Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6214–6216

Synthesis of (−)-lapatin B

Steven J. Walker and David J. Hart*

Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, OH 43210, USA

Received 3 May 2007; accepted 18 June 2007
Available online 23 June 2007

Abstract—The synthesis of (−)-lapatin B (**1**) has been achieved from L-tryptophan. The key reactions involve oxidative cyclization of *N*,*N*-diacetylglyantrypine (**8**) using PhI(OH)(OTs), and an indole-to-oxindole transformation in the penultimate step.

(−)-Lapatin B (**1**) is a member of a growing family of spirooxindole-containing quinazolinone alkaloids whose structure was reported by the Larsen group in 2005 after isolation from the fungus *Penicillium lapatayae*.[1] Lapatin B closely resembles (+)-alantrypinone (**2**) whose structure was reported in 1998 after isolation from *Penicillium thymicola*.[2,3] One interesting relationship between lapatin B and alantrypinone is their pseudo-enantiomeric relationship. The absolute configuration of alantrypinone was initially determined by X-ray crystallography and has been confirmed by synthesis of its enantiomer.[2,4,5] The absolute configuration of lapatin B has been suggested based on a comparison of its CD spectrum with that of alantrypinone.[1] This Letter describes an enantioselective synthesis of (−)-lapatin B (**1**) from L-tryptophan that confirms the aforementioned assignment of absolute stereochemistry.[6]

The strategy used to prepare lapatin B (**1**), outlined in Figure 1, mimics our previously reported approach to alantrypinone. We planned to use (+)-glyantrypine (**3**) as a point of departure.[7] We hoped that C_2 oxidation of this alkaloid (lapatin B numbering), followed by an *N*-acyliminium ion cyclization, would provide bridged indole **4**. An indole-to-oxindole rearrangement was then to be used to provide lapatin-B (**1**).

Several syntheses of glyantrypine have been reported. The most efficient synthesis of (−)-glyantrypine was reported by the Liu group.[8] This synthesis requires only two steps from anthranilic acid, *N*-Boc-glycine and D-tryptophan methyl ester and relies on microwave reaction technology. The Avendano group has reported

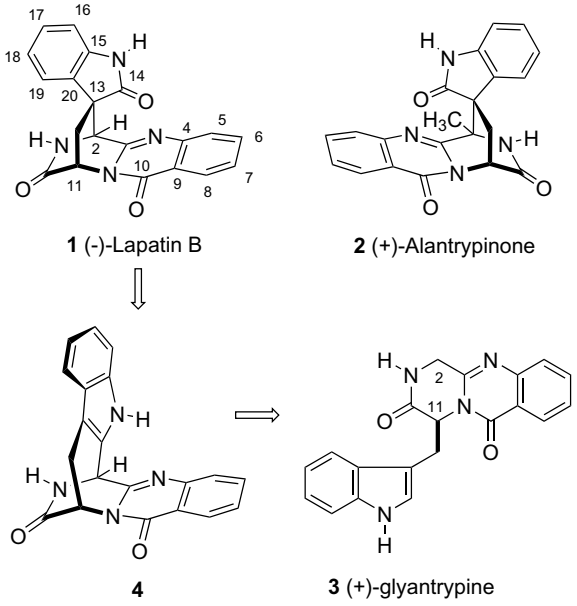
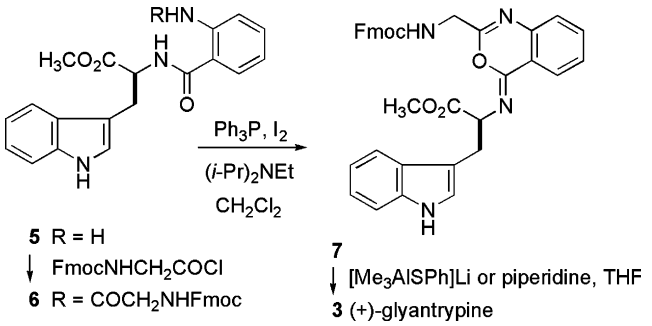


Figure 1. Structure of lapatin B and synthetic plan.

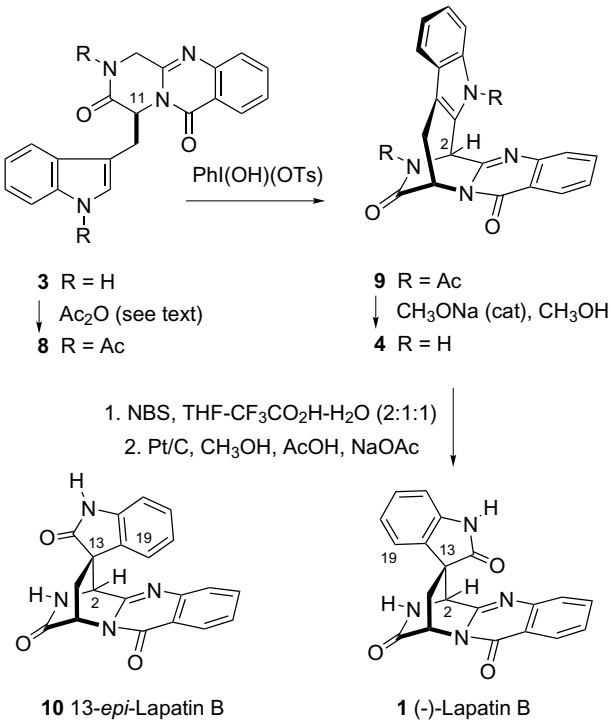
the syntheses of both enantiomers of glyantrypine that rely on an Eguchi cyclization in the key step.[9,10] The Ganesan group has reported a four-step synthesis of (−)-glyantrypine from anthranilic acid, D-tryptophan methyl ester and *N*-Fmoc-glycine.[11] We decided to prepare **3** using a variation of the Ganesan synthesis (Scheme 1). We began by preparing iminobenzoxazine **7** as described in the literature.[11] Isatoic anhydride was treated with the methyl ester of L-tryptophan to provide amide **5** in 61% yield. Acylation of aniline with the acid chloride of *N*-Fmoc-glycine provided **6** in 70% yield. Treatment of **6** with triphenylphosphine and iodine in

* Corresponding author. Tel.: +1 614 292 1677; fax: +1 614 292 1685; e-mail: hart@chemistry.ohio-state.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.089



Scheme 1. Synthesis of (+)-glyantrypine.



Scheme 2. Synthesis of (−)-lapatin B.

the presence of Hunig's base gave **7** in 67% yield. This rather unstable iminobenzoxazine was rearranged to **3** using two procedures. Ganesan accomplished this rearrangement in 87% yield by reacting **7** with piperidine followed by chromatography over silica gel.[11] We found that this procedure proceeded in comparable yield (57% from **7**) in our hands. We also examined [Me$_3$AlSPh]Li as a reagent for promoting the iminobenzoxazine-to-quinazoline rearrangement. This is a reagent we used for a comparable transformation in our synthesis of *ent*-(−)-alantrypinone.[4,12] We found that the use of this aluminum reagent, followed by a brief treatment with piperidine to remove the Fmoc protecting group, mediated the transformation of **7** to (+)-glyantrypine (**3**) in 47% yield.

A few comments about glyantrypine are warranted. The (+)-glyantrypine (**3**) prepared as described in Scheme 1 was purified by crystallization from methanol. Crystals of this material (regardless of the method of preparation) contained 1 equiv of methanol by both ^{1}H and ^{13}C NMR spectroscopies. The melting point of (+)-**3** prepared by either rearrangement method (158–161 °C) matched two reports in the literature (159–161 °C[11] and 155–157 °C[8]), but did not match a third report (mp 86–87 °C[9]). The specific rotations of the (+)-**3** prepared as described in Scheme 1 {$[\alpha]_D$ +522 (*c* 0.12, $CHCl_3$) using piperidine[11] and +512 (*c* 0.12, $CHCl_3$) using the aluminum reagent[4]} compared well with three values reported for the enantiomer {$[\alpha]_D$ −522 (*c* 0.24, $CHCl_3$),[11] −535 (*c*, 0.028, $CHCl_3$),[8] −541 (*c* 0.24, $CHCl_3$)[10]}, but did not compare well with a fourth report {$[\alpha]_D$ +150 (*c* 0.105, DMSO),[8] whereas the material prepared as described in Scheme 2 exhibited $[\alpha]_D$ +662 (*c* 0.13, DMSO)}. We note that the specific rotations for our materials are corrected for the amount of methanol known to be present in each sample. We are unable to tell whether or not methanol was present in materials for which data are reported in the literature.[8,10,11] We think the aforementioned data, in addition to comparison data in the literature, indicate that the (+)-**3** used in our subsequent studies was largely one enantiomer (although we did not perform a chiral HPLC analysis).[8]

The conversion of (+)-glyantrypine (**3**) to lapatin-B (**1**) is outlined in Scheme 2. The key step, an oxidative cyclization of *N*,*N*-diacetylglyantrypine (**8**) to bridged indole **9**, was modeled after reports from the Avendano group.[13,14] Thus, heating (+)-**3** with a large excess of acetic anhydride (243 equiv) and pyridine (2 equiv) at 150 °C for 19 h provided **8** in 67% yield. Unfortunately, complete racemization occurred at C_{11} during the course of this reaction. With the hope of eliminating this problem, acylation was conducted using acetic anhydride (225 equiv), pyridine (2 equiv) and 4-dimethylaminopyridine (0.15 equiv) at 80 °C for 1.5 h or at room temperature for 24 h. This gave **8** in 81% yield, but nearly complete racemization was still observed. We next examined acidic acylation conditions and found that treatment of (+)-**3** with acetic anhydride (219 equiv) and boron trifluoride etherate (2 equiv) at room temperature for 72 h provided optically active **8** {$[\alpha]_D$ +212 (*c* 0.10, $CHCl_3$)} in 62% yield. Treatment of (+)-**8** with Koser's reagent [PhI(OH)(OTs)][15] (1.1 equiv) in acetonitrile at 85 °C for 5 h gave bridged indole **9** {$[\alpha]_D$ +150 (*c* 0.19, $CHCl_3$)} in 35% yield after purification by column chromatography. We were surprised to find that the ^{1}H NMR signal for the C_2 methine appeared as a singlet at δ 7.93. Support for this assignment, however, was readily available from the HMQC spectrum, which revealed a correlation between this signal and a methine at δ 50.5 in the ^{13}C NMR spectrum of **9**. This extraordinary downfield shift most likely results from sandwiching of the C_2 methine between the two oxygens of the acetyl groups in **9**. Upon treatment with a catalytic amount of sodium methoxide in methanol, the *N*-acetyl groups of **9** were removed to provide (+)-**4** in 60% yield {$[\alpha]_D$ +119 (*c* 0.10, EtOAc)}. In accord with expectations, the C_2 methine appeared at a more normal chemical shift of δ 5.34 in **4**. The synthesis of (+)-lapatin B was completed upon treatment of **4** with *N*-bromosuccinimide (4 equiv) in THF–TFA–H_2O (2:1:1) for 5 h, followed by hydrogenolysis of the resulting brominated oxindoles over Pt–C in methanol and acetic acid con-

taining a small amount of sodium acetate.[16,17] Separation of the resulting mixture of products by preparative thin layer chromatography over silica gel (eluted with ethyl acetate) gave (−)-lapatin B (**1**) and 13-*epi*-(+)-lapatin B (**10**), both in 11% yield. Spectral data (^{1}H NMR, ^{13}C NMR, HRMS, CD) and the specific rotation {$[\alpha]_D$ −22.1 (*c* 0.375, EtOH), lit.[1]{$[\alpha]_D$ −20 (*c* 1.6, EtOH)} of synthetic **1** were in agreement with those reported for the natural product. The 13-*epi*-(+)-lapatin B (**10**) exhibited spectral data consistent with the assigned structure.[18] In particular H_{19} appeared as a doublet ($J = 7.5$ Hz) at δ 6.05, an upfield chemical shift consistent with this proton being disposed over the π-system of quinazolinone.[19,20]

In summary, the first enantioselective synthesis of lapatin B (**1**) has been accomplished. Although the penultimate step of the synthesis suffers from a low yield, the work confirms the absolute configuration of the natural product and clearly establishes its pseudo-enantiomeric relationship with alantrypinone (**2**).

Acknowledgments

We thank Dr. Olivier Loiseleur and his coworkers for disclosure of their work on lapatin B and for copies of NMR spectra of (*rac*)-**1** and (*rac*)-**10**, and Mr. Eric King and Dr. Thomas Magliery for assistance with the CD spectrum.

Supplementary data

^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.089.

References and notes

1. Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Sørensen, D.; Frisvad, J. C.; Hansen, M. E. *J. Nat. Prod.* **2005**, *68*, 871–874.
2. Larsen, T. O.; Frydenvang, K.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **1998**, *61*, 1154–1157.
3. For other members of this family of alkaloids, see: Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471–476 (spiroquinazoline); Ariza, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Christophersen, C.; Barrero, A. F. *J. Nat. Prod.* **2001**, *64*, 1590–1592 (serantrypinone); Kuriyama, T.; Kakemoto, E.; Takahashi, N.; Imamura, K.; Oyama, K.; Suzuki, E.; Harimaya, K.; Yaguchi, T.; Ozoe, Y. *J. Agric. Food Chem.* **2004**, *52*, 3884–3887 (alantrypinone and serantrypinone); Proença Barros, F. A.; Rodrigues-Filho, E. *Biochem. Syst. Ecol.* **2005**, *33*, 257–268 (alanditrypinone, alantryphenone and alantryleunone); For a relevant review see: Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787–9826.
4. Hart, D. J.; Magomedov, N. A. *Tetrahedron Lett.* **1999**, *40*, 5429–5432; Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892–5899.
5. For a synthesis of *rac*-alantrypinone see: Chen, Z.; Fan, J.; Kende, A. S. *J. Org. Chem.* **2004**, *69*, 79–85.
6. A total synthesis of (*rac*)-lapatin B has recently been described: Leca, D.; Gaggini, F.; Cassayre, J.; Loiseleur, O.; Pieniazek, S. N.; Luft, J. A. R.; Houk, K. N. *J. Org. Chem.* **2007**, *72*, 4284–4287.
7. For the insolation and structure determination of glyantrypine see: Penn, J.; Mantle, P. G.; Bilton, J. N.; Sheppard, R. N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1495–1496. This paper provides spectral data for the natural product, but no melting point or specific rotation measurements were reported. Thus, whereas both enantiomers of glyantrypine have been prepared by total synthesis,[8–11] the absolute configuration of the natural product remains unknown.
8. Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339–6345.
9. Cledera, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **2000**, *65*, 1743–1749.
10. Hernández, F.; Lumetzberger, A.; Avendaño, C.; Söllhuber, M. *Synlett* **2001**, 1387–1390.
11. Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022–1030.
12. For other work describing this type of rearrangement see: He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397–1399; Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973–980.
13. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *J. Org. Chem.* **2001**, *66*, 5731–5735.
14. Martín-Santamaría, S.; Espada, M.; Avendaño, C. *Tetrahedron* **1999**, *55*, 1755–1762.
15. Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487–2489.
16. A number of oxindole-to-indole reaction sequences have been reported. We followed the protocols described by Pellegrini [Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979–1992; Stahl, R.; Borschberg, H.-J.; Acklin, P. *Helv. Chim. Acta* **1996**, *79*, 1361–1378] and did not examine other protocols.
17. The predominant products from this procedure were brominated at C_{18} prior to hydrogenolysis. This behavior was also reported in our work on alantrypinone.[4]
18. Some properties of 13-*epi*-lapatin B (**10**) follow: ^{1}H NMR (DMSO-d_6) δ 2.35 (dd, $J = 11.2$, 2.8 Hz, 1H, CH_2), 4.40 (d, $J = 4.4$ Hz, 1H), 5.55 (d, $J = 1.2$ Hz, 1H), 6.05 (d, $J = 7.5$ Hz, 1H, ArH), 6.67 (t, $J = 6.0$ Hz, 1H), 6.90 (d, $J = 6.4$ Hz, 1H), 7.17 (t, $J = 6.0$ Hz, 1H), 7.32–7.66 (m, 2H), 7.88 (t, $J = 6.0$ Hz, 1H), 8.27 (d, $J = 6.4$ Hz, 1H), 9.24 (q, $J = 1.2$ Hz, 1H), 10.72 (br s, 1H); The geminal partner to the C_{12} methylene signal at δ 2.35 is obscured by signals from the solvent (DMSO-d_6), but its presence was revealed in the COSY spectrum. Therefore the chemical shift of the other C_{12} methylene is approximately δ 2.50, but we cannot report its multiplicity; ^{13}C NMR (DMSO-d_6) δ 34.3 (CH_2), 49.7 (C), 53.1 (CH), 59.4 (CH), 110.2 (CH), 120.9 (C), 121.9 (CH), 124.3 (CH), 127.1 (CH), 128.0 (CH), 128.1 (CH), 129.4 (CH), 129.7 (C), 135.4 (CH), 142.3 (C), 147.1 (C), 151.3 (C), 158.6 (C), 169.1 (C), 177.9 (C); $[\alpha]_D$ −4.9 (*c* 0.35, CH_3CN); HRMS (electrospray ionization) calcd for $C_{20}H_{14}N_4O_3Na$ 381.0964, found 381.0964; Compound **10** ($R_f = 0.21$ on silica gel eluted with ethyl acetate) was considerably more polar than **1** ($R_f = 0.40$ on silica gel eluted with ethyl acetate) as expected based on its structure. We have reported similar observations for alantrypinone (**2**) and its related epimer.[4]
19. NMR spectra (^{1}H and ^{13}C) of the synthetic (−)-lapatin B (**1**) and 13-*epi*-lapatin B (**10**) matched the spectra of synthetic (*rac*)-**1** and (*rac*)-**10**.[6]
20. Chiral HPLC analysis (Chiracel OJ column eluted with hexane/*i*-PrOH, 4:1) of synthetic **1** indicated the presence of only one enantiomer. (*rac*)-Lapatin, prepared from (*rac*)-**8** (see text) was used to develop a baseline separation of **1** and (*ent*)-**1**.