The spiroquinazoline family of alkaloids: a review

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This review is dedicated to Professor James Cook, my former GTA and a long-time contributor to the field of alkaloid chemistry, on the occasion of his 65th birthday

Abstract
The article presents a review of the structures, biological activities and studies directed toward syntheses of the spiroquinazoline family of alkaloids.

Keywords: Alkaloids, total synthesis, oxindoles, hetero-Diels-Alder, *N*-acyliminium ions

Table of Contents

1. Introduction

In 1994 Barrow and Sun, from the Sterling-Winthrop group, reported the structure of spiroquinazoline **1**, a fungal metabolite isolated during a search for compounds that would inhibit the binding of the neuropeptide substance-P (SP) to the human NK-1 receptor.[1] Spiroquinazoline was truly a unique natural product at the time. No other natural products containing the carbon skeleton present in spiroquinazoline had been reported. In the 15 years that have followed the Barrow-Sun report, several more natural products that closely resemble spiroquinazoline have been reported as isolates from a variety of fungi. This review will describe the isolation and structures of these natural products, their biological properties, and several approaches to the synthesis of selected members of what will now be called the spiroquinazoline family of natural products (Figures 1–4). Several numbering schemes appear in the literature in regard to the spiroquinazoline family of natural products. The numbering scheme originally used to describe spiroquinazoline will be used throughout this review.

2. Structures

2.1 Isolation and structure determination

Spiroquinazoline **1** was isolated from ethyl acetate extracts of a fermentation broth derived from *Aspergillus flavipes*, followed by additional solvent partitioning and chromatography. A total of 16 mg of **1** was isolated from 2.75 liters of fermentation broth. The structure of **1** was assigned largely on the basis of NMR spectroscopy although other analytical tools were used to provide evidence for substructures within the natural product. For example, the molecular formula was established by high resolution FAB-MS, and the UV spectrum indicated the presence of a quinazolinone, a heterocyclic substructure that appears in a wide variety of natural products.[2] The four-spin systems of the two aromatic rings (C-5–C-8 and C-18–C-21) were identifiable in the ^{1}H NMR spectrum, as well as two exchangeable protons (NH), an isolated methyl group (C$_2$-Me), a methylene group (C-12) coupled to a methine (C-11), and a methine (C-14) with long-range coupling to a methylene (C-15). The connectivity of the aforementioned spin systems was established using a variety of NMR experiments (COSY and HMQC). The stereochemistry at C-14 was established by nOe experiments that established the proximity of this proton to the C-2 methyl group (rather than the C-12 methylene). The absolute configuration of spiroquinazoline was not determined.
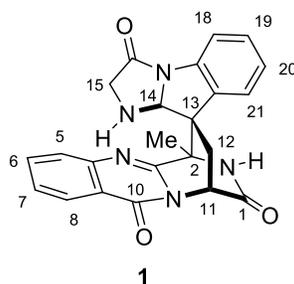
Figure 1. Structure of spiroquinazoline **1**.

Over ten years passed before the structure of lapatin A **2** was reported by Larsen and co-workers.[3] This natural product was isolated from extracts of *Penicillium lapatayae* (5.3 mg of **2** isolated from 200 Petri dishes inoculated with the fungus and grown for 14 days) in a search guided by an automated comparison of UV spectra with those of known compounds. The UV spectrum of **2** was a good match with that of spiroquinazoline and LC-MS established the molecular formula of the natural product. NMR spectroscopy again was the major tool used to establish the structure of lapatin A **2**, including the relative stereochemistry. An nOe between the lactam NH and C-21 aromatic-ring proton established stereochemistry at the spiro center (C-13), an nOe between the H-14 and H-12 indicated stereochemistry at the *N,N*-acetal (C-14), and an nOe between the methyl group at C-15 and H-2 established stereochemistry at C-15 Thus, the major structural differences between **2** and **1** were (1) the substitution pattern at C-2 (methyl in **1** and hydrogen in **2**), (2) the amino acid involved in bridging C-14 to the indoline nitrogen (glycine in **1** and alanine in **2**), and (3) a difference in stereochemistry at C-14 relative to the C-12 methylene group. The absolute stereochemistry of lapatin A was also assigned as shown in Figure 2. The basis of this assignment will be explained later in this section.
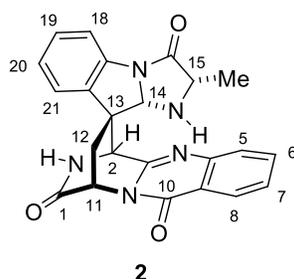
Figure 2. Structure of lapatin A **2**.

The structures of three more alkaloids closely related to spiroquinazoline were reported by the Rodrigues-Filho group in 2005 (Figure 3).[4] These compounds were produced by a *Eupenicillium* fungus isolated from leaves of the plant *Murraya paniculata*. Alanditrypinone **3** (121 mg), alantryphenone **4** (6 mg) and alantryleunone **5** (2.8 mg) were isolated from extracts of

cultures of *Eupenicillium* mycelia grown on white corn for three weeks. The structures of **3-5** were based largely on NMR spectroscopy. As with spiroquinazoline, the relative stereochemistry at C-14 in **3** was established by nOe experiments that showed the proximity of H-14 to the C-2 methyl group (rather than C-12 methylene). The *trans*-relationship between the hydrogens at C-14 and C-15 was also established by nOe experiments. Thus the relative stereochemistry of alanditrypinone was assigned as shown in Figure 3. The structure of alantryphenone **4** was assigned on the basis of similar spectroscopic data, and the structure of alantryleunone **5** was assigned by analogy. The absolute stereochemistry of alkaloids **3-5** was not determined. It is notable and puzzling that the relative stereochemistry between C-14 and C-15 of lapatin A **2** is different from that reported for alkaloids **3**–**5** (hydrogens *cis* in **2** and *trans* in **3**–**5**).

In 2009 the Tomoda group reported the structure of fungal metabolite quinadoline B **6** (6.5 mg isolated from 20 L of fermentation broth of *Aspergillus* sp. FKI-1746).[5] The structure of **6** was ultimately determined by X-ray crystallography. The C-15 stereogenic center was shown to have the *S*-configuration by degradation studies that afforded L-proline, thus defining the absolute configuration of quinadoline B as shown in Figure 3.

3 R = 3-indolylmethyl
4 R = benzyl
5 R = isobutyl

6
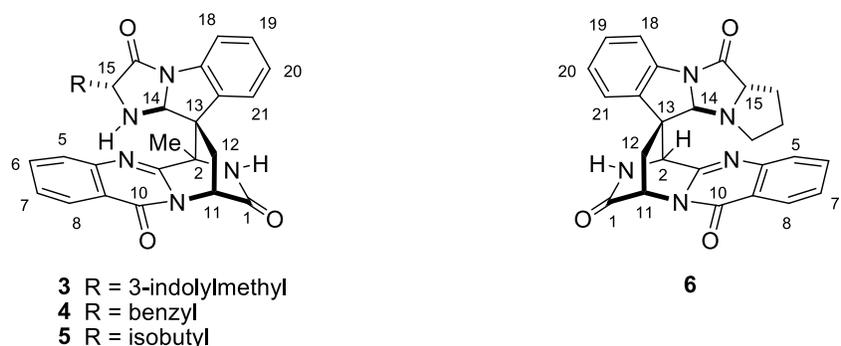
Figure 3. Structures of alanditrypinone **3**, alantryphenone **4**, alantryleunone **5** and quinadoline B **6**.

Alkaloids **1**–**6** have the same carbon skeleton, if one excludes the C-2 and C-15 substituents. In 1998 the Larsen group reported the structure alantrypinone **7** isolated from cultures of the fungus *Penicillium thymicola* (18 mg isolated from 2 L of broth). Alantrypinone differs from spiroquinazoline by virtue of the higher oxidation state at C-14, and necessarily, the absence of an amino acid bridge between C-14 and the oxindole nitrogen.

7 R = Me
8 R = CH$_2$OH

9
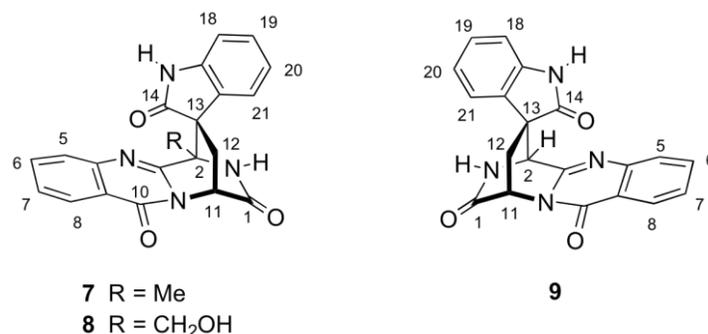
Figure 4. Structures of alantrypinone **7**, serantrypinone **8** and lapatin B **9**.

The structure of alantrypinone was established by X-ray crystallography (Figure 4).[6] Alantrypinone co-crystallized with DMSO and acetonitrile and thus, it was possible to determine its absolute configuration using the anomalous dispersion technique. Finally, the CD spectrum of **7** was essentially the mirror image (opposite Cotton effect) of the CD spectrum of lapatin A **2** (vide supra). These data provided the rationale for assigning the absolute configuration of lapatin A as shown in Figure 2. Alantrypinone has since been isolated from extracts of *Aspergillus terreus* (111 mg from 8 kg of culture) and several other fungal strains of the genus *Penicillium*.[7, 8]

Two structurally related oxindole alkaloids have been reported. Serantrypinone **8** was reported by the Larsen group (6 mg from *Penicillium thymicola*) in 2001.[9] Screening of a number of fungal cultures in an assay directed at identifying insect GABA receptor inhibitors also lead to the isolation of **8** from *Aspergillus terreus* (56 mg from 8 kg of culture broth). The structure of **8** was assigned on the basis of NMR spectroscopy. The CD spectrum of serantrypinone from *Penicillium thymicola* was essentially identical to that of alantrypinone, leading to assignment of absolute configuration as shown in Figure 4. The sign of the specific rotation of serantrypinone isolated from *Aspergillus terreus* (levorotatory),[7] however, was opposite to that isolated from *Penicillium thymicola* (dextrorotatory).[9] It was subsequently shown, by comparison of synthetic material with natural product, that both fungi produce the same enantiomer of serantrypinone (vide infra).

Lapatin B **9** (2.5 mg) has been isolated as a congener with lapatin A (vide supra), from *Penicillium lapatayae* (2.5 mg).[3] The structure was assigned on the basis of spectroscopic data (mainly NMR). The absolute configuration was based on its CD spectrum (same Cotton effect as lapatin A and opposite Cotton effect as alantrypinone and serantrypinone) and has been confirmed by synthesis (vide infra).

Finally, the indoline-containing structure **10** was reported for alantrypinene B, a minor compound also isolated by the Rodrigues-Filho group from *Eupenicillium* fungus (Figure 5).[4] This structure, however, has recently been retracted based on a comparison of signals for the natural product with those of spiroindoline **11** (critical signals noted at C-14, C-17, and C-22 in Figure 5).[10a–c]
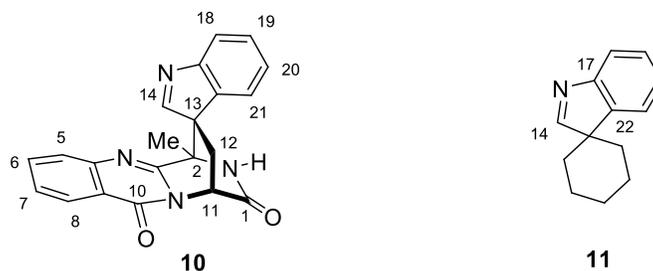
Figure 5. Structure proposed for alantrypinene B **10** and model **11** for NMR analyses.

In summary, nine members of the spiroquinazoline family of natural products have been reported. The complete structures of five of these alkaloids have been established **2** and **6**–**9**. The structures of four of the remaining alkaloids **1** and **3**–**5** seem secure based on spectroscopic data, but their absolute stereochemistry is uncertain. It appears that application of circular dichroism (CD) spectroscopy to these materials should resolve this issue.

2.2 Spectroscopy

Selected chemical shifts taken from ^{1}H and ^{13}C NMR spectra of **1**–**9** are shown in Tables 1 and 2. Trends can be seen that may be of value to research groups identifying new members of this family of natural products, or determining the structures of compounds prepared as intermediates in synthetic studies. For example, H-8 and H-6 in the quinazolinone ring always appear downfield (δ 8.18–8.32 and δ 7.67–7.90, respectively) relative to other aryl hydrogens, due to the electron-withdrawing nature of the C-9 carbonyl group. Presumably due to the different orientation of the indoline *N*-acyl groups, H-18 is upfield in the oxindoles **7**–**9** relative to H-18 in the indolines **1**–**6**.

It has already been mentioned that all of the natural products described in section 2.2 display UV spectra typical of quinazolinones. The spectra consist of a series of absorption maxima with diminishing extinction coefficients in a range from approximately 210 to 315 nm. For a side-by-side comparison of the of lapatin A **2**, alantrypinone **7** and lapatin B **9** the reader is referred to the primary literature.[3]

As mentioned above, CD spectra for lapatin A **2**, alantrypinone **7**, serantrypinone **8** and lapatin B **9** have been reported. Lapatins A and B show similar Cotton effects, while **7** and **8** have similar but opposite Cotton effects (relative to **2** and **9**), resulting (in part) in the absolute configuration assignments depicted in Figures 2 and 3.

Table 1. Chemical shifts (δ) for selected protons in compounds **1**–**9**

Cpd[a]	1	2	3	4	5	6	7	8	9
H-5	7.70	7.64	7.70	7.82	7.73	7.70	7.68	7.75	7.67
H-6	7.76	7.84	7.85	7.90	7.80	7.79	7.85	7.89	7.87
H-7	7.52	7.56	7.59	7.60	7.53	7.50	7.58	7.61	7.60
H-8	8.30	8.18	8.28	8.27	8.34	8.29	8.19	8.22	8.22
H-11	5.67	5.48	5.66	5.69	5.57	5.87	5.58	5.55	5.55
H-12	1.88	2.44	1.85	1.80	1.83	2.35	2.41	2.36	2.38
H-12	3.26	2.62	3.19	3.28	3.10	2.65	2.53	2.41	2.41
H-14	5.47	5.32	5.04	4.99	5.42	5.37	–	–	–
H-15	7.67	7.87	7.60	8.22	6.94	7.31	–	–	–
H-18	7.55	7.46	7.53	7.60	7.50	7.54	6.95	6.89	6.94
H-19	7.33	7.40	7.32	7.36	7.23	7.32	7.31	7.29	7.31
H-20	7.16	7.23	7.14	7.18	7.20	7.11	7.11	7.07	7.09
H-21	7.51	7.16	7.43	7.43	7.32	7.33	7.18	7.22	7.20
2-X[b]	1.74	4.62	1.55	1.57	1.77	4.62	1.19	–	4.33

[a]Spectra taken in CDCl$_3$ except for **7** (DMSO-d_6/CD$_3$CN, 10:1) and **8**, **9**, (DMSO-d_6).
[b]Chemical shift of Me or H on C-2; shift of CH$_2$OH for **8** at δ 3.57 and 3.71.

Table 2. Chemical shifts (δ) for selected carbons in compounds **1**–**9**

Cpd[a]	1	2	3	4	5	6	7	8	9
C1	171.3	170.2	174.8	170.2	172.3	170.7	169.5	169.6	169.3
C2	61.8	56.6	65.0	63.3	63.1	60.6	61.9	64.9	58.8
C3	152.6	152.7	155.2	155.2	154.3	151.1	152.7	152.0	151.0
C4	146.7	147.5	149.8	147.1	150.1	146.6	146.9	146.5	146.9
C5	127.9	127.2	127.6	127.1	127.5	127.1	127.2	127.6	127.1
C6	136.7	134.5	134.6	134.0	134.0	135.0	134.0	134.5	134.5
C-7	127.7	126.7	127.5	127.0	127.0	127.8	126.5	127.1	125.9
C-8	127.2	126.3	127.0	126.2	126.2	127.3	126.0	126.1	126.2
C-9	120.6	120.2	123.7	120.3	123.7	120.9	120.2	120.1	120.1
C-10	158.9	158.5	161.0	162.4	161.3	158.7	158.4	158.3	158.1
C-11	52.0	53.1	52.1	53.0	52.3	53.0	51.8	51.9	52.4
C-12	33.3	36.2	33.0	33.0	25.0	33.9	35.9	37.3	34.5
C-13	56.4	51.4	55.0	55.8	55.8	53.5	54.7	52.5	51.0
C-14	81.1	83.4	80.0	77.5	79.8	91.8	176.6	176.8	176.4
C-15	52.8	58.8	63.0	64.3	62.0	69.4	–	–	–
C-16	170.1	171.0	174.5	173.2	170.0	174.1	–	–	–
C-17	138.0	136.8	141.0	139.0	139.5	137.7	142.4	142.4	141.7
C-18	116.2	114.3	116.3	115.0	116.5	116.8	109.5	109.6	109.7

Table 2. Continued

Cpd[a]	1	2	3	4	5	6	7	8	9
C-19	129.4	129.1	128.0	128.4	128.0	129.6	128.8	128.9	128.9
C-20	126.4	124.7	121.0	126.0	125.5	126.7	122.0	121.8	121.8
C-21	124.0	125.9	124.2	123.2	128.3	123.9	123.6	123.6	123.8
C-22	135.5	138.0	139.1	135.0	136.3	136.8	129.8	129.6	130.5
2-X[b]	15.0	–	15.0	14.3	17.7	–	12.8	57.6	–

[a]Spectra taken in CDCl$_3$ except for **7** (DMSO-d_6-CD$_3$CN, 10:1) and **8**, **9** (DMSO-d_6).
[b]Chemical shift of Me or CH$_2$OH on C-2.

While alkaloids **1**–**9** all exhibit appropriate parent ions in their mass spectra, a distinct *retro-Diels-Alder* fragmentation gives the base peak in the MS of six of these compounds (**3**–**5** and **7**–**9**), regardless of the ionization method used to produce spectra (EI, ES and APCIMS). This fragmentation is illustrated for alantrypinone in Figure 6 in positive ion mode (**7** → **12** + **13**). Mass spectroscopy in negative ion mode provides the corresponding peak at *m/z* 226.[4] It is likely that this fragment appears in all of the alkaloids shown in Figures 1–4. It is notable that a Diels-Alder reaction that accomplishes the reverse of this fragmentation, provides an effective route to oxindole-containing members of the spiroquinazoline family of alkaloids (vide infra).[11]
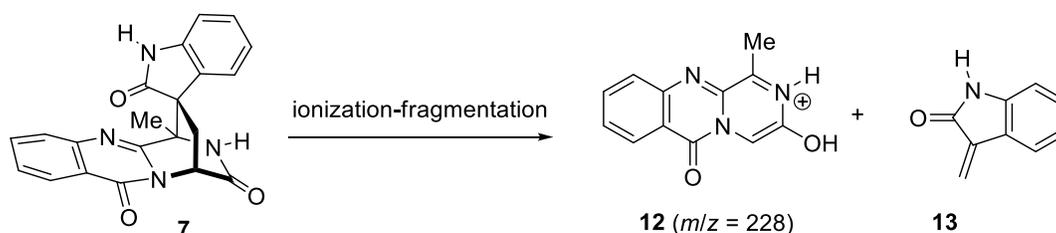
Figure 6. Retro-Diels-Alder fragmentation is typical of spiroquinazoline alkaloids.

2.3 Biosynthetic speculation

The structures of the spiroquinazoline family of alkaloids suggest they are derived from amino acids. Anthranilic acid and tryptophan substructures are clearly present in all members of this family of alkaloids as illustrated for spiroquinazoline in Figure 7. The amino acid alanine, or a derivative thereof, is most likely used to incorporate C-3, C-2 and the 2-methyl group for compounds **1**, **3**–**5**, and **7**. Of course, some oxidation would have to take place at C–2 of the alanine to enable formation of a bond to C–13 (C–3 of the tryptophan residue). Thus, pyruvate or dehydroalanine might also be involved in the biosynthesis of these alkaloids. Glycine (for **2**, **6**, and **9**) and serine or a dehydroalanine (for **8**) would be anticipated to replace alanine for the remaining spiroquinazolines. Finally, an amino acid bridge links the tryptophan-derived substructure from C-14 to the indole-derived nitrogen. This amino acid is glycine in the case of

spiroquinazoline **1** and alanine, tryptophan, phenylalanine, isoleucine and proline, respectively, in the cases alkaloids of **2**–**6**.
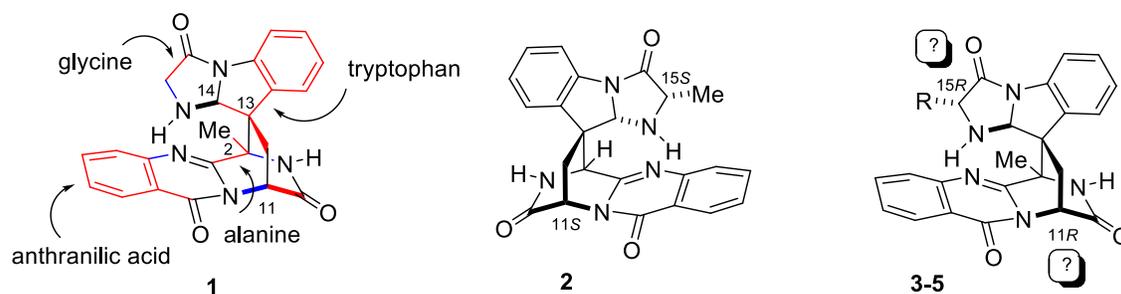
Figure 7. Proposed biosynthetic origins of spiroquinazoline **1** [carbon skeleton in red and a-amino bonds in blue] and lapatin A **2**, and stereochemical questions associated with alkaloids **3**–**5**.

The stereochemistry of the tryptophan and bridging amino acids determines the absolute configuration of the alkaloids. The *S*-configuration at C-11 in lapatin A **2**, quinadoline B **6**, and lapatin B **9** suggests that L-tryptophan is incorporated into these alkaloids. The *S*-configuration at C-15 indicates that an L-amino acid provides the amino acid bridge in **2** and **6**. The story is different for alantrypinone **7** and serantrypinone **8**. The *R*-configuration at C-11 indicates that D-tryptophan is incorporated into these alkaloids. Another possibility is that L-tryptophan is incorporated early in the biosynthesis of **7** and **8**, followed by a post-translational epimerization at the incipient C-11 prior to construction of the C-2–C-13 bond.[12]

The absolute configuration of spiroquinazoline **1** and alkaloids **3**–**5** has yet to be determined. In the case of spiroquinazoline, the only issue is which enantiomer of tryptophan is formally incorporated in the natural product. In the case of alkaloids **3**–**5**, the issue is more complicated. Based on nOe studies, the relative stereochemistry between C-11 and C-15 has been assigned as shown in Figure 3. Thus, if C-11 turns out to have the *R*-configuration (derived from D-tryptophan as for alkaloids **7** and **8**), the bridging amino acid would be derived from the corresponding D-amino acid. Of course, if C-11 has the *S*-configuration, then the bridging amino acid would formally belong to the L-series of amino acids. Barring post-translational epimerization, either two D-series or two L-series amino acids must be incorporated into alkaloids **3**–**5**. CD studies should resolve uncertainties in assignment of absolute configuration of **1** and **3**–**5**. Feeding studies might resolve the question of which enantiomers of tryptophan and the bridging amino acids are really involved in the biosynthesis of these alkaloids.

Before leaving the biosynthetic origins of the spiroquinazolines, it is worth mentioning several biosynthetically related quinazolinone-containing natural products (Figure 8). Glyantrypine **14** is a fungal metabolite that has been isolated from *Aspergillus clavatus*.[13] Feeding studies have shown that anthranilic acid, tryptophan and glycine are incorporated in this natural product.[14] Whereas both enantiomers of this natural product have been prepared by total

synthesis, the absolute configuration of this alkaloid is still unknown, in part because DL-tryptophan was used in the aforementioned feeding studies.

14 R^1 = R^2 = H
15 R^1 = Me, R^2 = H
16 R^1 = H, R^2 = Me

17
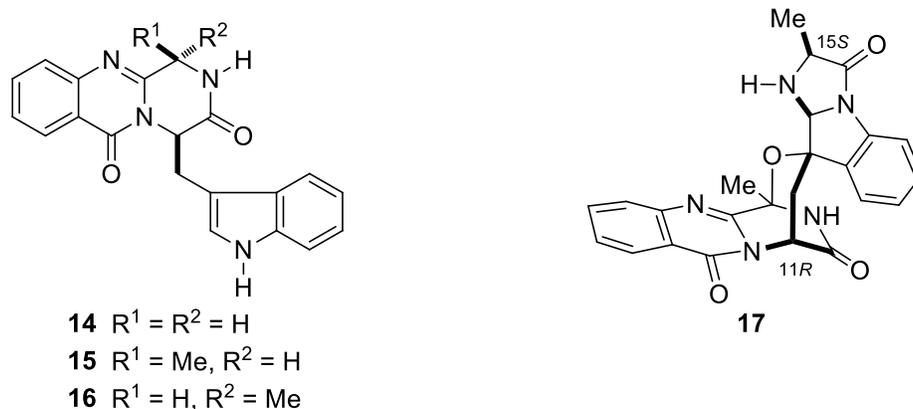
Figure 8. Structures of glyantrypine **14** and fumiquinazolines G **15**, F **16** and C **17**.

Fumiquinazolines G **15** and F **16** have also been isolated from fungi (*Penicillium thymicola* and *Aspergillus fumigatus*). In each case the absolute configuration has been determined by synthesis (see Figure 8).[15,16] It is clear that the fungi produce these natural products with formal introduction of D-tryptophan. Finally, fumiquinazoline C **17** has been isolated from *Aspergillus fumigatus*.[15] The absolute configuration of **17** was determined by a combination of X-ray crystallography and degradation studies (to give L-alanine) and confirmed by total synthesis.[15,17] The structure of fumiquinazoline C clearly resembles the spiroquinazolines, the difference being insertion of an oxygen atom in the bridge connecting C-2 and C-11. Thus, there is ample precedence for the formal incorporation of D-tryptophan into alkaloids closely related to the spiroquinazolines.

3. Biological Activities

The reason why fungi produce spiroquinazoline-type alkaloids is not known, but biological activities have been observed for several of these natural products. A brief summary will be presented here.

As mentioned in the introduction, spiroquinazoline was discovered during a search for inhibitors of SP binding to the human NK-1 receptor, possible lead compounds for development of analgesics. Spiroquinazoline **1** inhibited binding of tritiated-SP to human astrocytoma cells (a rich source of NK-1 receptors) with a K$_i$ of 95 μM.[1] This is regarded as a low level of activity.[18]

Quinolidine B **6** was initially shown to be a weak inhibitor of lipid droplet synthesis in mouse macrophages.[5] Lipid droplets have been invoked in the uptake and storage of esters derived from cholesterol (CE) and triacylglyerols (TG) in the development of obesity and atherosclerosis.[19]

Further studies showed that **6** inhibited CE synthesis with an IC_{50} of 93 μM, but had no effect on TG synthesis.[5] Inhibitors with nearly a thousand-fold greater activity are known and thus, these compounds are unlikely to be of interest for treatment of disorders that involve lipid synthesis.

The isolation of oxindole-containing members of the spiroquinazoline family by the Larsen group was not driven by biology.[3,6,8,9] However, a search for insect GABA inhibitors from fungal cultures was the driving force behind the discovery of alantrypinone **7** and serantrypinone **8** by Ozoe and coworkers.[7] GABA receptors are believed to be targets for several insecticides as they are involved in neurotransmission events associated with the nervous system of insects. Receptor binding was determined by examining extracts for inhibition of tritiated-EBOB **18** (Figure 9) binding to housefly head membranes. It was shown that **7** and **8** inhibited such binding with IC_{50} values of 0.34 μM and 2.1 μM, respectively. Since GABA receptors also play important physiological roles in mammals, **7** and **8** were also evaluated in rat brain membranes where they exhibited IC_{50} values of 16 μM and 128 μM, respectively. Thus, **7** and **8** are 47-fold and 61-fold more selective for the insect GABA receptor than the mammalian GABA receptor (in rats). This suggested that these alkaloids might be less toxic toward mammals than insects.[7]

	2-R	6-R	7-R	20-R
19	Me	H	Cl	H
20	Me	H	F	H
21	Me	Cl	H	H
22	Me	H	H	Cl
23	Me	H	Cl	Cl
24	Bn	H	H	H
25	*i*-Pr	H	H	H
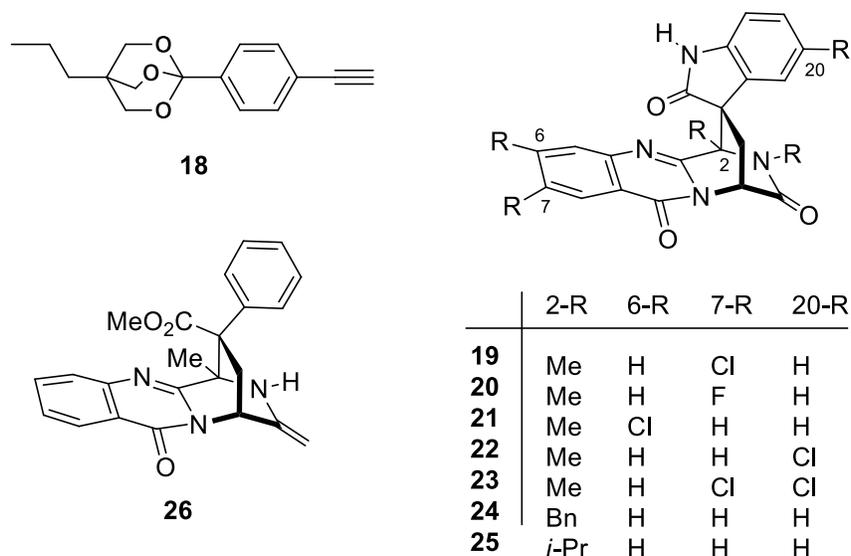
Figure 9. Synthetic inhibitors of EBOB **18** binding to housefly head membranes.

Since the initial report from the Ozoe group, it has been shown that *ent*-alantrypinone and *ent*-serantrypinone inhibit EBOB binding to housefly head membranes with IC_{50} values of 2.31 μM and 6.36 μM, respectively. Thus, the enantiomers of the natural products retain some GABA inhibition activity, and racemic alantrypinone is nearly as active as the natural product.[20, 21] Furthermore it has been shown that lapatin B **9** also inhibits EBOB binding to housefly head membranes with an IC_{50} of 17 μM.

Finally, GABA binding inhibition of about 30 racemic synthetic analogs of alantrypinone have been evaluated.[21] This study identified compounds **19**, **20** and **23**–**25** as inhibitors with IC_{50}

values of 1 µM or better (similar to alantrypinone itself), and compounds **21**, **22** and **26** as compounds with IC$_{50}$ values of close to 10 µM. It was also found that alkyl substitution at the lactam nitrogens decreased activity, with substitution at the oxindole nitrogen having the larger effect. C-13 epimers tended to show much reduced activity.

4. Synthesis

4.1 Total Synthesis of Alantrypinone (7) and *ent*-Alantrypinone (27 or *ent*-7)

The first synthesis of *ent*-alantrypinone **27** was described in 1999.[22,23] This research was actually a diversion of a synthetic program directed at spiroquinazoline **1**, whose synthesis from L-tryptophan was being pursued when the structure of **7** was reported.[6] The late stages of the synthetic plan were inspired by the biosynthetic speculation described in Section 3 of this review (Scheme 1). It was anticipated that protonation of enamide **29** would be followed by an electrophilic aromatic substitution reaction to provide indole **28**. Transformation of **28** into oxindole **27** was then to be accomplished using prior art.[24]
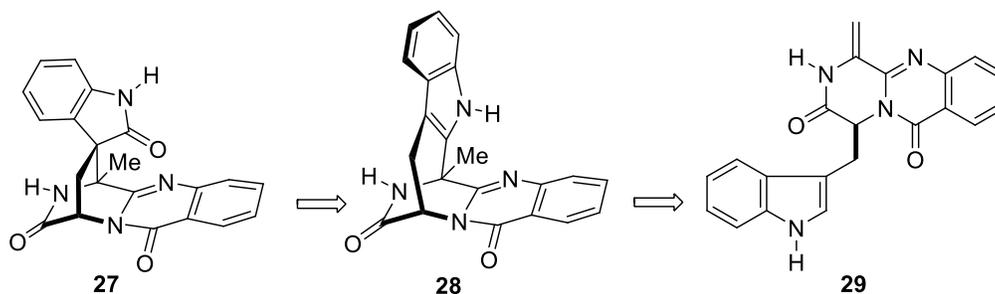
Scheme 1. Plan for synthesis of *ent*-alantrypinone **27**.

The synthetic plan was well grounded in the work of Ottenheijm who had shown that diketopiperazine **30** was converted to **32** upon treatment with acid, perhaps via indoline **31** (Scheme 2).[25] Evidence for the speculation of **31** as an intermediate was later supplied when **33** was treated with pyruvoyl chloride (acylation of the hydroxamic acid) followed by trifluoroacetic acid to provide **34** in 72% yield along with 12% of indoline **35** as a minor product (Scheme 2).[26]
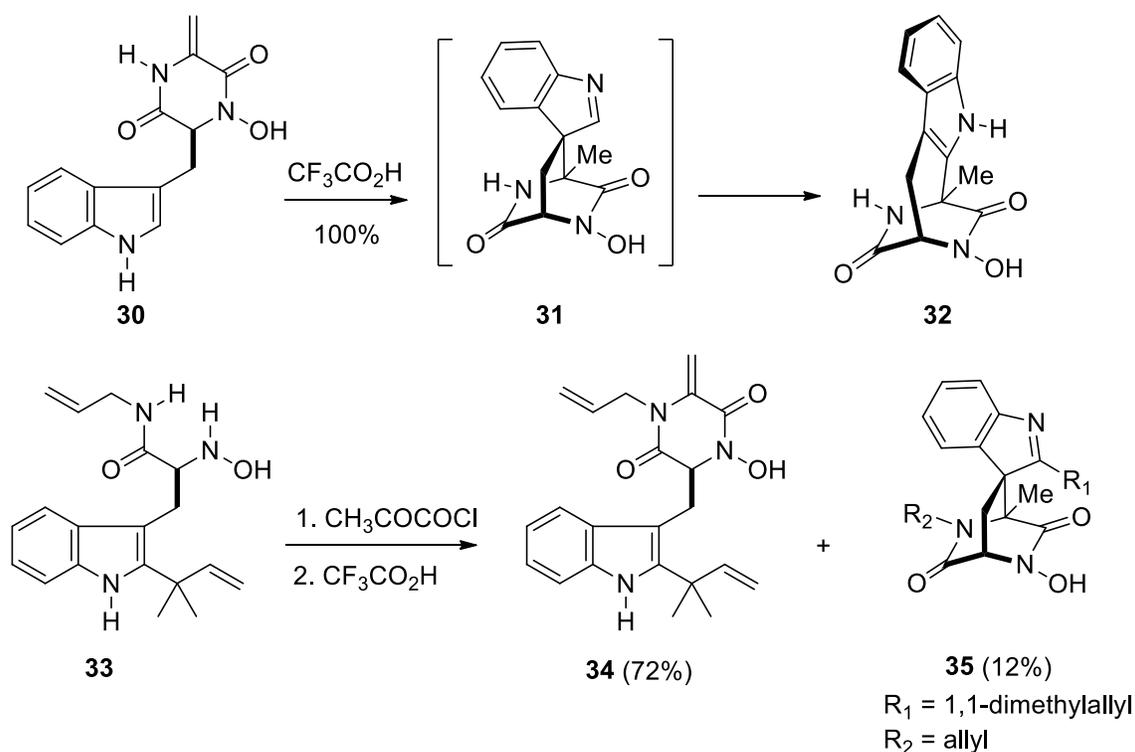
Scheme 2. Ottenheijm's studies in the field of diketopiperazine chemistry.

The synthesis of *ent*-alantrypinone **27** began with the preparation of enamide **29** as shown in Scheme 3. This material had previously been prepared by Snider using a different route.[16a] Acylation of dipeptide **38**, prepared from L-tryptophan methyl ester **36** and isatoic anhydride **37**, with the acid chloride derived from *N*-Fmoc-*S*-methylcysteine gave tripeptide **39**. This material was converted to iminobenzoxazine **40**, which rearranged to quinazolinone **42** upon treatment with Li[Me₃AlSPh],[27] possibly via the intermediacy of iminothioester **41**. Removal of the Fmoc group provided **43**. This cyclodehydration procedure is a modification of the Ganesan-Mazurkiewicz cyclization, a process that has played an important role in the synthesis of a number of quinazolinone-containing alkaloids.[16a-16d,28]

The synthesis of **29** was completed by oxidation of sulfide **43** to a mixture of diastereomeric sulfoxides **44** followed by elimination of methanesulfenic acid in the presence of triphenylphosphine as a sulfenic acid trap.
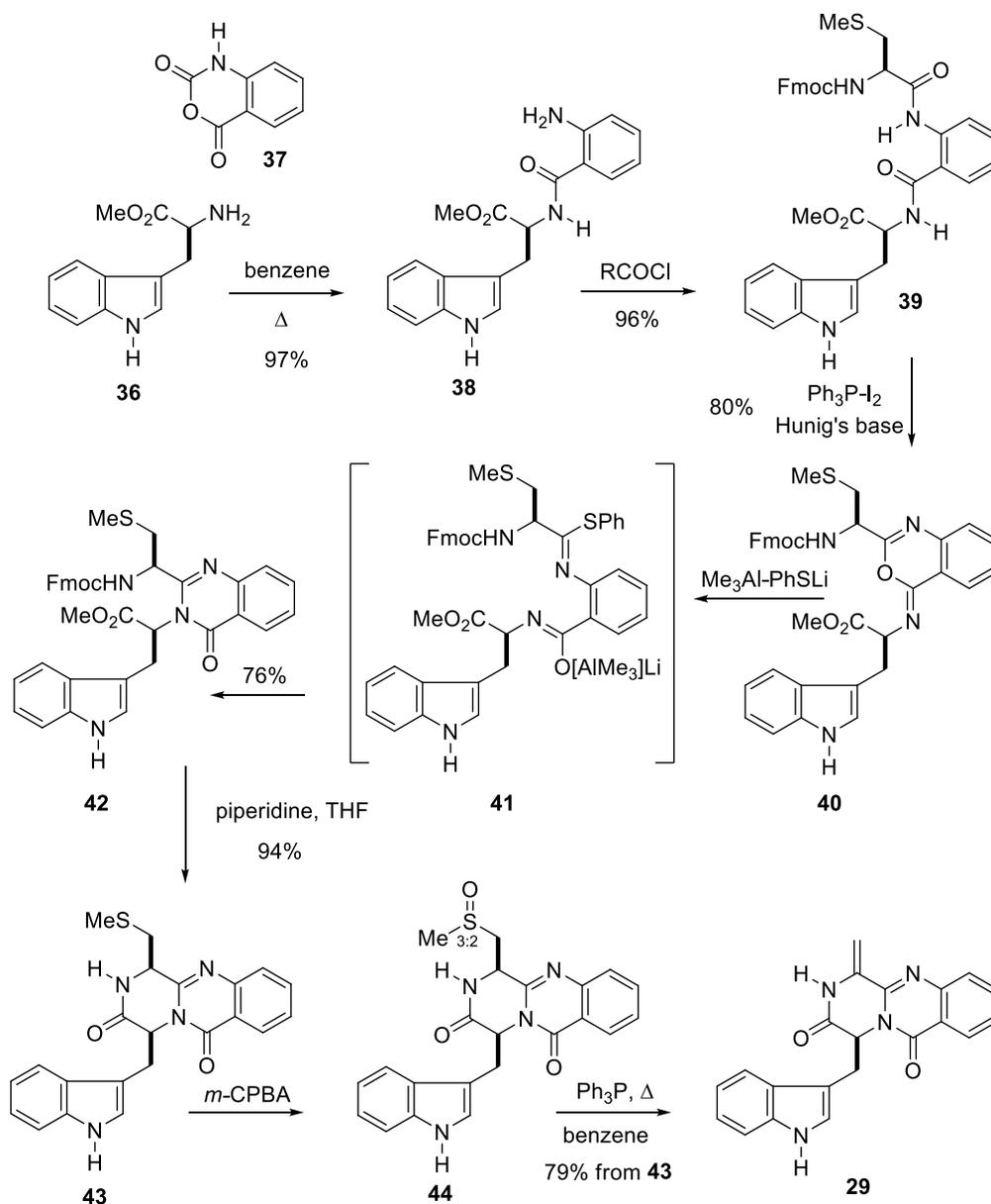
Scheme 3. Preparation of enamide **29** en route to *ent*-alantrypinone.

The synthesis of *ent*-alantrypinone **27** was completed in three steps as shown in Scheme 4. Treatment of **29** with trifluoroacetic acid gave bridged indole **28** as expected based on the precedence provided in Scheme 2. Treatment of **28** with NBS under aqueous acidic conditions provided a mixture brominated oxindoles (largely brominated at C-20). Hydrogenolysis of the aryl bromides gave *ent*-alantrypinone (**27** or *ent*-**7**) and the C-13-epimer of *ent*-alantrypinone **45**. As well documented in the literature, the indole-oxindole conversion most likely passes through an intermediate bromohydrin and/or the corresponding indoline. Oxindoles **27** and **45** were readily separated by chromatography over silica gel. This is presumably a result of the oxindole

lactam in **45** [R_f (SiO$_2$) = 0.34 in EtOAc] being much more accessible to the silica gel surface than the corresponding lactam in **27** [R_f (SiO$_2$) = 0.49 in EtOAc]. The ^{1}H NMR spectra of **27** and **45** were similar with a glaring exception in the chemical shift values for the oxindole aromatic protons. Most notable is the appearance of H-21 at δ 5.87, an upfield shift (relative to alantrypinone) that no doubt reflects its disposition to the π-system of the quinazolinone ring system. The polarity and spectroscopic differences noted for *ent*-**7** and **45** appear to be reliable markers for distinguishing these C-13 epimers from one another.
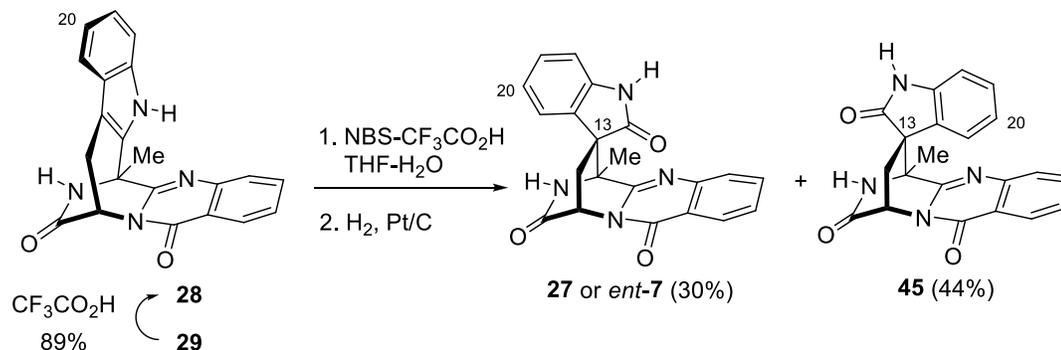
Scheme 4. Synthesis of *ent*-alantrypinone (**27** or *ent*-**7**) and its C-13 epimer **45**.

The synthesis of *ent*-alantrypinone **27** confirmed the absolute stereochemical assignment for alantrypinone **7** made earlier on the basis of X-ray crystallography.[6] The conversion of indole **28** to oxindole **27**, however, lacked stereocontrol at C-13. A racemic synthesis of alantrypinone, reported by the Kende group, presents an interesting solution to this problem.[29,30]

The Kende synthesis follows the Diels-Alder route eluded to in the discussion of Figure 6 (vide supra). The key reaction is a cycloaddition between heterocyclic dienophile **52** (Scheme 5) and 3-alkylidene oxindoles. Dienophile **52** was prepared in six steps as shown in Scheme 5. Anthranilic acid **46** was converted lactam **50** via a reaction sequence that relied on the aforementioned Ganesan-Mazurkiewicz cyclization. Ethylation of the lactam oxygen gave **51** and oxidation using DDQ to provided dienophile **52** as a crystalline solid.
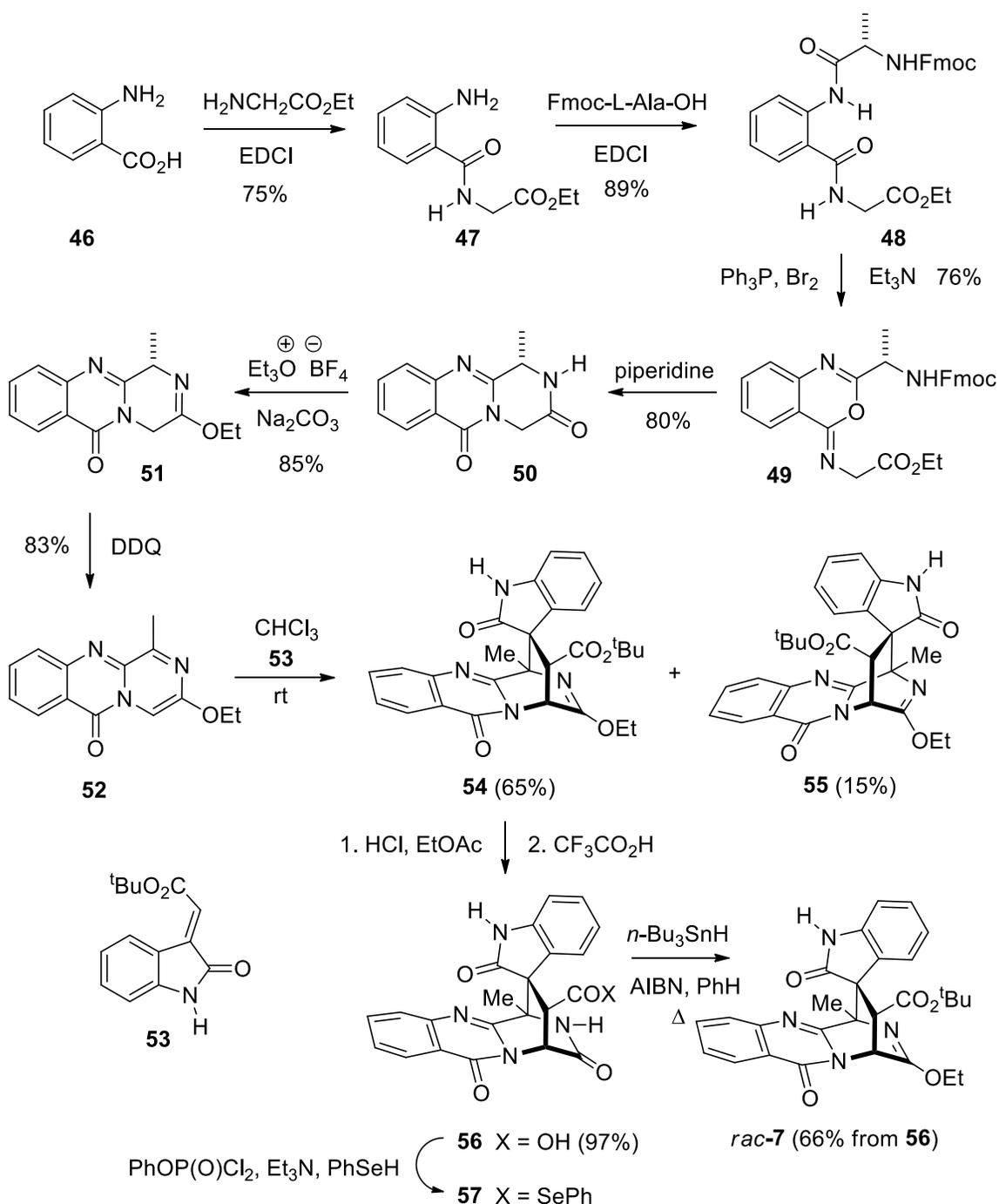
Scheme 5. Kende's first generation synthesis of racemic alantrypinone (*rac*-**7**).

In a first generation synthesis, dienophile **52** was treated with oxindole **53** (from isatin and Ph₃P=CHCO₂ᵗBu) at room temperature to give a mixture of cycloadducts **54** and **55**, separable by chromatography over silica gel.[30] Isomer **54** was hydrolyzed (first the imidate with aqueous HCl and then the ester with trifluoroacetic acid) to give carboxylic acid **56**. The acid was then

converted to the corresponding selenoester **57**, which was reduced under free radical conditions to provide racemic **7**.

In a second generation synthesis (Scheme 6), the Kende group simply used oxindole **13** (from isatin and trimethylsilylmethylmagnesium chloride according to a literature procedure) as the dienophile. The cycloaddition between **52** and **13** proceeded smoothly to provide **58** and **59** in 55% and 18% yields, respectively. The diastereomeric cycloadducts were separated and independently hydrolyzed to give racemic **7** (from **58**) and **45** (from **59**).
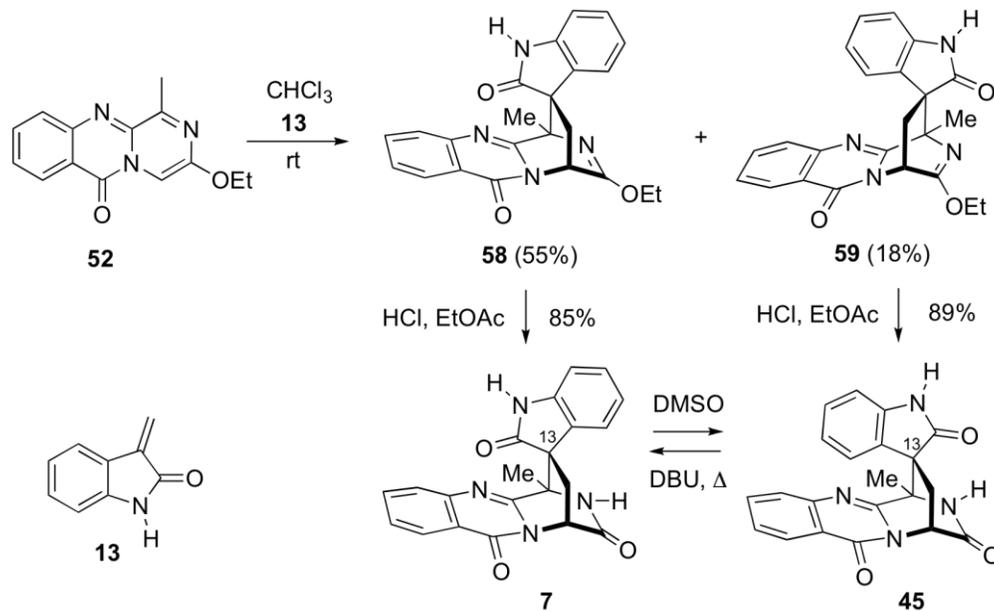
Scheme 6. Kende's second generation synthesis of racemic alantrypinone (*rac*-**7**).

Finally, the Kende group made the important observation that **7** and **45** can be interconverted under basic conditions. For example, heating either **7** or **45** in DMSO containing DBU provided an approximately 3:1 mixture of **7** and **45**, respectively. This process requires epimerization at a quaternary carbon. The Kende group conclusively showed that this epimerization did not involve a retro-Diels-Alder process and suggested that instead, the epimerization involved an anionic retro-Mannich process. Regardless, this provides a means for achieving some degree of control over stereochemistry at C-13.

The Kende synthesis is quite versatile. Indeed a variation of this method was used for the extensive analog program, developed in the groups of Nishida, Arisawa, Ozoe and Meiji Seika Kaisha as described in Figure 9.[21] A tactical change in this work was the use of microwave technology to expedite the synthesis of intermediate **50** (Scheme 7). Thus, anthranilic acid **46** was first coupled with *N*-Boc-L-alanine, followed by addition of ethyl glycinate and microwave irradiation for a short period of time, to provide **50** in 57% yield. Microwave technology was introduced to the field by the Liu group in their syntheses of glyantrypine and related natural products.[16f] An interesting aspect of this work was demonstration that cycloadduct **58** could be

used to differentially functionalize the two secondary lactams in alantrypinone (Scheme 7). Thus, *N*-alkylation of **58** followed by iminoether hydrolysis gave **60**. On the other hand, *N*-sulfonation of oxindole **58**, followed by iminoether hydrolysis, *N*-alkylation, and removal of the benzenesulfonyl group from the oxindole nitrogen, gave **61**.
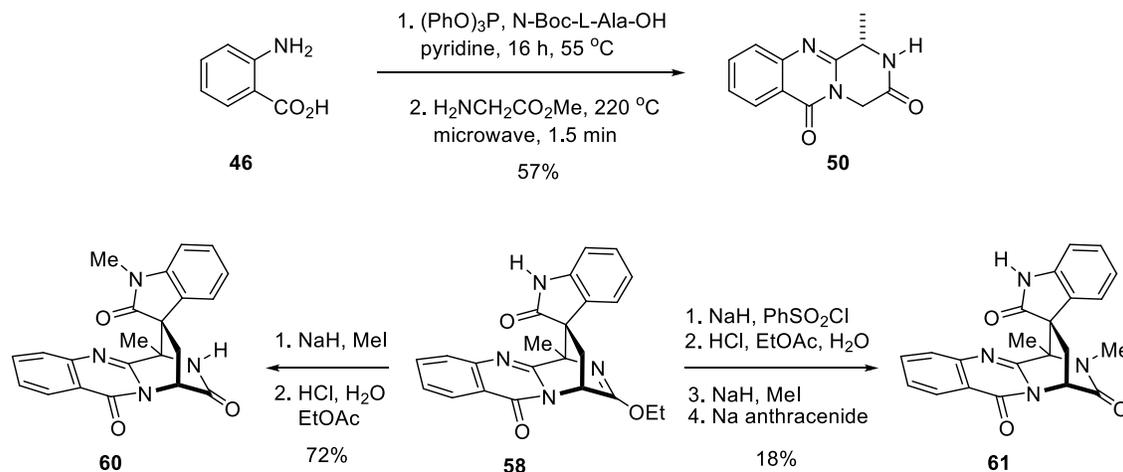
Scheme 7. Tactical improvements on the Kende synthesis and lactam differentiation.

The Avendaño group has described a formal synthesis of alantrypinone that intercepts the aforementioned *ent*-alantrypinone synthesis (Schemes 3 and 4) at the stage of indole **28**. The synthesis proceeds through (–)-glyantrypine **14** as shown in Scheme 8.[16e,31] D-Tryptophan methyl ester **36** was converted to diketopiperazine **63**. Conversion of **63** to bis-lactim ether **64** was followed by a regioselective acylation with *o*-azidobenzoyl chloride to provide **65**. An intramolecular Staudinger reaction (sometimes referred to as the Eguchi reaction when imides serve as the electrophilic component of the reaction) was used to provide (–)-glyantrypine **14**.[32,33]

(–)-Glyantrypine was converted to *ent*-**28** as shown in Scheme 9. The indole and lactam nitrogens were first protected with Boc groups to provide **66**. Methylenation at C-2 was accomplished using a procedure that resembles the Vilsmeier reaction and most likely proceeds through the enamine tautomer of **66**. The resulting mixture of **67** and **68**, was converted to *ent*-**28** upon prolonged warming with trifluoroacetic acid. This reaction sequence gave a lower overall yield of *ent*-**28** when the Boc protection step (**65** → **66**) was omitted. The *ent*-**28** prepared in this manner had a specific rotation (Na D-line) equal in magnitude but opposite in sign to that reported for **28** and thus this work can be regarded as a formal synthesis of alantrypinone **7**.[34]
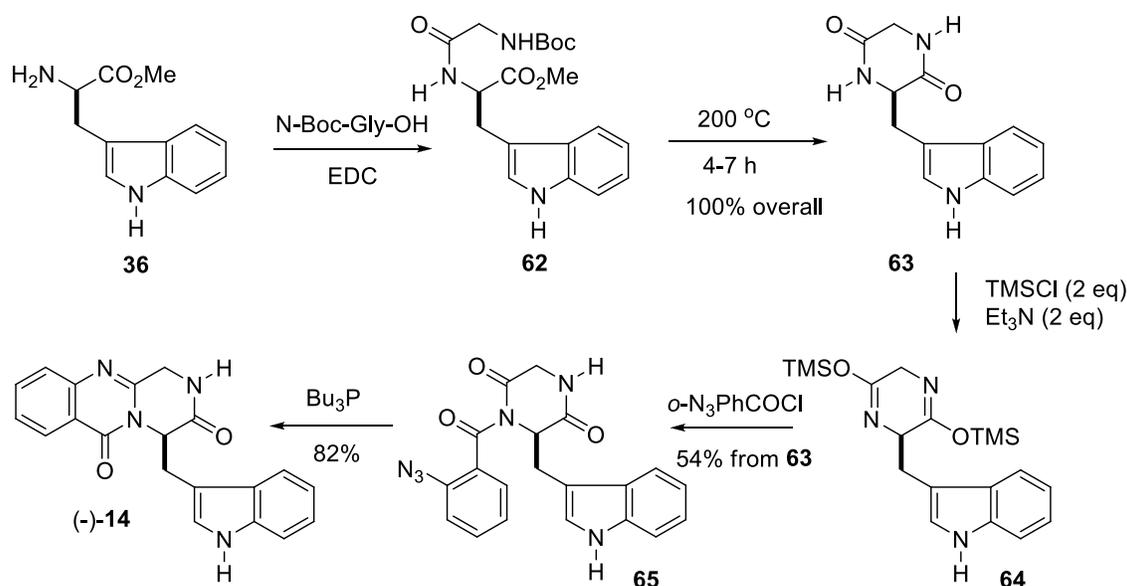
Scheme 8. Avendaño synthesis of (−)-glyantrypine **14** en route to alantrypinone.
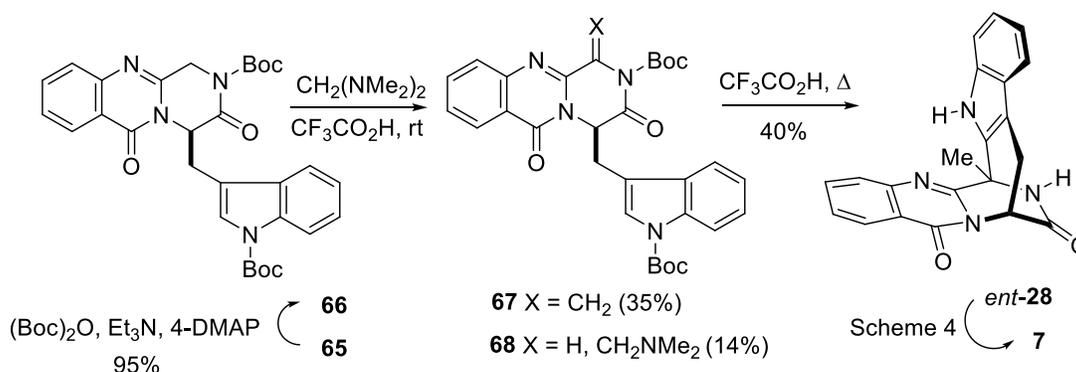
Scheme 9. Completion of Avendaño's formal synthesis of alantrypinone **7**.

4.2 Total synthesis of serantrypinone (8)

The only synthesis of serantrypinone (to date) was reported in 2007.[35] The synthesis actually provided the enantiomer of the natural product (*ent*-**8**), but was important in that it resolved issues regarding the absolute configuration of this alantrypinone derivative (see Section 2.1 of this review and the primary literature for a complete discussion of the problem).

The synthesis mimicked the pathway defined by the first synthesis of alantrypinone and followed the chemistry described in Scheme 10. The original idea was use an electrophile-initiated cyclization of enamide **29** to afford compounds of type **69** in which the electrophile could be converted to the hydroxyl group required by serantrypinone. Attempts to epoxidize the exocyclic olefin of **29** failed, although it is still expected that this epoxide, if it could be prepared, would provide **69a** upon treatment with acid. Treatment of **29** with iodine in THF provided **69b**

in 50% yield.[36] Hydrogen iodide produced in this reaction, however, gave **28** (20%) as an unwelcome side product. This problem was eliminated by including an HI trap (styrene oxide) in the reaction mixture. In this manner, the **28** was not formed and the yield of iodide **69b** improved to 57–75%.[36] Conversion of the hindered iodo group to a hydroxyl group, either before or after conducting the indole-to-oxindole transformation, was not successful. Treatment of **29** with phenylselenenyl chloride gave selenide **69c** in 78% yield. The hope was that a seleno-Pummerer reaction could be used to convert the selenide to the corresponding alcohol via reduction of an intermediate aldehyde. Oxidation of **69c** provided a mixture of diastereomeric selenoxides **70**. Treatment of this mixture with acetic anhydride under typical Pummerer conditions provided a complex mixture of products from which **71** was isolated as the only identifiable material. Thus, this reaction sequence unexpectedly gave a compound that would clearly have value in a serantrypinone synthesis, albeit it low yield.
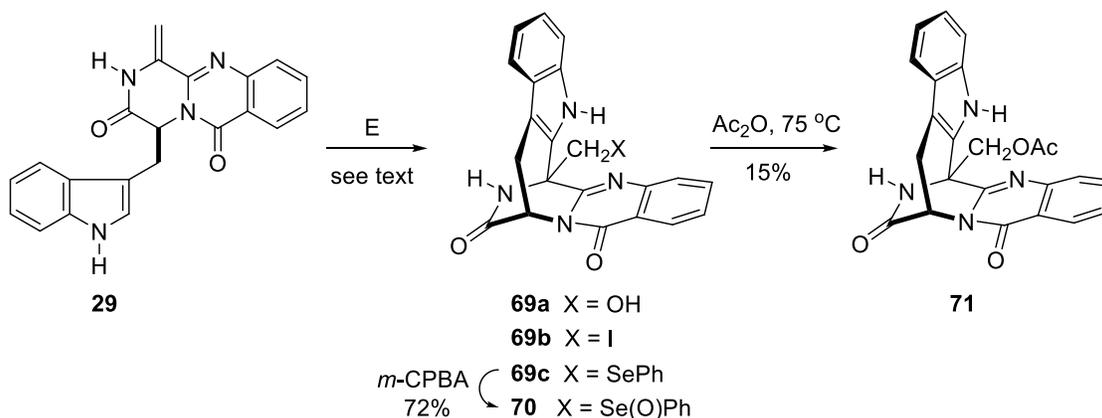
Scheme 10. Unexpected conversion of selenoxide **70** to acetate **71**.

It was speculated that **71** was formed by a series of events that involved (1) acetylation of the lactam nitrogen of **70** by acetic anhydride, (2) activation of the selenoxide via acylation of the oxygen by acetic anhydride, (3) intramolecular displacement of PhSeOAc from carbon by the *N*-acetyl carbonyl group, and (4) capture of the resulting reactive intermediate followed by breakdown to give **71**. This hypothesis suggested that the overall yield of **69c** from **71** might be improved by intentional *N*-acetylation of the selenide prior to oxidation and subjection of the selenoxide to an activating agent. This was accomplished as shown in Scheme 11.

Selective *N*-acylation of the lactam nitrogen (over the indole nitrogen) was accomplished using acetic anhydride. Oxidation of the resulting imide **72** gave a mixture of selenoxides, which was immediately treated with acetic anhydride to provide acetate **71** in 30–53% yields. When acetic anhydride-d_6 was used to acetylate **69c**, and seventy equivalents of unlabelled acetic anhydride were used in the subsequent rearrangement, only a CD_3 group appeared in the O-acetyl group of **71**. This provided strong evidence in support of the proposed mechanism.
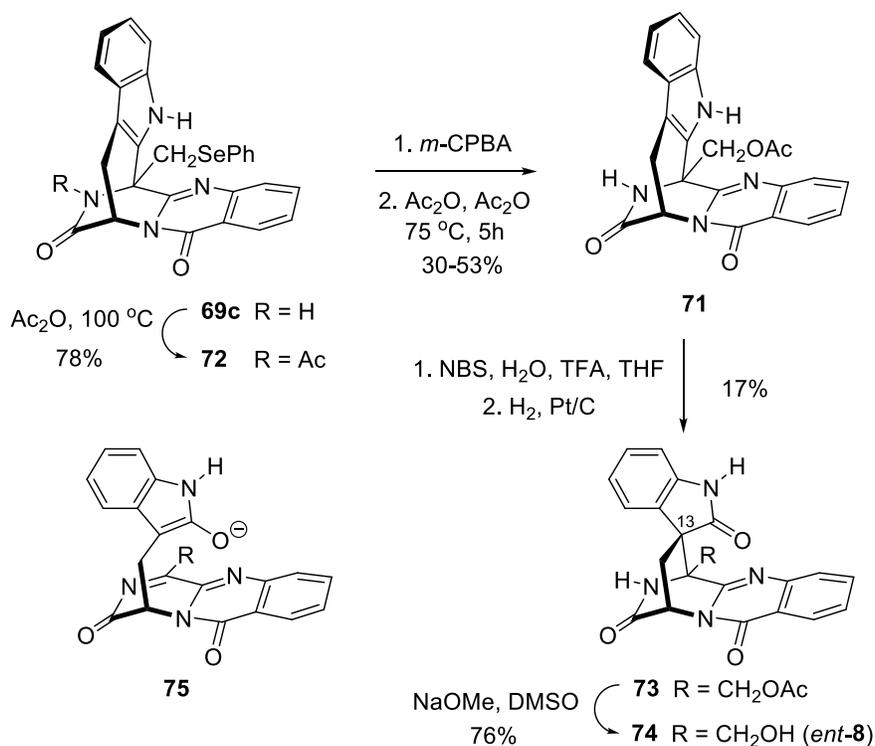
Scheme 11. Completion of *ent*-serantrypinone synthesis (**74** = *ent*-**8**).

The synthesis was completed in a manner similar to that used to prepare *ent*-alantrypinone. Indole **71** was converted into oxindole **73** in the usual manner. The C-13 epimer of **73** was also obtained from this process in 4% yield. Removal of the hindered acetate was accomplished using excess sodium methoxide in DMSO at room temperature over a period of 3 days. The rate of transesterification increased at elevated temperatures, but epimerization at C-13, presumably via **75** as proposed for alantrypinone by Kende, was also observed. A head-to-head comparison (HPLC over a chiral support) of synthetic *ent*-serantrypinone with natural product isolated from *Aspergillus terreus*, and comparison of the CD spectrum of synthetic material with that reported for serantrypinone isolated from *Penicillium thymicola*, established the identity of the natural product.

4.3 Total synthesis of lapatin B (9)

Two syntheses of Lapatin B have been reported.[37,38] The first synthesis, from the Syntenta group in Switzerland, followed the Kende approach to alantrypinone and gave racemic material. The second synthesis followed the aforementioned routes to *ent*-alantrypinone and *ent*-serantrypinone and confirmed that the absolute configuration of lapatin B **9** is pseudoenantiomeric with alantrypinone **7** and serantrypinone **8**.

The Syngenta synthesis began with the preparation of azadiene **76** from anthranilic acid **46** using a four-reaction sequence that applied a combination of the chemistry described in Schemes

5 and 7 (Scheme 12). Reaction of **76** with methyleneoxindole **13** gave a 7:1 mixture of endo and exo cycloadducts (**78** and **77**, respectively). When the reaction was promoted by triflic acid, the ratio of endo and exo isomers changed to 1:1. Hydrolysis of iminoester **77** under mild conditions afforded amino acid hydrochloride **79**, and more forcing conditions gave racemic lapatin B (*rac-***9**).
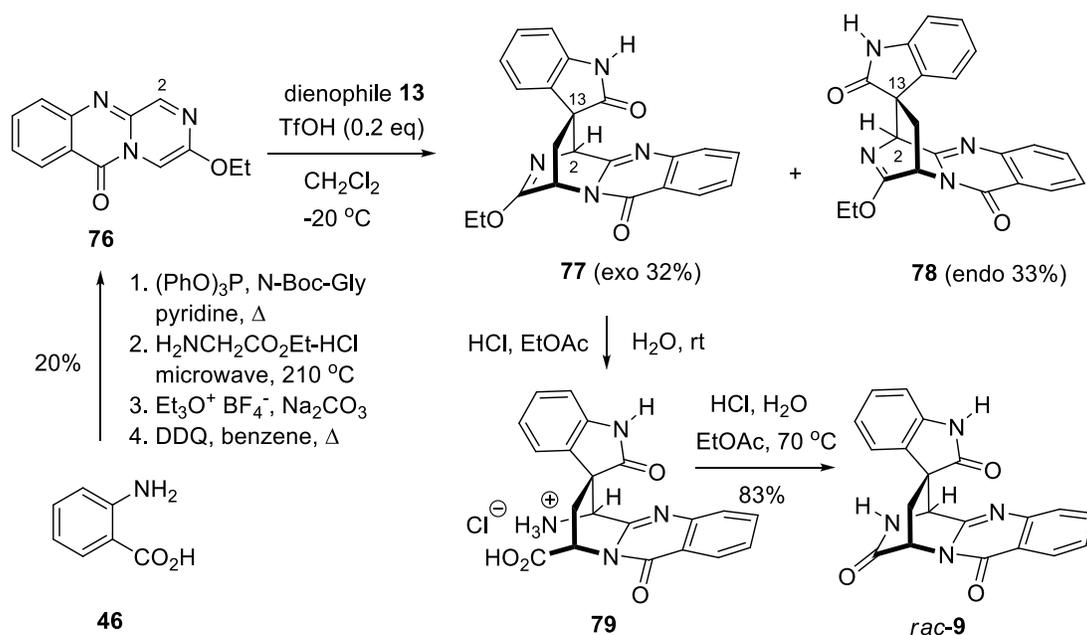
Scheme 12. Syngenta synthesis of racemic lapatin B (*rac-***9**).

The Syngenta group also investigated the effect of solvents and acid catalysts on the cycloaddition between azadiene **52** and dienophile **13** used in the Kende synthesis of alantrypinone (see Scheme 6). In the hands of the Syngenta group, this reaction gave a 1:2 mixture of exo and endo cycloadducts (**58** and **59**, respectively) in chloroform at room temperature. Computational studies suggested that the more polar the solvent, the greater should be the exo selectivity. In this regard it was found that use of acetonitrile as the solvent gave a 2:1 mixture of the exo **58** and endo **59** cycloadducts. In terms of Lewis acid promotion, it was found **52** and **13** reacted in the presence of one equivalent of Eu(fod)$_3$ to provide only endo cycloadduct **59** in 73% yield. However, use of triflic acid as a catalyst (0.2 equivalents) gave exo cycloadduct **58** with high selectivity in 68% yield. The difference of behavior between azadienes **76** (less stereoselective) and **52** (more stereoselective) indicates the size of the C-2 substitutent influences stereoselectivity. In a practical sense, these observations provided a tactical improvement to the Kende alantrypinone synthesis and enabled the first synthesis of lapatin B.
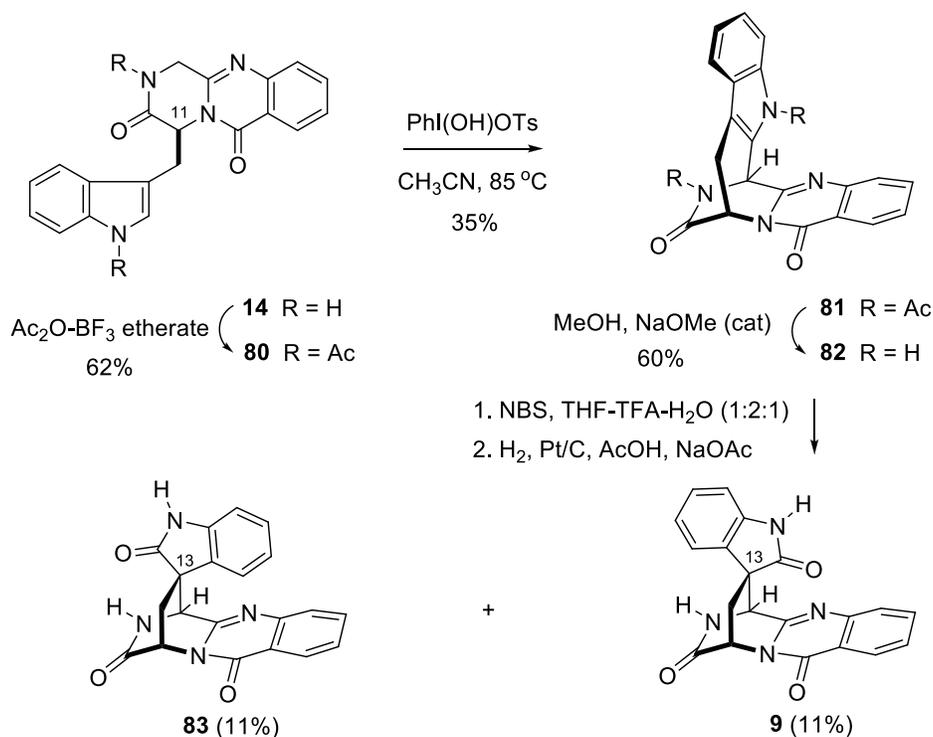
Scheme 13. Enantioselective synthesis of lapatin B **9**.

The first enantioselective synthesis of lapatin B is described in Scheme 13.[38] The synthesis began with the preparation of (+)-glyantrypine **14** from L-tryptophan methyl ester using either the method of Ganesan, or the modification of the Ganesan-Mazurkiewicz cyclization shown in Scheme 3, to accomplish the critical imino-benzoxazine-to-quinazolinone rearrangement. From a tactical standpoint, the Ganesan procedure gave slightly better yields.[16c] Heating **14** with excess of acetic anhydride in the presence of pyridine, with 4-dimethylaminopyridine as a catalyst, gave **80** in 81% yield, but with racemization at C-11. Use of acidic acetylation conditions, however, provided **80** without any epimerization at C-11 (Scheme 13). Oxidative cyclization of **80** was accomplished using Kosar's reagent [PhI(OH)OTs] in acetonitrile to give indole **81** in 35% yield. The oxidation portion of this reaction was modeled after observations reported by the Avendaño group during the course of their studies of the chemistry of pyrazino[2,1-*b*]quinzaline-3,6-diones.[39] Methanolysis of the acetyl groups under basic conditions gave **82**. The indole-to-oxindole rearrangement, followed by hydrogenolysis of extraneous aryl bromides, completed the synthesis of lapatin B **9** and also provided the C-13 epimer of lapatin B **83** in low yields.

4.4 Approaches to spiroquinazoline (1)
Several approaches to spiroquinazoline have been reported but none have succeeded to date. This section will briefly review approaches that have been attempted or are underway.

One failed approach to spiroquinazoline is described in Schemes 14–16.[40,41] The plan (Scheme 14) was to generate an *N*-acyliminium ion of type **85** by electrophile initiated ionization

of an N,S-acetal of type **84**. Scheme 14 depicts a methyl cation equivalent (iodomethane for example) as the S-activating group, but a number of alternatives were imagined. It was hoped that **85** might cyclized with C-3 of the indole behaving as a nucleophile. Furthermore it was hoped that the resulting *N*-acyliminium ion **86** might be captured by the glycine-derived nitrogen to provide spiroquinazoline **1** after deprotection of the nitrogens.
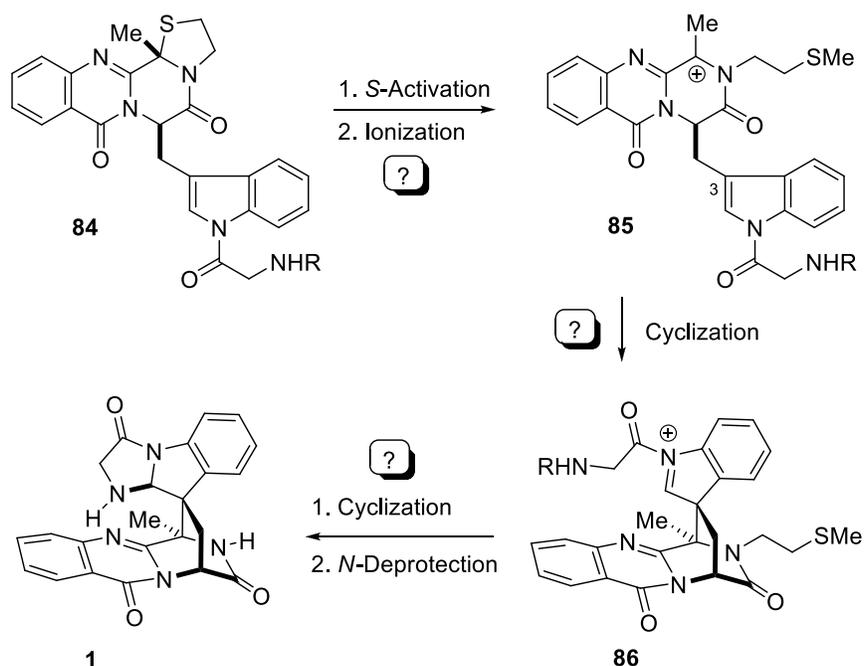
Scheme 14. Plan for conversion of **84** to spiroquinazoline **1** via a cyclization cascade.

The plan did not work, but unveiled chemistry of some relevance to the field. Racemic **88** was prepared from the known quinazolinone **87** as indicated in Scheme 15. Attempts to activate **88** by alkylation or with other electrophiles such as mercuric triflate gave no identifiable products. Activation of the sulfur via oxidation to sulfoxide **89** led to some interesting chemistry. Warming **89** with trifluoroacetic acid gave ring expansion product **92** in a high yield. It was proposed that this transformation was mechanistically analogous to the Morin rearrangement of penams to cephams.[42] In fact, it had been hoped that the presumed intermediate *N*-acyliminium ion **91** might initiate the double cyclization sequence outlined in Scheme 14, but this was not the case; **92** was a dead end as studies with CF_3CO_2D indicated that it was not protonated to give **91**.
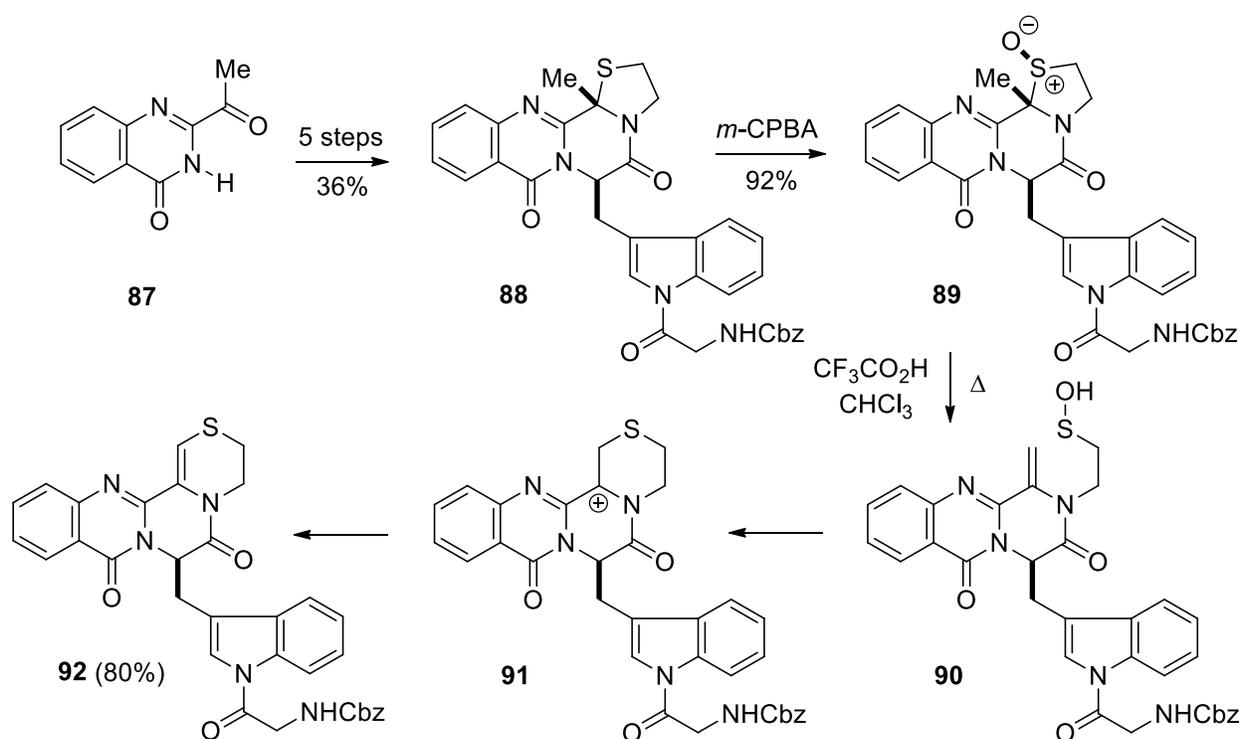
Scheme 15. Failure to capture a possible intermediate cation with an *N*-acylated indole.
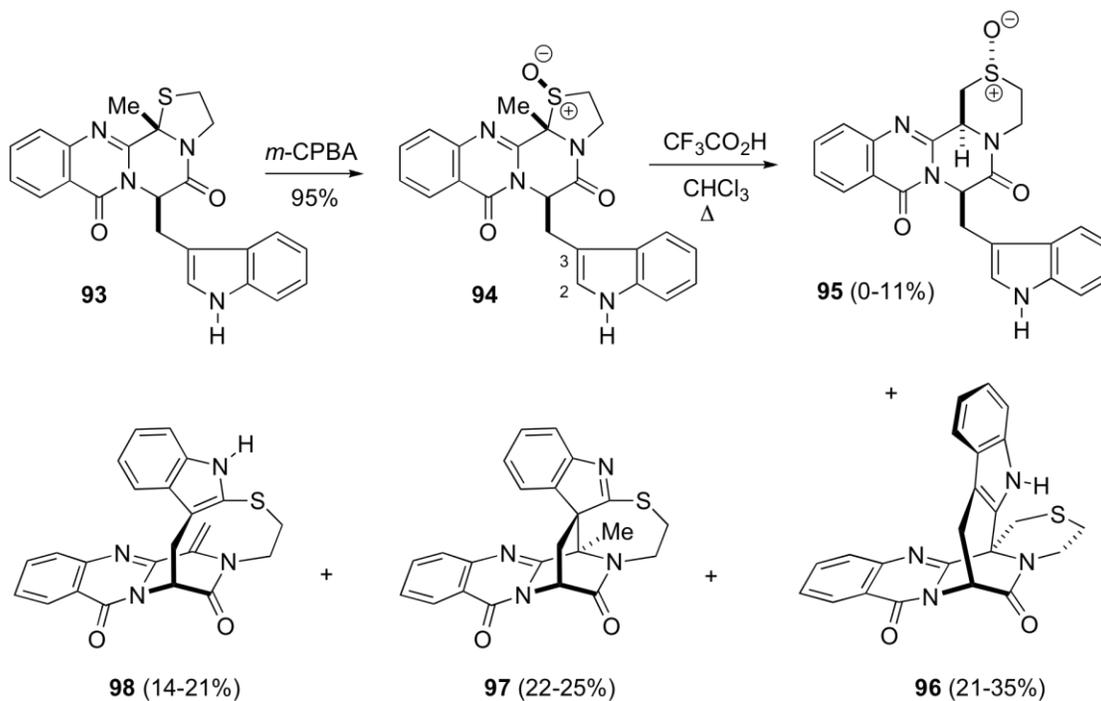
Scheme 16. Acid promoted chemistry of **94** provides structures related to the spiroquinazolines.

The result shown in Scheme 15 indicated that an acylated indole was not a good enough nucleophile to capture an intermediate cation. This observation resulted in examination of sulfoxide **94**, prepared from **93**, the penultimate intermediate in the synthesis of **88**. Sulfoxide **94** gave a number of products **95**–**98** upon treatment with trifluoroacetic acid (Scheme 16). Three of the products **96**–**98** appear to be derived from the indole capturing a reactive intermediate analogous to deacylated **91**. It is also notable that isomers **97** and **98** are in equilibrium under the reaction conditions. Whereas the reader should consult the primary literature for a mechanistic interpretation of the results shown in Scheme 16, the results provide evidence that at least a portion of the plan outlined in Scheme 14 can be realized.

Another approach to spiroquinazoline would be to pass through alantrypinone as an intermediate. This plan would require methodology for the conversion of an oxindole to an imidazoloindoline. Two methods for accomplishing this task have been reported (Scheme 17).[43] One method relies on the Eguchi reaction (**99** → **100** → **101** → **102**)[33] and the other on a rather unusual imide reduction (**99** → **103** → **104** → **105** → **102**).
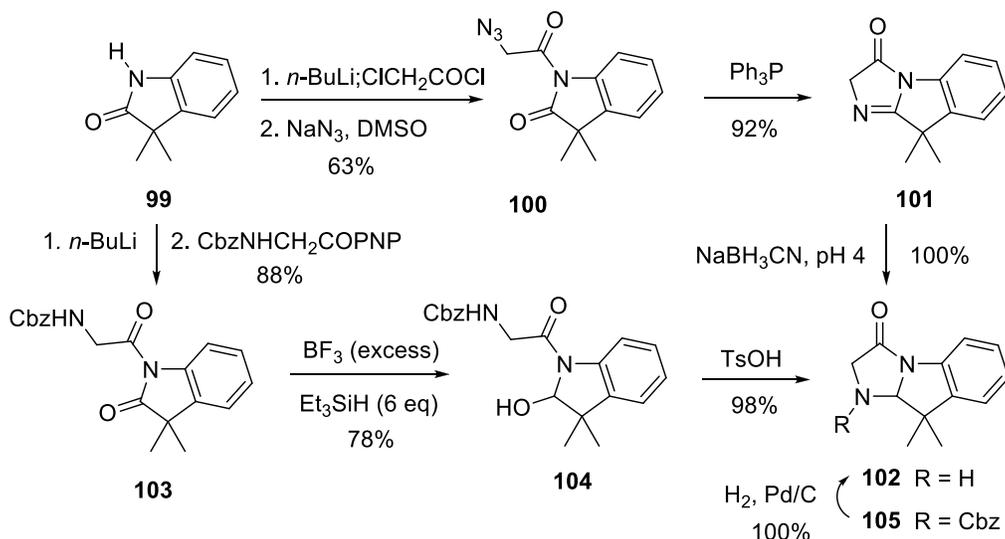
Scheme 17. Model studies for conversion of alantrypinone to spiroquinazoline.

Both methods, however, failed to convert *ent*-alantrypinone to spiroquinazoline (Scheme 18).[44] It was not possible to prepare **106** using the procedure described in Scheme 17. Whereas acylation of the nitrogen was possible, treatment of the resulting chloride with sodium azide gave only *ent*-alantrypinone. It was possible to prepare **106** in 71% yield by using *p*-nitrophenyl α-azidoacetate as the acylating agent, but reaction of **106** with Ph$_3$P, *n*-Bu$_3$P or (Me$_2$N)$_3$P gave only *ent*-**7** via a deacylation reaction. The fate of the azido group in these reactions was not determined. It was also possible to prepare glycine derivative **107** in 70% yield using the procedure set forth in Scheme 17. Treatment of this imide with BF$_3$•Et$_3$SiH led to a slow reaction that once again provided *ent*-**7** as the only identifiable product. A detailed explanation for the

difference in behavior of the model systems shown in Scheme 17 and **106/107** has been set forth.[44] Without going into details, it was proposed that a combination of steric effects and conformational differences are responsible for the observed behavior of these systems.

A model system based on anthracene derivatives was examined as an afterthought (Scheme 18). Acylation of lactam **108** was accomplished as described in Scheme 17, but conversion of the chloride to the corresponding azide failed. Only deacylation to return **108** was observed. Acylation of the anion derived from **108** using *p*-nitrophenyl α-azidoacetate as the electrophile, however, gave the desired azide in 66% yield. Treatment of the azide with triphenylphosphine in benzene at room temperature, gave a 37% yield of **109**. Reduction of **109** using the standard Borch conditions provided a 78% yield of a 5:1 mixture of diastereomeric *N,N*-acetals from which each isomer was isolated in reduced yield. The stereochemistry of these isomers was easily determined by nOe studies.

106 X = N₃

107 X = NHCbz

ent-**7**

108

109

110

Scheme 18. More model studies for conversion of alantrypinone to spiroquinazoline.

Thus results shown in Scheme 18 seem consistent with the failed attempts to use this chemistry to convert alantrypinone to spiroquinazoline. The yield of the Eguchi cyclization is low and *N*-deacylation problems persist throughout the conversion of **108** to **109**. Furthermore compound **109** was unstable and was converted completely to anthracene upon standing in CDCl₃ at room temperature for a day (NMR tube experiment). Finally, the stereochemical course of the reduction of **109** to **110** does not bode well for obtaining the C-14 stereochemistry required by spiroquinazoline using this methodology (C-H bond formation last). This result suggests that final C-N bond construction might be more desirable in related approaches to spiroquinazolines. In this regard, it has been observed that imine **11** reacts with the acid chloride of *N*-Ts-glycine **112** to give a 62% yield of **111** (Scheme 19).[45] Thus, if the conversion of

alantrypinone to **10** can be accomplished, variations of this approach might provide access to spiroquinzoline **1** and possibly alkaloids **3–5**.

Scheme 19. Conversion of imine **11** to *N,N*-acetal **111**.

An approach to spiroquinazoline that is very different from either the cycloaddition or *N*-acyliminium ion routes has recently been described (Schemes 20–22).[46] The plan (Scheme 20) was to prepare members of the spiroquinazoline family of alkaloids from an intermediate of type **113** with a focus on construction of the N–C-17 bond. Intermediates of type **113** were to be prepared from diketopiperazine derivatives of type **114**. An intramolecular S_N2' reaction of a substrate of type **115** was to provide **114**. Use of this type of process had precedence in the Williams group approach to the brevianamides and paraherquamides.[47]
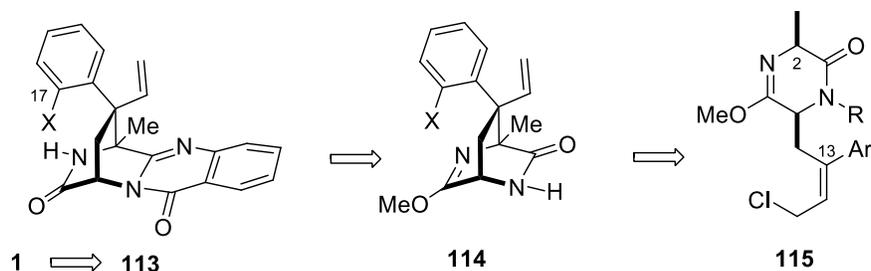
Scheme 20. Chen-Williams approach to synthesis of spiroquinazolines.

The approach began with development of an enantioselective route to functionalized α-amino acids.[48] This method was used to prepare **116** in two steps (62% yield) from *N*-(*tert*-butoxycarbonyl)-L-iodoalanine methyl ester (Scheme 21). The Boc group was removed and replaced with a *p*-nosyl group. Alkylation of the sulfonamide with 3,4-dimethoxybenzyl bromide, removal of the nosyl group and acylation of the resulting amine with *N*-Fmoc-L-alanine, and removal of the Fmoc group, completed the synthesis of diketopiperazine **117** (32% overall from **116**). Pd-mediated coupling of the vinylstannane with $Ph_2I^+Cl^-$ introduced the incipient C-13 phenyl group. Conversion of the secondary lactam into the imino ether, reduction of the ester, and conversion of the resulting allylic alcohol to a chloride gave cyclization substrate **118** (46% overall from **117**). Cyclization of **118** gave separable diketopiperazine

derivatives **119** and **120**. It is notable that the Pd-mediated arylation (SnMe$_3$ → Ph) was also used to introduce *o*-bromophenyl and *o*-nitrophenyl groups, but the subsequent intramolecular S$_N$2′ reactions were unsuccessful. The *N*-aryl group was removed from **120** to provide **121**.
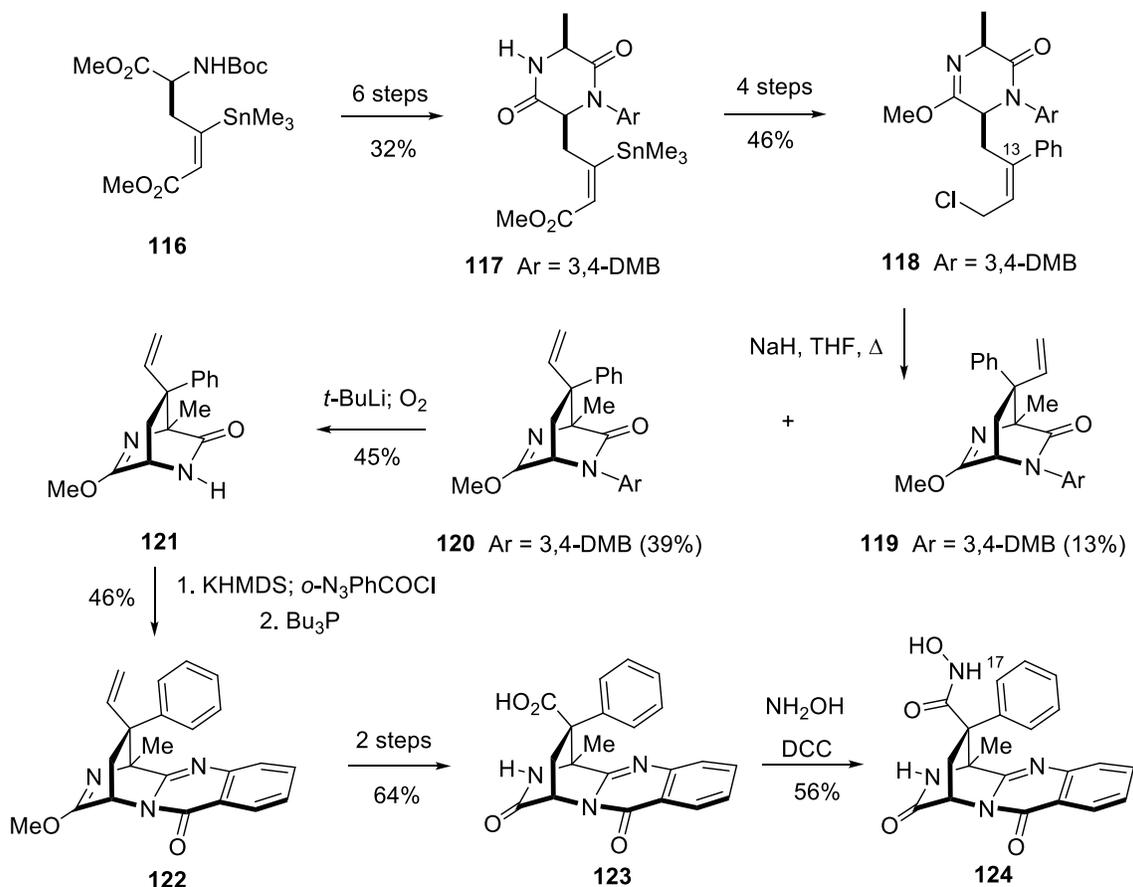
Scheme 21. Synthesis of hydroxamic acid **124** from amino acid **116**.

    Application of the Eguchi protocol gave quinazolinone **122**. Ozonolysis of the vinyl group was followed by oxidation of the resulting aldehyde, concomitant with hydrolysis of the imino ether, to give carboxylic acid **123**. The acid was converted to hydroxamic acid **124**, but construction of the N–C-17 bond has not yet been accomplished. Overall this is a creative and enantioselective approach to the spiroquinazolines and it is unfortunate that *o*-substituted aromatics did not undergo the key cyclization reaction.

5. Conclusions

What is known and what is not known about the structures of the spiroquinazoline-type alkaloids reported thus far? The carbon skeletons of nine members of this family are secure **1**–**9**.

Stereochemical aspects of several of these natural products also seem secure **6**–**9**. The relative and absolute stereochemistry assigned to lapatin A **2** appears to be correct. It is notable that the stereochemistry at the *N,N*-acetal (C-14) in **2** (determined by NMR) is the opposite of that found in **6** (determined by X-ray) and **3**-**5** (determined by NMR). The absolute stereochemistry of **1** and **3**–**5** has yet to be determined.

What is known about the biosynthesis of the spiroquinazoline-type alkaloids? No experiments have been directed toward unraveling how nature makes these alkaloids. This may be interesting to study. Some of the alkaloids appear to incorporate D-tryptophan while others incorporate L-tryptophan. Some appear to incorporate D-amino acids in the C-14-indoline nitrogen bridge, while others appear to incorporate L-amino acids. It is not known if post-translational epimerizations play a role in the apparent incorporation of D- or L-series amino acids. Feeding studies are needed to sort out the possibilities. Are there any trends? It appears that compounds, in which a hydrogen appears at C-2 formally incorporate L-tryptophan **2**, **6** and **9**. The two cases where non-hydrogen atoms appear at C-2 formally incorporate D-tryptophan **7** and **8**. There are not enough data points to be sure of anything, but if this correlation holds, spiroquinazoline **1** and alkaloids **3**–**5** will formally incorporate D-tryptophan.

How about biological activity? It appears that the spiroquinazolines display a variety of biological activities that have attracted the attention of those interested in analgesics or insecticides. None of the activities, however, seems to be high enough to be of serious interest at this time.

52   R = Me
76   R = H
125
126
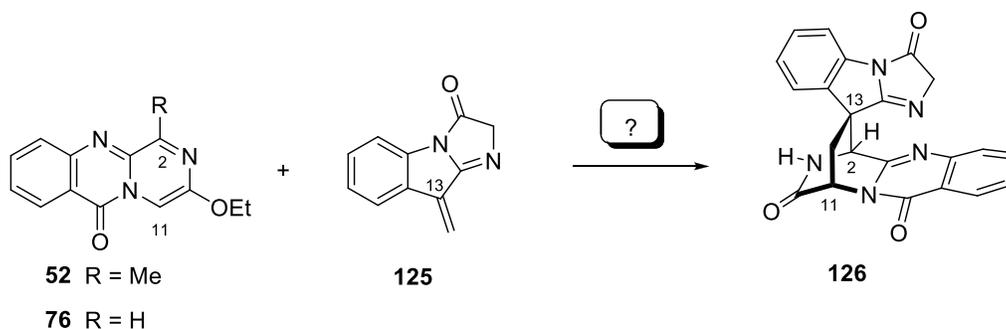
Scheme 22. A possible variation on the Diels-Alder theme.

What about synthesis? Two versatile routes to the alkaloids lacking a C-14–N bridging amino acid **7**–**9** have been developed. The most practical route involves Diels-Alder chemistry. This provides racemic material. A route that involves an intramolecular *N*-acyliminium ion cyclization seems less practical. This route might be improved by focusing on generation and cyclization of intermediates of type **75** under basic conditions. This would require oxidation of the tryptophan-derived indole to an oxindole prior to cyclization, and would also require *N*-acylimine generation under basic conditions. It is notable that the *N*-acyliminium ion cyclization

route does provide single enantiomers that are a function of the enantiomer of tryptophan used as a starting material.

No synthesis of an alkaloid containing an amino acid bridge between C-14 and nitrogen has been accomplished. Several attempts to append a glycine bridge to alantrypinone have failed. One route that still has promise would involve reduction of the oxindole of alantrypinone (or lapatin B), followed by fusing the bridging amino acid to the resulting imine **10**. An observation that model compound **109** readily provides anthracene suggests that it might be worthwhile to study Diels-Alder reactions of dienophiles such as **52** and **76** with as yet unknown dieneophiles of type **125** (Scheme 22). Finally, fusion of the Diels-Alder approach with ideas for late N–C-17 bond formation proposed by Chen and Williams would provide another possible route to amino acid bridged spiroquinazolines.

It is the author's opinion that much has been done in this area of natural products chemistry, but a number of logical and interesting goals have yet to be accomplished. The author for one will be interested to see what transpires during the next decade.

6. Acknowledgements

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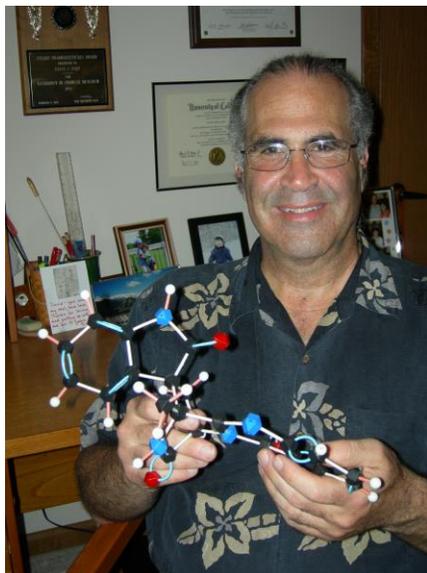
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