (100 W), <150 °C, 10 h	no reaction
3	1,2,4-$C_6H_3Cl_3$ MW (100 W), 160 °C, 10 h	**4** (42%) + **9** (12%) + **10** (15%) + unidentifiable mixture
4	1,2,4-$C_6H_3Cl_3$ MW (100 W), 180 °C, 10 h	**4** (28%) + **9** (18%) + **10** (21%) + unidentifiable mixture
5	1,2,4-$C_6H_3Cl_3$ MW (100 W), 200 °C, 10 h	**4** (19%) + **9** (28%) + **10** (25%) + unidentifiable mixture

With compound **4** in hand, we attempted to complete the total synthesis of luotonin A (**2**) (Scheme 5). Initially, we attempted to convert compound **4** into compound **13** by the reduction of the ester moiety to an alcohol following the reported procedures.[10a,d] However, treatment of **4** with $NaBH_4$ and $CaCl_2$ did not afford **13**, and **4** remained unreacted. Furthermore, attempts to reduce the ester moiety with other reducing agents, including $LiBH_4$, DIBAL-H, L-Selectride, and $LiAlH_4$, were also unsuccessful. These resulted in either no reaction or an unidentifiable complex mixture.

Scheme 5. . Total Synthesis of Luotonin A (2)



Since we were unable to directly convert the ester moiety in **4** to an alcohol, we decided to search for an alternative strategy to affect this transformation. Basic hydrolysis of the ester moiety in **4** provided the corresponding carboxylic acid **11** with quantitative yield. When compound **11** was treated with BH_3,[21] the starting material remained in solution, even after prolonged reaction times, and the desired alcohol was not detected. On the basis of these results, we deduced that the ester moiety could be converted into a more reactive functional group, such as acyl chloride **12**, to increase reactivity toward the reducing agent. Therefore, we converted carboxylic acid **11** into acyl chloride **12** with the use of oxalyl chloride. The resulting crude product was subsequently treated with $NaBH_4$ in THF, without further purification, to give the desired alcohol **13** in 94% yield from carboxylic acid **11** over two steps. Intramolecular Mitsunobu reaction[18] of the resultant alcohol product generated the 5-membered C′-ring needed to complete the total synthesis of luotonin A (**2**). Thus, the total synthesis of luotonin A (**2**) from **5** was completed in only four steps with an overall yield of 34%.

In conclusion, we have developed a novel approach to skeletal-divergent synthesis to access both rutaecarpine (**1**) and luotonin A (**2**) from the common intermediate. This approach proceeds through the controlled formation of a B,C- and B′,C′-fused polycyclic ring system, respectively. Treatment of aldimine **5**, obtained from ethyl 2-aminocinnamate **6** and quinazolinone-2-carbaldehyde **7**, with cyanide led to **3**, an indole-3-acetic acid ethyl ester bearing a quinazolinone moiety at the 2-position (i.e., the formation of the 5-membered B-ring in rutaecarpine (**1**) via a cyanide mediated imino-Stetter reaction). Subsequent reduction of the ester moiety into an alcohol, followed by the Mitsunobu reaction, afforded rutaecarpine (**1**) in only four steps in 38% overall yield from known starting materials. On the other hand, microwave-assisted thermal 6π-electrocyclization of the same aldimine intermediate **5** afforded the corresponding quinoline **4** [i.e., the formation of the 6-membered B′-ring in luotonin A (**2**)]. Hydrolysis of the ester moiety and subsequent conversion of the carboxylic acid to acyl chloride with oxalyl chloride,

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followed by reduction of the resulting acid chloride with $NaBH_4$, afforded the corresponding alcohol **13**. This latter compound underwent Mitsunobu reaction [i.e., the formation of the 5-membered C′-ring in luotonin A (**2**)] to complete the total synthesis of luotonin A (**2**) from **5**, in four steps, with 34% yield. Further development of skeleton-divergent total synthesis designed by unique reaction mechanisms is currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02597.

Detailed experimental procedure and spectral data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cheon@korea.ac.kr.

Notes

The authors declare no competing financial interest.

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