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Synthesis of (−)-alantrypinone

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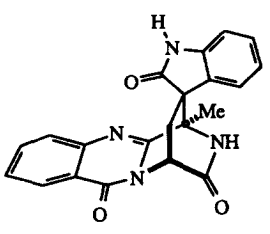
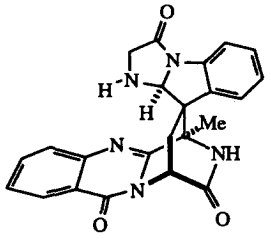
Abstract

A synthesis of (−)-alantrypinone is described. The synthesis features the use of [Me_3AlSPh]Li as a promoter of a 4-iminobenzoxazine to 4-quinazolinone rearrangement and as a reagent for the deprotection of an Fmoc-protected amino acid derivative.

(+)-Alantrypinone (**1**) is a structurally interesting natural product recently isolated from the fungus *Penicillium thymicola*.[1] Whereas no biological activity has been reported for alantrypinone, it is structurally related to spiroquinazoline (**2**), a fungal metabolite from *Aspergillus flavipes* and competitive inhibitor to the binding of substance P at the human NK-1 receptor.[2] In this paper we report a short synthesis of the enantiomer of alantrypinone.[3,4]



1 (+)-Alantrypinone



2 Spiroquinazoline

Our approach to the enantiomer of **1** revolved around cyclization of an *N*-acyliminium ion that was to be derived from protonation of the double bond of enamide **12**. The synthesis of **12** is described in Scheme 1. Treatment of isatoic anhydride (**3**) with the methyl ester of (*S*)-(−)-tryptophan (**4**) in benzene gave **5** in 97% yield.[5] Reaction of **5** with the acid chloride derived from *N*-Fmoc-*S*-methylcysteine[6] under Schotten–Baumann conditions gave amide **6** in 96% yield. Cyclization of **6** to benzoxazine **7** was accomplished in 80% yield using triphenylphosphine–iodine and Hunig's base in dichloromethane. We note that this result is consistent with observations reported by Mazurkiewicz,[7] but inconsistent with results reported by Ganesan[8] and recently corrected by Snider.[9] Treatment of **7** with 10 equivalents of

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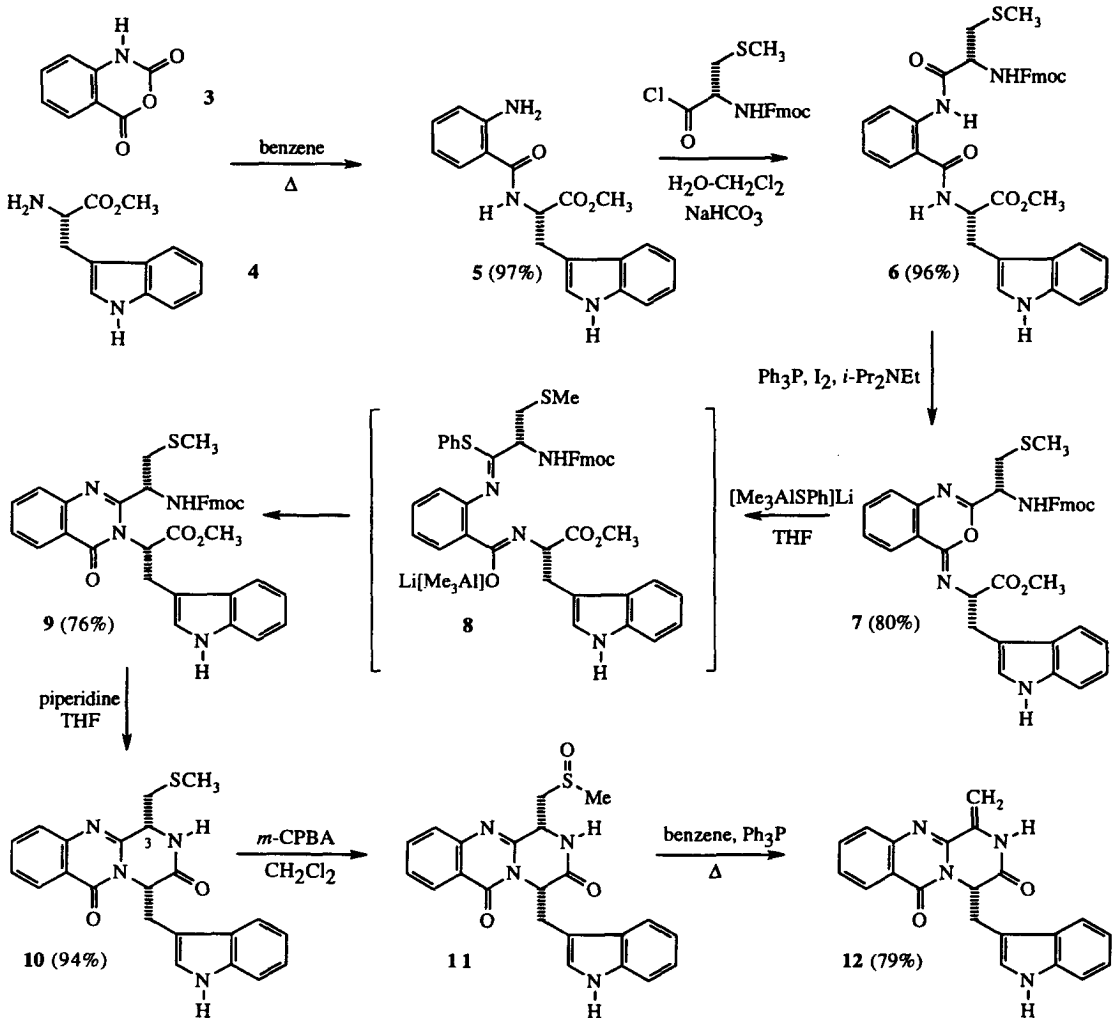
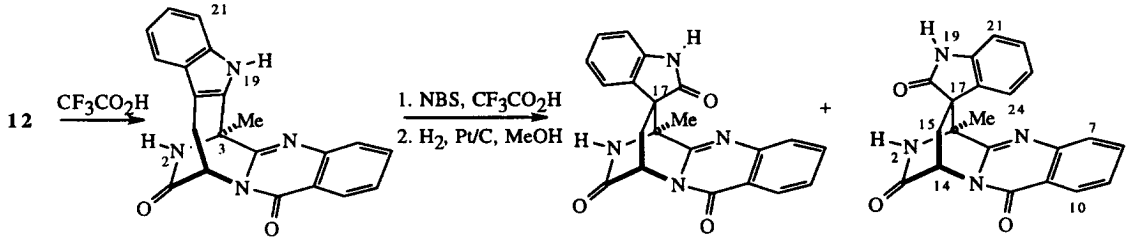
[Me_3AlSPh]Li in tetrahydrofuran at −78°C (30 min) → −10°C (12 h) → rt (8 h) gave a 46% yield of **10**.[10] Alternatively, treatment of **7** with 5 equivalents of [Me_3AlSPh]Li in tetrahydrofuran at −78°C (30 min) → −10°C (36 h) gave a 76% yield of **9** along with 8% of **10**. Treatment of **9** with piperidine in tetrahydrofuran at 0°C for 90 min also provided **10** in 94% yield. We imagine that the isomerization of **7** → **9** occurs via an intermediate thioimidate such as **8**, and that Fmoc removal from **9** is accompanied by cyclization of an intermediate aluminium amide to provide **10**.[11,12] Oxidation of **10** with *m*-CPBA in dichloromethane at −78°C provided a 3:2 mixture of diastereomeric sulfoxides **11**, which gave enamide **12** in 79% yield (from **10**) upon warming in benzene under reflux in the presence of triphenylphosphine for 18 h.[4,13]



Scheme 1.

With enamide **12** in hand, we turned to the final stages of the synthesis as shown in Scheme 2. Treatment of **12** with trifluoroacetic acid at 70°C for 2 h gave an 89% yield of indole **13**.[14] Treatment of **13** with *N*-bromosuccinimide in trifluoracetic acid–tetrahydrofuran–water, followed by hydrogenolysis of the resulting crude product mixture over platinum on carbon in methanol, gave a mixture of (−)-alantrypinone (**14**) and (+)-17-epialantrypinone (**15**), in 30% and 44% yields, respectively, after separa-

tion by preparative TLC.[15] The structure of **14** was based on a comparison of spectral data and physical properties with those reported for its enantiomer (**1**).[16] The structure of **15** was based on spectral data, including the diagnostic appearance of H_{24} as a doublet at 5.87 ppm (DMSO-d_6), an indication of the shielding effect experienced by this proton due to its stereochemical relationship to the quinazolinone substructure.[17] Consistent with this assignment of stereoisomers, it is notable that (–)-alantrypinone (**14**) was much less polar than (+)-17-epialantrypinone (**15**).[18]



13 (89%) $[\alpha]_D$ = +267 (c=0.243, EtOAc) **14** (30%) **15** (44%)

Scheme 2.

In summary, a synthesis of the enantiomer of alantrypinone has been reported. This synthesis requires 10 steps from isatoic anhydride, proceeds in 12% overall yield, confirms the absolute configuration of alantrypinone previously determined by the anomalous dispersion technique, and describes a new application of [Me_3AlSPh]Li in organic synthesis. Studies directed toward the conversion of **14** into the presumed enantiomer of spiroquinazoline are in progress.

Acknowledgements

This paper is dedicated to Professor Richard G. Lawton on the occasion of his 65th birthday. We thank the National Institutes of Health for generous support (GM27647).

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3. For our earlier studies directed toward spiroquinazoline see Hart, D. J.; Magomedov, N. *J. Org. Chem.* **1999**, *64*, 2990.
4. For other relevant studies and a different synthesis of **12** see He, F.; Snider, B. B. *Synlett* **1997**, 483.
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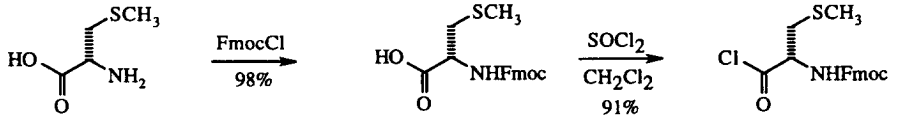
6. This acid chloride was prepared from *S*-methyl cysteine using standard procedures as shown below: Carpino, L. A.; Cohen, B. J.; Stephens Jr., K. E.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732.



mp 131.5-132 °C (from dichloromethane/hexane) $[\alpha]_D$ = –16.4 (c = 1.48, EtOAc)

mp 130.5-131 °C (dec) (from pentane/dichloromethane) $[\alpha]_D$ = +7.9 (c = 1.15, $CHCl_3$)

7. Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973.
8. Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432.
9. He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1597. At the time this paper appeared we were aware, through our own studies to be reported at a later date, that the Ganesan report was in error.
10. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361.

11. To our knowledge, this is the first example of Fmoc deprotection using this reagent.
12. On one large scale conversion of **7** to **10**, we isolated a 4% yield of what appears to be the C_3 epimer of **10**, stereochemistry being based on a chemical correlation with **12**.
13. Rich, D. H.; Tam, J. P. *J. Org. Chem.* **1977**, *42*, 3815.
14. For an analogous cyclization see Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147. The regiochemistry of **13** was established using difference NOE experiments. For example, irradiation of H_{19} (11.21 ppm in DMSO-d_6) gave enhancements of signals due to H_{21} (7.37 ppm) and the C_3 methyl group (2.13 ppm), and irradiation of the C_3 methyl group gave enhancements of signals due to H_{19} and H_2 (9.57 ppm).
15. For the conversion of indoles to oxindoles see Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. The conversion of **13** → **14+15** was shown to involve rapid formation of a mixture of diastereomeric bromoindolines followed by slower conversion to a mixture of 23-bromo-**14**, 23-bromo-**15** and polybromination products. The mixture of crude bromoindoles was converted to **14** and **15** by hydrogenolysis over either platinum (faster) or palladium (slower) on carbon.
16. Data for **14** were identical to those reported for alantrypinone (**1**) with the exception of the specific rotation: $[\alpha]_D$=–40.4 (c=0.27, EtOH) for **14** and $[\alpha]_D$=+37 (c=2.08, EtOH) reported for **1**.[1]
17. $[\alpha]_D$=+84.3 (c=0.12, THF); IR (KBr) 3196, 2926, 1723, 1684, 1622, 1608, 1470 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.24 (s, 3H, CH_3), 2.32 (dd, *J*=14.3, 3.9 Hz, 1H, H_{15}), 2.56 (dd, *J*=14.3, 1.9 Hz, 1H, H_{15}), 5.57 (ddd, *J*=3.9, 1.9, 1.9 Hz, 1H, H_{14}), 5.87 (d, *J*=7.5 Hz, 1H, H_{24}), 6.66 (ddd, *J*=7.5, 7.5, 0.9 Hz, 1H, H_{23}), 6.87 (d, *J*=7.5 Hz, 1H, H_{21}), 7.15 (ddd, *J*=7.5, 7.5, 1.1 Hz, 1H, H_{22}), 7.62–7.71 (m, 2H, H_7 and H_9), 7.88 (ddd, *J*=8.3, 7.2, 1.5 Hz, 1H, H_8), 8.27 (dd, *J*=7.8, 1.5 Hz, 1H, H_{10}), 9.28 (d, *J*=1.9 Hz, 1H, H_2), 10.73 (s, 1H, H_{19}); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 13.3 (q), 35.2 (t), 52.2 (d), 52.6 (s), 61.9 (s), 109.5 (d), 120.1 (s), 121.6 (d), 123.3 (d), 126.5 (d), 127.6 (d), 127.9 (d), 128.9 (d), 129.2 (s), 135.0 (d), 142.4 (s), 146.3 (s), 152.4 (s), 158.2 (s), 168.9 (s), 177.1 (s); MS (EI) *m/z* (relative intensity) 372 (M^+, 4), 228 (14), 227 (100), 199 (42), 145 (33), 117 (28), 90 (24). Exact mass calcd for $C_{21}H_{16}N_4O_3$ *m/z* 372.1222, found *m/z* 372.1276.
18. Compounds **14** and **15** have R_f values of 0.49 and 0.34 (silica gel eluted with ethyl acetate), respectively. The R_f of **14** was identical to that of an authentic sample of **1** kindly provided by Dr. Thomas O. Larsen. The ^1H NMR spectrum of this authentic sample was also identical to that recorded for **14**.