Natural Products Synthesis

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Total Syntheses of (±)-Spiroquinazoline, (−)-Alantryphenone, (+)-Lapatin A, and (−)-Quinadoline B**

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Since (−)-spiroquinazoline (**1**; Figure 1) was isolated by Barrow and Sun in 1994,[1] eight other spiroquinazoline alkaloids have been isolated from a variety of fungi of the genera *Penicillium* and *Aspergillus*.[2] These natural products all contain a tricyclic pyrazino quinazolinedione moiety, but

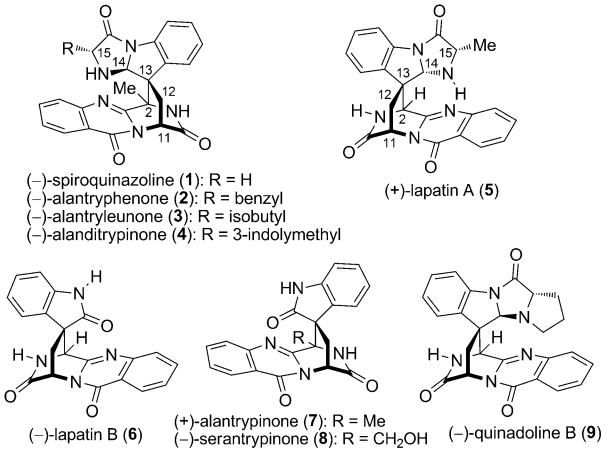

Figure 1. Structures of spiroquinazoline alkaloids.

differ in the substructures which bridge C2 and C11. (−)-Spiroquinazoline (**1**), (−)-alantryphenone (**2**),[2d] alantryleunone (**3**),[2d] alanditrypinone (**4**),[2d] (+)-lapatin A (**5**),[2c] and (−)-quinadoline B (**9**)[2e] are bridged by indoline-containing substructures with different C15 substituents, while lapatin B (**6**),[2c] alantrypinone (**7**),[2b] and serantrypinone (**8**)[2a] are bridged by a 3-methyleneoxindole unit. Preliminary studies have revealed that these alkaloids possessed significant biological activities. For example, **1** inhibits substance P (SP) binding to human NK-1 receptor and therefore may serve as a lead compound for developing analgesics.[1] Alantrypinone (**7**) potently inhibits insect GABA receptors but is much less active toward mammalian GABA receptors.[2a] Additionally, **9** was found to inhibit lipid droplet synthesis in mouse macrophages.[2e]

Since **1** has a skeleton unprecedented in nature, it is not surprising that synthetic interest in this target and related alkaloids has been considerable.[3] To date, several synthetic routes to the core of **1** and total syntheses of two oxindole-containing spiroquinazoline alkaloids have been published,[4] however, the indoline-containing spiroquinazoline alkaloids have not, as yet, succumbed to synthesis.[5] Herein, we wish to report the first total syntheses of (±)-spiroquinazoline (**1**), (−)-alantryphenone (**2**), (+)-lapatin A (**5**), and (−)-quinadoline B (**9**).

A key challenge to the total synthesis of the indoline-containing spiroquinazoline alkaloids is the installation of their aminal moieties. Indeed, despite successful model studies, Hart and Magomedov described that they could not construct the aminal unit in **1** from two alantrypinone derivatives (**10**; Figure 2).[3,5b] Their result implied that

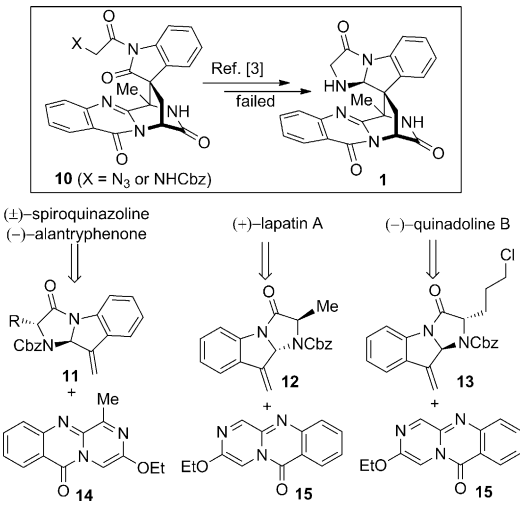

Figure 2. Retrosynthetic analysis of spiroquinazoline alkaloids. Cbz = benzyloxycarbonyl.

formation of the aminal part at an early stage in the synthesis of **1** is necessary. In synthesis of **7**, reported by Kende et al., an aza-Diels–Alder reaction of the azadiene **14** with 3-methyleneoxindole was employed to construct its carbon framework.[4c,d] Inspired by their results, we decided to explore the possibility to utilize the olefins **11**–**13** as the dienophiles for similar transformations. The success of this cycloaddition would provide quick access to indoline-containing spiroquinazoline alkaloids. However, this remained a challenging task at the outset because the stability of these unprecedented

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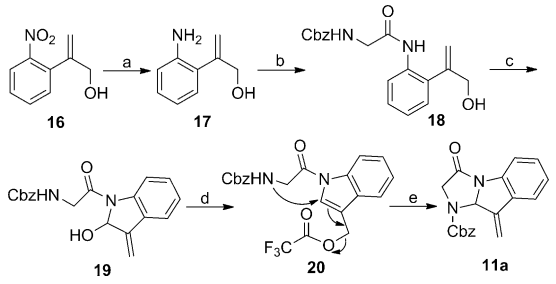


Scheme 1. Reagents and conditions: a) Fe, AcOH, 88%; b) EDCI, *N*-Cbz-glycine, Et_3N, CH_2Cl_2, 82%; c) Dess–Martin periodinane, 95%; d) CF_3CO_2H, $CHCl_3$; e) PhBr, 160°C, 50% yield for two steps.

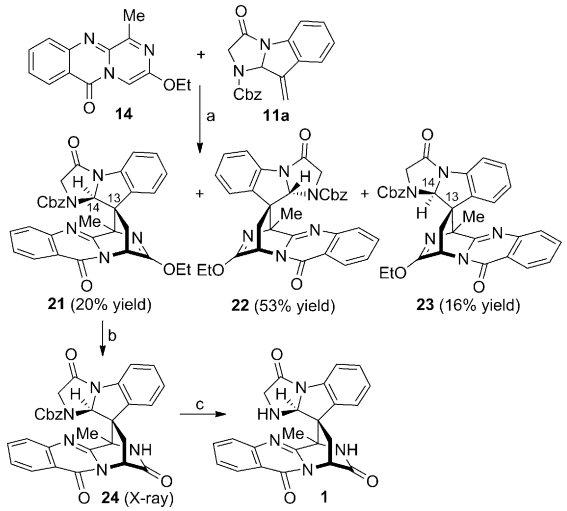
olefins was hitherto unknown, and their reactivity in an aza-Diels–Alder reaction[6] with **14** and **15**[7] was questionable.

As depicted in Scheme 1, the preparation of the olefin **11a** began with the Fe/HOAc reduction of **16**, a known compound which was prepared from commercially available 2-nitrophenylacetic acid in three steps.[8] The resultant aniline **17** was condensed with *N*-Cbz-glycine to afford the amide **18**. Dess–Martin oxidation of **18** with concomitant intramolecular condensation provided the cyclic hemiaminal **19**. Our initial studies focused on obtaining **11a** directly from **19** by treatment with suitable acids because similar transformations have been reported.[5b,9] Unfortunately, exposure of **19** to TsOH or $Sc(OTf)_3$ gave complex mixtures, presumably because the resultant N acyliminium is rather unstable under these reaction conditions. Occasionally, we found that the indole **20** could be isolated in 58% yield when **19** was treated with 1 equivalent of TFA. We envisioned that this side product could be converted into **11a** by a concerted nucleophilic addition-elimination process, and therefore attempted to improve the reaction yield. Gratifyingly, when 12 equivalents of TFA was added, **20** could be obtained in 95% yield. After some experimentation, we found that heating **20** at 160°C in bromobenzene could deliver **11a**. Fortunately, **11a** was stable during long-term storage at room temperature, although it underwent complete decomposition after few days in $CDCl_3$.

With the olefin **11a** in hand, we next investigated its aza-Diels–Alder reaction with the azadiene **14** (Scheme 2). After some optimization, we were pleased that heating a mixture of **11a** and **14** in xylene at 130°C afforded the desired adduct **21** in 20% yield, together with its two isomers, **22** and **23**. Their structures were determined by NMR analysis and further confirmed by subsequent studies. Interestingly, regiochemistry in the adducts **21**–**23**, as well as the preferred *exo*like stereochemistry (displayed by **21** and **22**), are consistent with those observed in the cycloaddition of **14** and 3-methyleneoxindole,[4c,d] although the C–C double bond in **11a** is much less polar than that of 3-methyleneoxindole. Further mechanism investigations are required to rationalize these results.

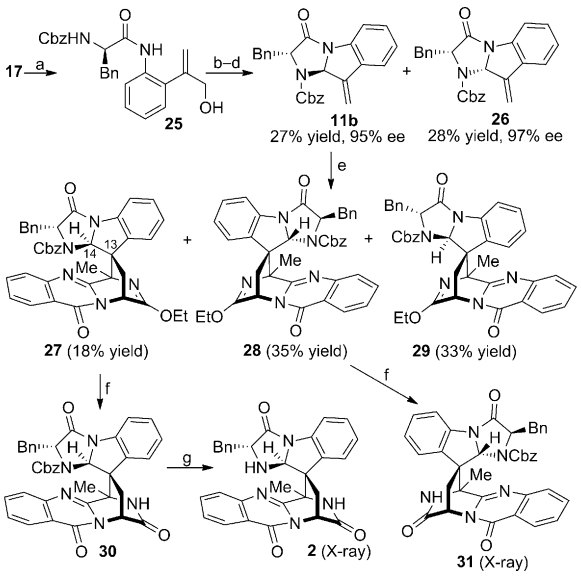
Hydrolysis of **21** with hydrochloride acid in EtOAc produced the lactam **24**, whose structure was confirmed by X-ray analysis.[10] Finally, hydrogenolysis of **24** furnished **1**.[11]

In view of this encouraging result, we next explored if this strategy could be extended to the synthesis of other indoline-containing spiroquinazolines. Accordingly, condensation of **17** with *N*-Cbz-D-phenylalanine provided the amide **25**



Scheme 2. Reagents and conditions: a) xylene, 130°C, 3 days; b) HCl, EtOAc, 95%; c) Pd/C, H_2, EtOAc, 80%.

(Scheme 3). By using a procedure similar to the one for preparation of **11a**, **25** was transformed into **11b** and its diastereomer **26**. To our delight, both **11b** and **26** retained satisfactory enantiopurity, thus indicating that almost no

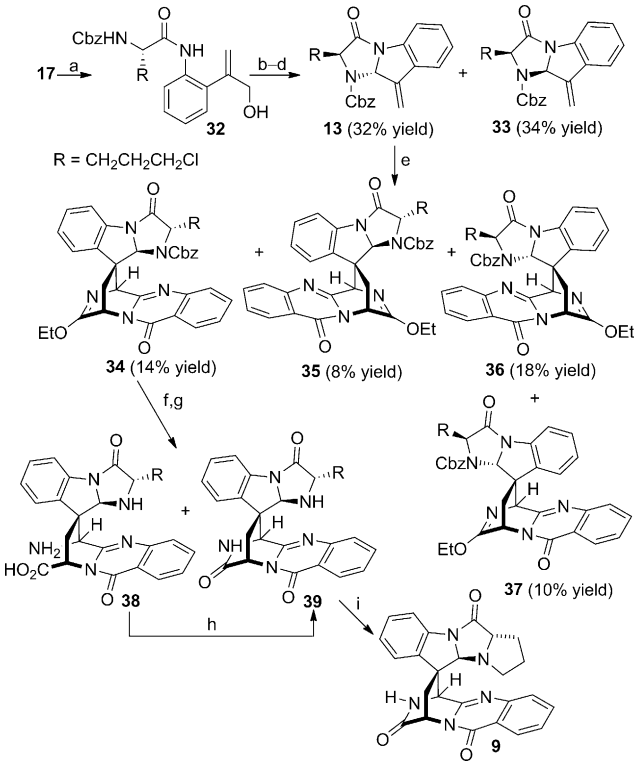


Scheme 3. Reagents and conditions: a) EDCI, *N*-Cbz-D-phenylalanine, Et_3N, CH_2Cl_2, 76%; b) Dess–Martin periodinane; c) CF_3CO_2H, $CHCl_3$; d) PhBr, 160°C; e) **14**, xylene, 130°C, 2 days; f) HCl, THF, 91–94%; g) Pd/C, H_2, THF, 86%. EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide, THF = tetrahydrofuran.

racemization occurred during their synthesis. The aza-Diels–Alder reaction of **11b** and **14** took place under our previous reaction conditions, thus providing **27**–**29** in a combined yield of 88%. Hydrolysis of **27** and subsequent hydrogenolysis of the resultant **30** delivered **2** ($[\alpha]_D^{20} = -40$ ($c = 0.017$, MeOH); lit.[2d] $[\alpha]_D^{20} = -1.6$ ($c = 0.9$, MeOH)).[12] In a parallel procedure, **28** was hydrolyzed to lactam **31**. The structures for both the

synthetic **2** and **31** was confirmed by X-ray analysis,[10] thereby allowing us to confirm the structures of the adducts **27** and **28**.

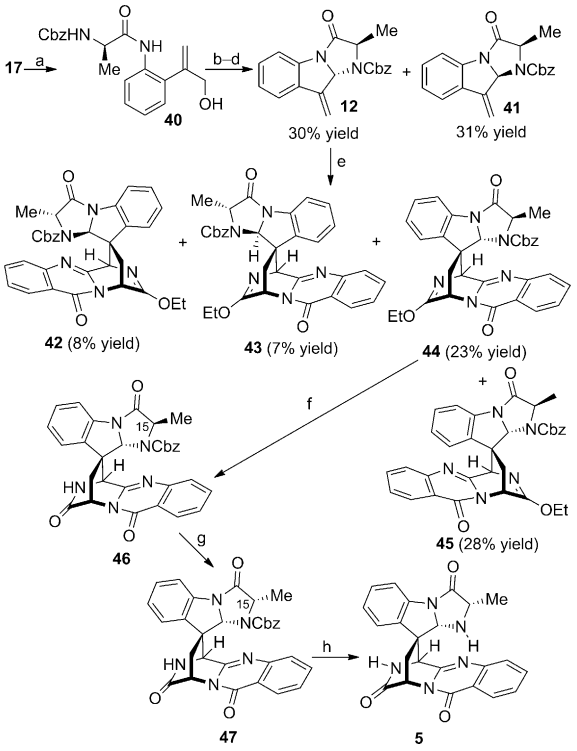
For the synthesis of (−)-quinadoline B (**9**), we condensed the aniline **17** with 2-(*S*)-(benzyloxycarbonylamino)-5-chloropentanoic acid[13] to afford the amide **32** (Scheme 4), which was converted into the desired olefin **13** in three steps and 32% overall yield. Cycloaddition of **13** with **15** produced the



Scheme 4. Reagents and conditions: a) EDCI, 2-(*S*)-(benzyloxy-carbonylamino)-5-chloropentanoic acid, Et_3N, CH_2Cl_2, 76%; b) Dess–Martin periodinane; c) CF_3CO_2H, $CHCl_3$; d) PhBr, 160°C; e) **15**, xylene, 130°C, 48 h; f) Pd/C, H_2, THF, MeOH, 90%; g) HCl, THF; h) toluene, reflux; i) iPr_2NEt, KI, MeCN, reflux, 40% for three steps.

adducts **34**–**37** in 50% combined yield. Notably, four stereoisomers are simultaneously formed in this case. These results illustrated that the substituents in azadienes have a significant influence on the stereochemical course. Next, deprotection of the expected isomer **34** provided a mixture of **39** and the ring-opened product **38**. The latter could be converted into **39** by refluxing in toluene.[14] Finally, treatment of **39** with iPr_2NEt/KI to form the pyrrolidine ring[15] afforded **9** ($[\alpha]_D^{20} = -52.7$ ($c = 0.1$, MeOH); lit.[2e] $[\alpha]_D^{20} = -44.7$ ($c = 0.01$, MeOH)). To our satisfaction, all ^1H NMR and ^{13}C NMR spectroscopic data for synthetic **9** correlated well with those reported for natural (−)-quinadoline B.

As shown in Scheme 5, we employed a slightly different route to achieve the total synthesis of (+)-lapatin A (**5**). After condensation of **17** with *N*-Cbz-D-alanine to give the amide **40**, our standard four-step conversion was conducted to yield the olefins **12** and **41**. Cycloaddition of **12** and **15** furnished the adducts **42**–**45**. Since **44** has the required stereochemistry for assembling **5**, except for its configuration at the C15



Scheme 5. Reagents and conditions: a) EDCI, *N*-Cbz-D-alanine, Et_3N, CH_2Cl_2, 81%; b) Dess–Martin periodinane; c) CF_3CO_2H, CH_2Cl_2; d) PhBr, 160°C, 4 h; e) **15**, xylene, 130°C, 48 h; f) HCl, THF, 90%; g) DBU, DMSO, 110°C, 73%; h) Pd/C, H_2, MeOH, 83%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethylsulfoxide.

stereocenter, we decided to use this intermediate for further transformation and planned to fix the C15 stereochemistry problem by epimerization at a late stage.[16] Accordingly, hydrolysis of **44** afforded the lactam **46**, which was treated with DBU in DMSO at 110°C to give a mixture of **46** and the desired isomer **47** in a ratio of 1:3.5. This mixture could be purified by column chromatography to give **47** in 73% yield. After hydrogenolysis of **47**, **5** ($[\alpha]_D^{20} = +41.3$ ($c = 0.09$, EtOH); lit.[2c] $[\alpha]_D^{20} = +22$ ($c = 0.01$, EtOH)) was isolated in 83% yield, and the analytical data are identical with those reported for natural (+)-lapatin A.

In conclusion, we have achieved the first total syntheses of four indoline-containing spiroquinazoline alkaloids, namely (±)-spiroquinazoline, (−)-alantryphenone, (+)-lapatin A, and (−)-quinadoline B. These syntheses each required only 11 to 12 steps from commercially available 2-nitrophenylacetic acid, and the key elements include formation of aminal-embodied olefins and their aza-Diels–Alder reaction with the azadienes. Our synthetic routes provide a quick access to indoline-containing spiroquinazoline alkaloids and their analogues, which will be of benefit for further evaluation of their biological activity. In addition, it is notable that aminal-embodied olefins we obtained are valuable building blocks for synthesizing other aminal-embodied alkaloids. Detailed mechanistic studies to the aza-Diels–Alder reaction, as well as attempts to improve stereoselectivity in this step, are actively being pursued in our group and the results will be disclosed in due course.

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[10] CCDC 937851 (**24**), 937852 (**2**), and 937853 (**31**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[11] There are some slight differences between the ^{1}H NMR and ^{13}C NMR data we measured for synthetic **1** and those reported for natural (±)-spiroquinazoline (see the Supporting Information), and might result from the difference in the conditions under which the measurements were taken.
[12] Besides rotation differences, we also found some differences between ^{13}C NMR data we measured for synthetic **2** and those reported for natural (−)-alantryphenone. However, the ^{1}H NMR data of synthetic **2** are in agreement with those reported for natural (−)-alantryphenone (see the Supporting Information).
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