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Synthesis and absolute configuration of (−)-serantrypinone

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Abstract—A synthesis of (−)-serantrypinone (**3**) has been achieved from L-tryptophan. A key reaction involves the transformation of a selenoxide to an acetate via trapping of a presumed intermediate in a seleno-Pummerer reaction.

Serantrypinone is a spirooxindole alkaloid whose structure was first reported by a Danish group in 2001 after isolation from the fungus *Penicillium thymicola* (Fig. 1).[1] This natural product was assigned structure **1** with the absolute configuration based on the similarity of its CD spectrum with that of (+)-alantrypinone (**2**), a structurally related alkaloid whose absolute configuration was initially based on X-ray crystallographic studies (anomolous dispersion method) and later supported by total synthesis of its enantiomer.[2,3] Serantrypinone was also isolated by Japanese scientists from the fungus *Aspergillus terreus*, and shown to have insecticidal properties based on its ability to bind to GABA (γ-aminobutyric acid) receptors.[4] Some doubt remains regarding the absolute configurations of these materials because the materials from *P. thymicola* and *A. terreus* were reported to be levorotatory and dextrorotatory, respectively. In addition, the reported optical rotations also differed in magnitude.

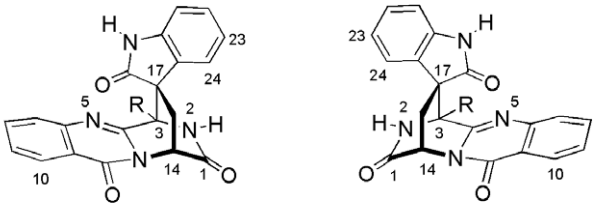

Figure 1. Structures of serantrypinone and alantrypinone.

To resolve this issue, we undertook a synthesis of serantrypinone, with the absolute configuration depicted by structure **3** in Figure 1, from L-tryptophan. Our results are reported here.

The synthesis began with compound **4**, prepared from L-tryptophan ethyl ester in six steps as previously described.[3] Treatment of **4** with phenylselenenyl chloride (1.0 equiv) in dichloromethane (rt, 60 min) provided bridged indole **5** in 78% yield (Scheme 1).[5] We hoped to convert the phenylselenyl group to the required hydroxyl group by sequential oxidation to the selenoxide, a seleno-Pummerer rearrangement,[6] hydrolysis of the resulting Se,O-acetal to the aldehyde, and reduction to a hydroxymethyl group. Oxidation to a mixture of diastereomeric selenoxides **6** was accomplished in 72% yield using *m*-CPBA. To our surprise, treatment of this mixture with acetic anhydride (75 °C, 5 h) gave material that was clearly acetate **7**, albeit in only 15% yield. The structure of **7** was clear based on spectroscopic data (MS, ^{1}H NMR, ^{13}C NMR, and selected COSY spectra).[7] For example, the AB system due to the acetoxymethyl group appeared as a doublet of doublets ($J = 11$ Hz) at δ 5.07 and 5.11 (DMSO-d_6).

In unpublished work, we had prepared iodide **8** and determined that it failed to undergo substitution reactions with several oxygen nucleophiles. Thus, we thought it unlikely that the acetoxy group was introduced by an intermolecular displacement reaction. It appeared more reasonable that the acetate be introduced by intramolecular delivery from N_2 of **7**. Based on this reasoning we converted **5** to imide **9** in 78% yield using acetic anhydride (100 °C, 21 h) (Scheme 2). Oxidation of **9** with *m*-CPBA followed by immediate reaction of the resulting mixture of selenoxides **10** with

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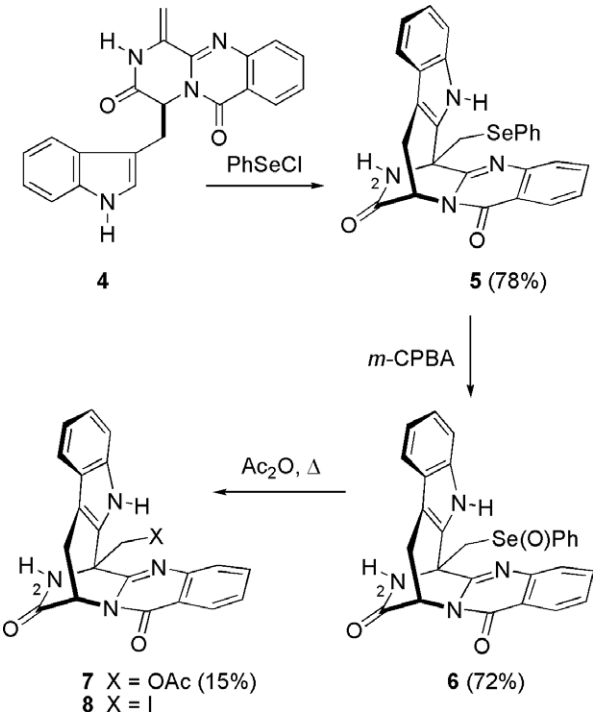
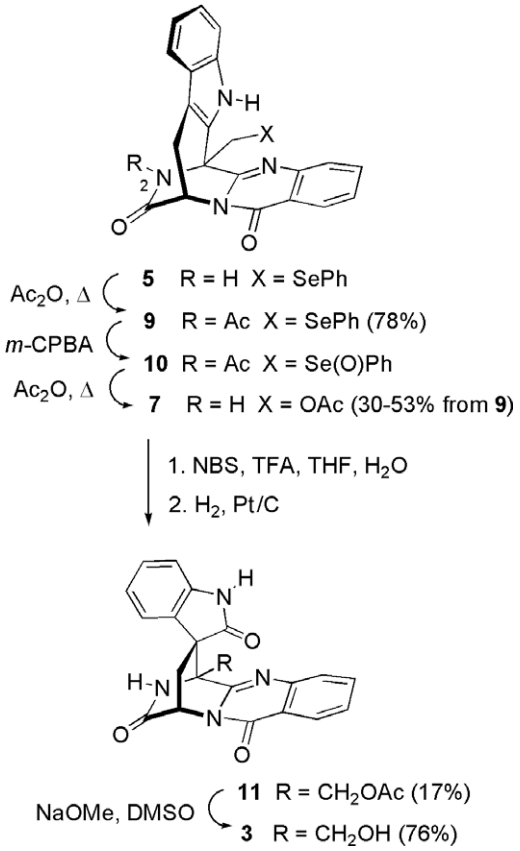
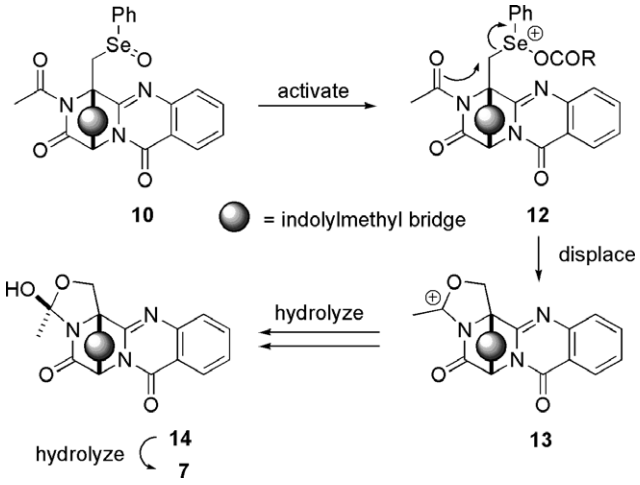


Scheme 1. Preparation of acetate **7** from enamide **4**.



Scheme 2. Synthesis of serantrypinone.

acetic anhydride (75 °C, 5 h) gave **7** in 30–53% overall yield.



Scheme 3. Possible mechanism for conversion of **10** to **7**.

We suggest that the conversion of selenoxide **10** to acetate **7** occurs via the mechanism outlined in Scheme 3. Acylation of the selenoxide activates the selenium for nucleophilic displacement. Neighboring group participation of the *N*-acetyl group of imide **12** affords an intermediate of type **13**, which is captured by water (or an equivalent nucleophile) to provide **14**. Breakdown of this tetrahedral intermediate occurs with cleavage of the imide N–C bond to afford the observed product **7**.[8]

The synthesis of serantrypinone was completed by oxidative rearrangement of **7** to spirooxindole **11** (17%) in a manner similar to that used in our syntheses of (−)-alantrypinone and (−)-lapatin B.[3,9] The rearrangement of **7** also provided 17-*epi*-**11** in 4% yield. Methanolysis of the ester (**11**) was accomplished in 76% yield using sodium methoxide (5.0 equiv) in DMSO at room temperature for 72 h. Spectral data of the synthetic serantrypinone (^{1}H NMR, ^{13}C NMR, and MS) agreed with those reported for serantrypinone by the Danish group.[1,10] This material was also identical (TLC, ^{1}H NMR, and ^{13}C NMR) to an authentic sample of serantrypinone isolated by the Japanese group.[4]

Compound **3** was levorotatory.[10] Chiral HPLC analysis indicated that **3** was the enantiomer of the serantrypinone reported by the Japanese group.[4,11,12] CD spectroscopy also indicated that **3** was the enantiomer of the serantrypinone isolated by the Danish group.[1] This establishes the absolute configuration of (−)-serantrypinone and (+)-serantrypinone as **3** and **1**, respectively, and suggests that *P. thymicola* and *A. terreus* both produce (+)-serantrypinone.

Acknowledgments

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References and notes

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5. We first examined oxygen electrophiles including dimethyldioxirane and *m*-CPBA without success. Details will be provided in a full account of this research.
6. For examples of seleno-Pummerer rearrangements see: Veerapen, N.; Taylor, S. A.; Walsby, C. J.; Pinto, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 227–239; Uneyama, K.; Tokunaga, Y.; Maeda, K. *Tetrahedron Lett.* **1993**, *34*, 1311–1312; Nagao, Y.; Ochiai, M.; Kaneko, K.; Maeda, A.; Watanabe, K.; Fujita, E. *Tetrahedron Lett.* **1977**, *18*, 1345–1348; Reich, H. J.; Shah, S. K. *J. Org. Chem.* **1977**, *42*, 1773–1776.
7. Characterization data for **7**: mp >200 °C; $[\alpha]_D^{22}$ +145 (*c* 0.85, EtOAc); IR (NaCl plates) 3306, 3080, 2904, 1735, 1690, 1608, 1468 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.14 (s, 3H, CH_3), 3.42 (dd, $J = 14.0$, 2.0 Hz, 1H, CH_2), 3.46 (dd, $J = 14.0$, 2 Hz, 1H, CH_2), 5.07 (d, $J = 10.9$ Hz, 1H, CH_2Se), 5.11 (d, $J = 10.9$ Hz, 1H, CH_2Se), 5.73 (broad s, 1H, CHN), 7.00 (t, $J = 8.0$ Hz, 1H, ArH), 7.13 (t, $J = 8.0$ Hz, 1H, ArH), 7.38 (d, $J = 8.0$ Hz, 1H, ArH), 7.41 (d, $J = 8.0$ Hz, 1H, ArH), 7.46 (t, $J = 8.0$ Hz, 1H, ArH), 7.56 (d, $J = 8.0$ Hz, 1H, ArH), 7.72 (t, $J = 8.0$ Hz, 1H, ArH), 8.07 (d, $J = 8.0$ Hz, 1H, ArH), 9.75 (broad s, 1H, NHCO), 11.32 (s, 1H, NH indole); ^{13}C NMR (DMSO-d_6, 125.75 MHz) δ 21.5 (CH_3), 26.0 (CH_2), 54.3 (CH), 56.9 (C), 62.9 (CH_2), 106.8 (C), 112.3 (CH), 118.6 (CH), 119.9 (CH), 120.7 (C), 123.0 (CH), 126.8 (CH), 127.4 (C), 127.7 (CH), 127.8 (CH), 131.4 (C), 135.2 (CH), 135.7 (C), 146.8 (C), 152.3 (C), 159.6 (CO), 169.3 (CO), 170.9 (CO); exact mass (EI) calcd for $C_{23}H_{18}N_4O_4$+Na: *m*/*z* 437.1226; found, *m*/*z* 437.1237.
8. To our knowledge, displacement of a selenenic acid ester in a substitution reaction has not been reported. A reaction that mechanistically resembles our proposal (Scheme 3) is the cyanogen bromide mediated cleavage of peptides at the carboxyl side of methionine residues: Gross, E. *Methods Enzymol.* **1967**, *11*, 238–255; Hancock, W. S.; Marshall, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 7488–7489.
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10. Some properties of (−)-serantrypinone: mp >240 °C; $[\alpha]_D$ −4.0 (*c* 0.2, EtOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 2.38 (dd, $J = 13.0$, 2.0 Hz, 1H, CH_2), 2.42 (dd, $J = 13.0$, 2.0 Hz, 1H, CH_2), 3.58 (dd, $J = 14.0$, 6.5 Hz, 1H, CH_2O), 3.71 (dd, $J = 14.0$, 6.5 Hz, 1H, CH_2O), 4.59 (t, $J = 6.5$ Hz, 1H, OH), 5.55 (d, $J = 2$ Hz, 1H, CHN), 6.89 (d, $J = 8$ Hz, 1H, ArH), 7.08 (t, $J = 7.5$ Hz, 1H, ArH), 7.22 (d, $J = 7$ Hz, 1H, ArH), 7.30 (t, $J = 8$ Hz, 1H, ArH), 7.61 (t, $J = 8$ Hz, 1H, ArH), 7.75 (d, $J = 7.5$ Hz, 1H, ArH), 7.88 (t, $J = 8$ Hz, 1H, ArH), 8.23 (dd, $J = 8$, 1.5 Hz, 1H, ArH), 9.78 (s, 1H, NHCO), 10.52 (s, 1H, NH oxindole); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 38.0 (CH_2), 52.6 (CH), 53.1 (C), 58.2 (CH_2), 65.5 (C), 110.3 (CH), 120.6 (C), 122.5 (CH), 124.3 (CH), 126.8 (CH), 127.8 (CH), 128.2 (CH), 129.6 (CH), 130.1 (C), 135.2 (CH), 143.0 (C), 147.1 (C), 152.7 (C), 158.8 (CO), 170.0 (CO), 177.3 (CO); exact mass (EI) calcd for $C_{21}H_{16}N_4O_4$+Na: *m*/*z* 411.1069; found, *m*/*z* 411.1069.
11. HPLC conditions: Column = Chiracel OJ (250 × 4.6 (ID) mm from Daicel Chemical Industries); Solvent = hexanes/isopropyl alcohol, 4:1; flow rate = 1 mL/min; retention times for **1** and **3** = 13.6 and 22.0 min, respectively.
12. The specific rotations reported for serantrypinone from *P. thymicola*[1] and *A. terreus*[4] are −12 and +21.7, respectively (Na D-line at room temperature).