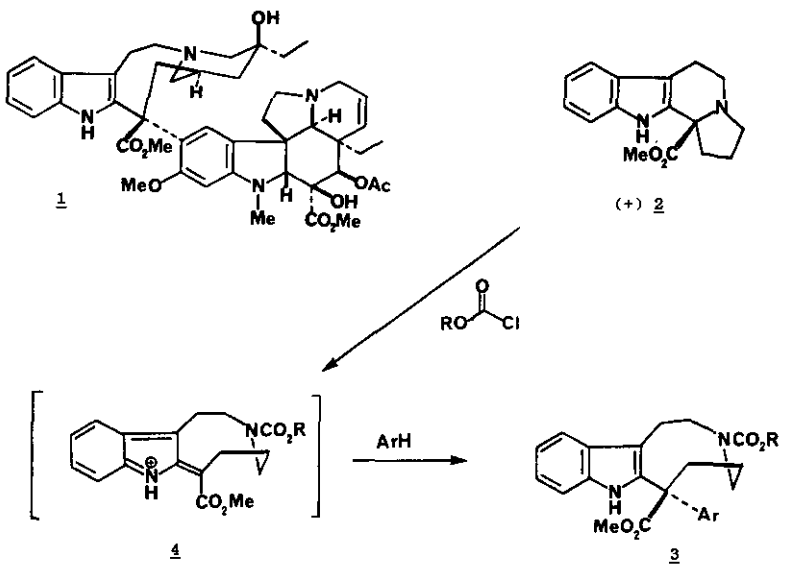
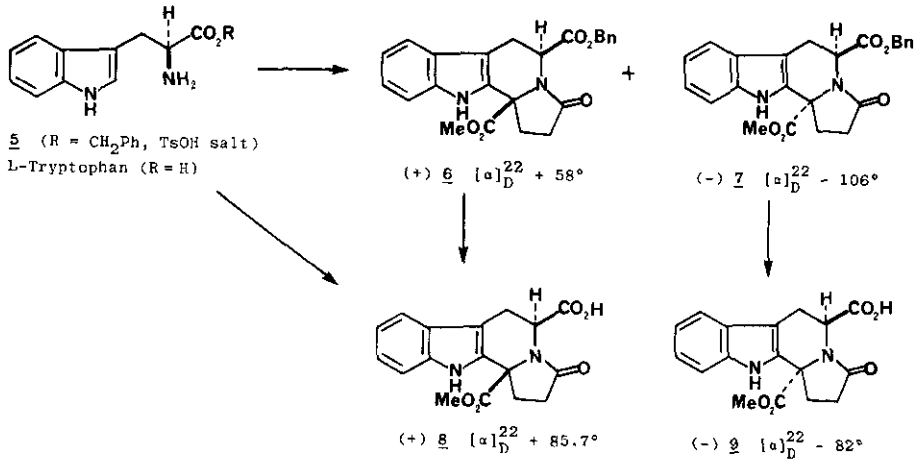
USE OF THE BARTON DECARBOXYLATION PROCEDURE IN INDOLE ALKALOID CHEMISTRY[1]

Philip Magnus*, Mark Ladlow, Chung Sook Kim, and Peter Boniface
Department of Chemistry, Indiana University,
Bloomington, Indiana 47405 U. S. A.
*After January 1, 1989, address correspondence to:
Department of Chemistry, The University of Texas at Austin,
Austin, Texas 78712 U. S. A.

Abstract - L-Tryptophan was condensed with dimethyl α-ketoglutarate to give the tetracyclic amide (+) **8** and its diastereoisomer (-) **9**. Conversion of (+) **8** into its derived N-hydroxy-2-thiopyridone ester **11** followed by t-butylthiol/hυ gave (+) **12**. This was converted into the desired tetracyclic amine (+) **2** in 30% overall yield. Similarly, starting with D-tryptophan gave (-) **2**, thus allowing access to both antipodes of **2**.

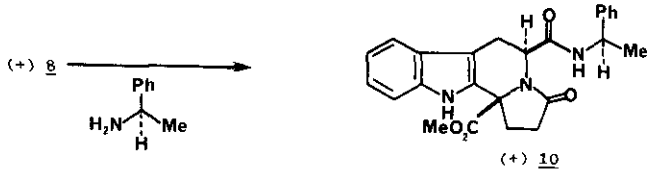
Our studies on the synthesis and mechanism of action of the clinically useful antitumor bis-alkaloid vinblastine **1** have required a straightforward way of making the tetracyclic amine **2**, in both enantiomeric forms and on a practical scale.[2] We have shown that treatment of **2** with tertiary amine cleaving electrophiles such as *chloroformates, in the presence of electron-rich aromatic nucleophiles,* provides good yields (60-90%) of adducts **3**.[3] This electrophilic aromatic substitution reaction presumably proceeds through the intermediacy of the iminium ion **4**, and we were curious to ascertain whether or not **4** could be generated in a chiral form from either (+) or (-)-**2**. The restricted ring conformers of **4** (atropoisomerism) should enable **4** to maintain the "memory" of its chiral origin.[4] Since we were unable to resolve (±) **2** using any of the usual methods, we devised a synthesis of (+) **2**, and its mirror image, from L-tryptophan and D-tryptophan respectively.





L-Tryptophan benzyl ester[5] p-toluene sulfonic acid salt **5** and dimethyl α-ketoglutarate were heated together in THF at reflux for 72h to give the diastereomers (+) **6** (43%) and (-) **7** (7%). The minor compound **7** could be epimerized to the mirror-image of **6** (identical ^{1}H Nmr, opposite $[\alpha]_D$) by treatment with DBU/benzene heated at reflux. Hydrogenolysis of the separated benzyl esters (+) **6** and (-) **7** gave the corresponding acids (+) **8** and (-) **9** in quantitative yields.

In these Pictet-Spengler cyclizations[6] the major diastereoisomer is the cis-diaxial adduct (+) **6**, presumably because of the $A^{1,3}$ interactions between the amide and $-CO_2Bn$ functionalities. ^{1}H nmr data did not allow unambiguous assignment of relative configuration, nor could we exclude acid catalyzed epimerization of the $-CO_2Bn$ group. Therefore, (+) **8** was converted into its derived isobutyl mixed anhydride and quenched with (R)-(+)-α-methylbenzylamine to give (+) **10** (90%), mp 163-164.5°C, $[\alpha]_D^{22}$ + 133° (c, 0.15 in $CHCl_3$).[7] Single crystal X-ray crystallography confirmed the absolute stereochemistry of (+) **10**, and consequently, all the other structures derived from (+) **8** (and its antipode). FIGURE 1 shows an ORTEP representation of (+) **10**.[8]



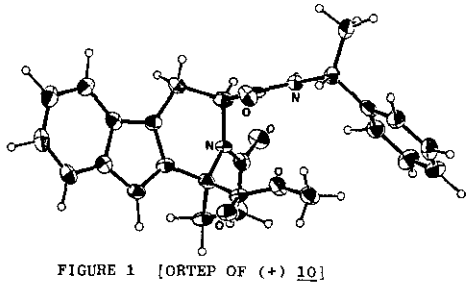
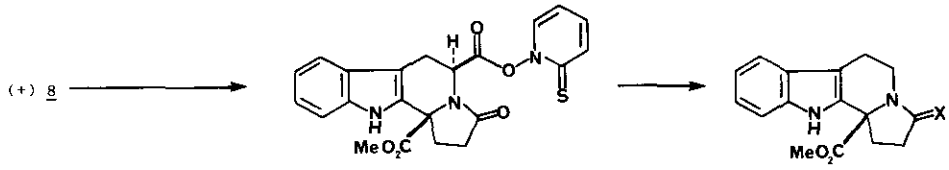


FIGURE 1 [ORTEP OF (+) 10]

Unfortunately, the most difficult and experimentally inconvenient aspects of the synthesis of (+) **8** were the preparation of the benzyl ester of L-tryptophan, and the tedious chromatographic separation of (+) **6** and (-) **7**. Fortunately, we found that L-tryptophan p-toluenesulfonate salt and dimethyl α-ketoglutarate condensed together in THF heated at reflux to give (+) **8** (40%) and (-) **9** (5%), and were readily separated by chromatography over silica gel eluting with THF/CH_2Cl_2/HOAc (4:16:1).

At this stage, we could apply the Barton radical decarboxylation procedure to both (+) **8** and (-) **9**. The isobutyl mixed anhydride of (+) **8** was made using isobutyl chloroformate/N-methylmorpholine/THF at -15° to -20°C, and treated with N-hydroxy-2-thiopyridone/Et_3N to give the O-hydroxamic ester **11**. This was immediately treated with t-butylthiol (10mol equiv), and the mixture irradiated with a 270W sun lamp to give (+) **12** [82% from (+) **8**]. Application of this procedure to (-) **9** did not work, because we could not make the corresponding hydroxamic ester without decarboxylation to give the 5,6-dehydro derivative of **12**. Consequently, (-) **12** was made from D-tryptophan. The tetracylic amide (+) **12** was converted into its derived thioamide (+) **13** (80-95%) by stirring with Belleau's reagent[11] in THF at 20°C. Desulfurization of (+) **13** with excess Raney nickel gave the required tetracyclic amine (+) **2** (≥95%).



(+) 12 (X = O)
(+) 13 (X = S)

This sequence of transformations, starting with L-tryptophan, provides the (+)-amine **2** in four steps in an overall yield of ca. 30%. The (-)-amine **2** is similarly available from D-tryptophan.

A particular feature of this sequence is the Barton radical decarboxylation procedure. *It is completely compatible* with the unprotected indole system. While we did not expose the carboxylic acid **8** to the more classical decarboxylation procedures,[12] it is doubtful that either the indole or 9-carbomethoxy group would have survived.

The availability of both antipodes of the tetracyclic amine **2**, from the natural *α-amino acid chiral pool has allowed* us to study mechanistic questions about the factors that influence the absolute stereochemistry of the crucial C-16′/C-15 bond connecting the two halves of vinblastine **1**.[3]

ACKNOWLEDGEMENTS

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EXPERIMENTAL

(+)-(5S,9R)-3-oxo-5-benzyloxycarbonyl-9-methoxycarbonylindolizino[8,7-b]indole (+) **6**, and (-) **7** (5S, 9S).

L-Tryptophan benzyl ester p-toluenesulfonic acid salt **5** (5.49g 11.8mmol) and dimethyl α-ketoglutarate (2.7g 15.3mmol) in THF (150ml) was heated at reflux for 72h. The mixture was concentrated in vacuo and the residue dissolved in dichloromethane and washed with sat aqueous $NaHCO_3$ soln, water, dried ($MgSO_4$) and filtered. The filtrate was evaporated in vacuo and the residue purified by chromatography over silica gel eluting with CH_2Cl_2/EtOAc (95:5) to give (+) **6** (2.1g 43%), $[\alpha]_D^{22}$ + 58° (c, 1.0 in $CHCl_3$). Ir 3350, 1740, 1715 and 1690cm^{-1}.

^{1}H Nmr (300MHz, $CDCl_3$) δ 8.86(1H, s), 7.46(1H, d, J = 7.5Hz), 7.33(1H, d, J = 7.8Hz), 7.09-7.23(7H, m), 5.54(1H, d, J = 6.6Hz), 4.98(2H, s), 3.70(3H, s), 3.32(1H, d, J = 16Hz), 3.10(1H, dd, J's = 16 and 7.8Hz), 2.91(1H, m), 2.62(1H, m), 2.47(1H, m), 2.16(1H, m). Ms calcd for $C_{24}H_{22}N_2O_5$ requires 418.1533. Found: M^+ 418.1531.
(-) **7** (370mg 7%), $[\alpha]_D^{22}$ - 106.4° (c, 0.53 in $CHCl_3$). ^{1}H Nmr (300MHz, $CDCl_3$) δ 8.45(1H, s), 7.10-7.50(9H, m), 5.37(1H, d, J = 12.6Hz), 5.20(1H, d, J = 12.6Hz), 4.50(1H, dd, J's = 10 and 5Hz), 3.35(1H, dd, J's = 16 and 10Hz), 3.05(1H, dd, J's = 16 and 5Hz), 2.68-2.80(1H, m), 2.50-2.65(2H, m), 2.30-2.43(1H, m). Ms calcd for $C_{24}H_{22}N_2O_5$ requires 418.153. Found: 418.1543.

(-) **6**.
Treatment of (-) **7** (118mg 0.28mmol) with DBU in benzene (8.0ml) heated at reflux for 24h gave (-) **6** (74.7mg) $[\alpha]_D^{22}$ - 54.6° (c, 3.7 in $CHCl_3$).

(+)-(5S, 9R)-3-Oxo-5-carboxy-9-methoxycarbonylindolizino[8,7-b]indole (+) **8**.
The benzyl ester (+) **6** (2.2g 5.26mmol) in THF (45ml) was exposed to H_2 (atmos press) in the presence of 10% Pd/C (300mg). When hydrogen uptake was complete the mixture was filtered through celite, and the filtrate evaporated under reduced pressure to give (+) **8** (1.73g 100%), mp 227°C (dec) $[\alpha]_D^{22}$ + 85.7° (c, 0.72 in $CHCl_3$). Ir ($CHCl_3$) 3460, 1710-1730 and 1630cm^{-1}. ^{1}H Nmr (300MHz, $CDCl_3$) δ 8.78(1H, s), 8.73(1H, s), 7.42(1H, d, J = 7.2Hz), 7.26(1H, d, J = 7.2Hz), 7.12(1H, m), 7.05(1H, m), 5.38(1H, d, J = 7.5Hz), 3.55(3H, s), 3.30(1H, d, J = 15.6Hz), 3.00(1H, dd, J's = 15.6 and 7.5Hz), 2.72-2.84(1H, m), 2.40-2.50(2H, m), 1.90-2.15(1H, m). Ms calcd for $C_{17}H_{16}N_2O_5$ requires 328.1059. Found: M^+ 328.1059.

(-)-(5S, 9S)-3-Oxo-5-carboxy-9-methoxycarbonylindolizino[8,7-6]indole (-) **9**.
Hydrogenolysis of (-) **7** (31.0mg) in the same way as for (+) **6** gave - **9** (24.0mg 99%). $[\alpha]_D^{22}$ - 82° (c, 2.5 in $CHCl_3$). Ir ($CHCl_3$) 3460, 2950, 2840, 1720cm^{-1}. ^{1}H Nmr (500MHz, $CDCl_3$ + trace d^4 MeOH) δ 9.63(1H, s), 7.47(1H, d, J = 7.7Hz), 7.34(1H, d, J = 7.8Hz), 7.17(1H, ddd, J = 9.4, 8.2 and 1.1Hz), 7.07(1H, ddd, J = 9.0, 7.0 and 1.0Hz), 4.43(1H, dd, J = 5.0Hz), 3.77(3H, s), 3.27(1H, dd, J = 16.0Hz), 3.01(1H, dd, J = 16.0 and 5.0Hz), 2.69(1H, m), 2.56(2H, m), 2.33(1H, m).

(+)-(5S, 9R)-3-Oxo-5-[(R)-α-methylbenzylamine carbonyl]-9-methoxycarbonylindolizino[8,7-b]indole (+) **10**.
The carboxylic acid (+) **8** (60mg 0.18mmol) in dry THF (3ml) at -20°C was treated with isobutyl chloroformate (26.1μl 0.2mmol) and N-methylmorpholine (18.5mg 201μl). After 20min (R)-(+)-α-methylbenzylamine (24.4mg 26μl) was added to the above mixture, and the solution warmed to 20°C. After a further 30min the solution was evaporated in vacuo and the residue dissolved in CH_2Cl_2, washed with sat aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give a foam. Purification by silica gel chromatography eluting successively with 30%, 50% and 100% petroleum ether/EtOAc gave (+) **10** (70.9mg 90%), as a colorless crystalline material, mp 163-164.5°C (from MeOH/H_2O). $[\alpha]_D^{22}$ + 133° (c, 0.15 in $CHCl_3$). Ir ($CHCl_3$) 3460, 3380, 1740, 1690cm^{-1}. ^{1}H Nmr (300MHz, $CDCl_3$) δ 8.60(1H, s), 7.51(1H, d, J = 7.8Hz), 7.09-7.35(8H, m), 5.25(1H, dd, J's = 7.8 and 2.1Hz), 5.01(1H, m), 3.61(1H, dd, J's = 15.9 and 1.8Hz), 3.33(3H, s), 3.02(1H, m), 2.61-2.78(2H,m), 2.41-2.52(1H, m), 2.15-2.28(1H, m), 1.77(1H, bs), 1.47(3H, d, J = 6.9Hz). Ms calcd for $C_{25}H_{25}N_3O_4$ requires m/e 431.1845. Found: (M+1) 432.1923.

(+) **8** Directly from L-Tryptophan **5** (R = H).
To a suspension of L-tryptophan (2.04g 10mmol) in THF (50ml) was added p-toluenesulfonic acid monohydrate (2.0g 10.5mmol). Benzene (150ml) was added to the suspension, and azeotropic distillation gave the anhydrous salt. Dry THF (60ml) was added to the above solid followed by dimethyl α-ketoglutarate (2.2g 12.6mmol). The heterogeneous mixture was heated at reflux for 15h and evaporated in vacuo. The residue was dissolved in

dichloromethane (100ml) and washed with water, dried ($MgSO_4$), and evaporated to give the crude product. Purification by chromatography over silica gel eluting with 10% EtOAc/CH_2Cl_2, followed by THF/CH_2Cl_2/HOAc (4:8:1) gave (+) **8** (1.33g 40%). Starting with D-tryptophan, (-) **8** was obtained, mp 227° (dec from EtOAc), $[\alpha]_D$ -83.5° (c, 1.034, $CHCl_3$).

(+)-(9R)-3-Oxo-9-methoxycarbonylindolizino[8,7-b]indole (+) **12**.

The carboxylic acid (+) **8** (63.7mg 0.19mmol) in dry THF (1.5ml) at -15°C was treated with isobutyl chloroformate (29.2mg 0.21mmol 1.1eq) and N-methylmorpholine (19.6mg 0.19mmol). After stirring the mixture for 5min N-hydroxy-2-thiopyridone (24.7mg 1.1eq) and triethylamine (23.3mg 1.1eq) were added. The mixture was stirred for a further 15min at -15°C and t-butylthiol (175mg) added. The above solution was irradiated at 20°C with a 270W sun lamp for 20min until the intermediate ester **11** had disappeared (tlc). The mixture was evaporated in vacuo, and the residue dissolved in CH_2Cl_2, washed with 2H HCl, dried (Na_2SO_4) and evaporated to give an oil. Purification by chromatography over silica gel eluting with EtOAc gave (+) **12** (45.2mg 82%), mp 217°C (dec) $[\alpha]_D^{22}$ + 138.5° (c, 0.28 in $CHCl_3$). Ir ($CHCl_3$) 3460, 3300, 1730 and 1680cm^{-1}. ^1H Nmr (300MHz, $CDCl_3$) δ 8.40(1H, s), 7.51(1H, d, J = 7.8Hz), 7.38(1H, d, J = 8.7Hz), 7.23(1H, t, J = 7.8Hz), 7.13(1H, t, J = 7.8Hz), 4.58(1H, m), 3.79(3H, s), 3.21(1H, m), 2.82(3H, m), 2.56(2H, m), 2.28(1H, m). Ms calcd for $C_{16}H_{16}N_2O_3$ requires m/e 284.1167. Found: M^+ 284.1164.

(+)-(9R)-3-Thio-9-methoxycarbonylindolizino[8,7-b]indole (+) **13**.

The tetracyclic amide (+) **12** (365mg 1.29mmol) in THF (7ml) was treated with Belleau's reagent (410mg 0.77mmol). After 1.5h at 20°C the mixture was evaporated under reduced pressure, and the residue purified by chromatography over alumina eluting with CH_2Cl_2, then over silica gel eluting with EtOAc to give (+) **13** (318mg 83%), mp 174-175°C, $[\alpha]_D$ + 225° (c, 0.51 in $CHCl_3$). Ir (film) 3360, 1740cm^{-1}. ^1H Nmr (300MHz, $CDCl_3$) δ 8.29(1H, s), 7.53(1H, d, J = 7.8Hz), 7.38(1H, d, J = 8.1Hz), 7.25(1H, t, J = 6.9Hz), 7.15(1H, t, J = 7.2Hz), 5.35(1H, m), 3.82(3H, s), 3.44(1H, m), 3.02-3.23(2H, m), 2.84-2.96(3H, m), 2.34-2.35(1H, m). ^{13}C Nmr (70MHz, $CDCl_3$) δ 200.73, 170.50, 136.58, 129.39, 125.81, 122.48, 120.03, 118.72, 111.24, 109.66, 72.19, 53.56, 43.50, 41.85, 33.97, 20.47. Anal calcd for $C_{16}H_{16}N_2O_2S$ requires C, 64.00; H, 5.33; N, 9.33. Found: C, 63.74; H, 5.43; N, 9.15%. Ms calcd for $C_{16}H_{16}N_2O_2S$ requires m/e 300.0936. Found: M^+ 300.0934.

(+)-(9R)-3H-9-Methoxycarbonylindolizino[8,7-b]indole (+) **2**.

The thioamide (+) **13** (905mg 3.02mmol) in THF (20ml) was treated with a large excess of freshly prepared W-2 Raney nickel at 20°C. When tlc indicated that (+) **13** had been consumed (15h), the Raney nickel was removed by filtration through celite and the celite washed with THF. The filtrate was evaporated in vacuo and the residue purified by chromatography over silica gel eluting with 50% EtOAc/petrol, followed by EtOAc to give (+) **2** (790mg 97%), $[\alpha]_D^{25}$ + 37° (c, 1.1 in $CHCl_3$). Ir ($CHCl_3$) 3460, 3400 and 1720cm^{-1}. ^1H Nmr (300MHz, $CDCl_3$) δ 8.25(1H, s), 7.50(1H, d, J = 7.5Hz) 7.34(1H, d, J = 7.8Hz), 7.18(1H, t, J = 7.0Hz), 7.10(1H, t, J = 7.0Hz), 3.77(3H, s), 3.33-3.37(2H, m), 3.15(1H, m), 2.88-3.01(2H, m), 1.94(1H, m), 1.73(1H, m). ^{13}C Nmr (70MHz, $CDCl_3$) δ 174.1(s), 136.03(s), 132.2(s), 126.4(s), 121.9(d), 119.1(d), 118.2(d), 110.8(d), 109.2(s), 66.3(s), 52.5(q), 49.2(t), 43.5(t), 37.1(t), 22.8(t), 15.6(t). Ms calcd for $C_{16}H_{18}N_2O_2$ requires m/e 270.1365. Found: (M+1) 271.1445 $C_{16}H_{19}N_2O_2$ (M+1) requires 271.1443. The (9S)(-) enantiomer has $[\alpha]_D^{25}$ - 37° (c, 1.32 in $CHCl_3$).

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7. Since (+) **8** gives (+) **10** as a single diastereomer the optical purity of (+) **8** must be ≥95%, as determined by nmr.

8. The complete details of the single-crystal X-ray structural determination of (+) **10** may be obtained from Dr. John C. Huffman, Molecular Structure Center, Indiana University, Bloomington, Indiana 47405. Ask for report No. 87125.

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