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Total Synthesis of (*S*)-(+)-Tylophorine Via Enantioselective Intramolecular Alkene Carboamination

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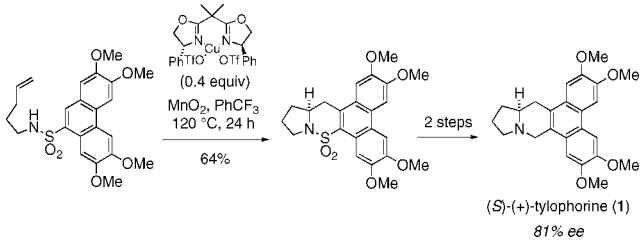

The enantioselective synthesis of (*S*)-(+)-tylophorine, a potent cancer cell growth inhibitor, has been accomplished in eight steps from commercially available 3,4-dimethoxybenzyl alcohol. A copper (II)-catalyzed enantioselective intramolecular alkene carboamination was employed as the key step to construct the chiral indolizidine ring.

The phenanthroindolizidine and phenanthroquinolizidine alkaloids have attracted human interest for centuries.[1] As early as the 1800s, the leaves of one of the plants, *Tylophora indica*, from which these compounds are isolated, was recommended in a medical text as an herbal remedy for conditions such as bronchitis, rheumatism, and dysentery in India.[2] Since the isolation of the major alkaloid, (*R*)-tylophorine, in 1935,[3] from *Tylophora indica*, over 60 compounds in this class have been isolated from the *Asclepiadaceae* and *Moraceae* plant families, found primarily in India and Japan.[1] The biological properties of these alkaloids range from cancer cell growth inhibition (in vitro and in vivo)[1b,4] and anti-inflammatory activity[2,5] to anti-ameobicidal[6] and anti-viral[7] activity. Structure−activity relationship studies focusing on the anticancer activity of these counpounds have drawn particular interest as many of them are low nanomolar inhibitors of cancer cell growth, including multidrug-resistant cell lines. Notably, based upon the NCI's COMPARE[8] analysis,[4d] their mode of action appears to be different from other known anticancer compounds.

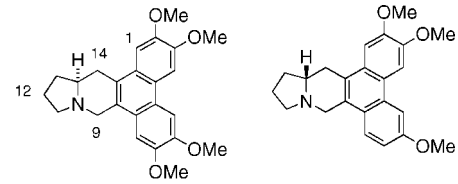

FIGURE 1. Phenanthroindolizidine natural products.

The structures of two particularly potent cancer cell growth inhibitors in vitro, (*S*)-tylophorine (**1**) and (*R*)-antofine (**2**), are illustrated in Figure 1. Although (*S*)-tylophorine is the unnatural enantiomer, it is a more potent inhibitor of cancer cell growth than (*R*)-tylophorine.[4c,d] Further investigations into the anticancer activity of (*S*)-tylophorine and (*R*)-antofine as well as tylophorinidine, a C(14) hydroxylated, C(2)-desmethoxy analog of tylophorine, revealed that they are only moderately potent tumor growth inhibitors in vivo, possibly because of suboptimal pharmakokinetics.[4d,e,g] Therefore, the development of a highly convergent synthesis useful for the discovery of more potent analogs is desirable.

It is noteworthy that a decrease in molecular complexity via removal of the indolizidine ring, dubbed the "limiting synthetic factor" by some researchers, led to substantial reduction of cancer cell growth inhibitory activity.[9] Thus, an efficient route to analogs with intact indolizidine rings is necessary.

A number of racemic synthetic routes to tylophorine and antofine have been published, some of them quite concise.[1,4g] Both the (*R*)- and (*S*)-tylophorine enantiomers have been synthesized selectively using the chiron approach, starting with either proline,[10] glutamic acid,[11] or pyroglutamate,[12] as well as the chiral auxiliary approach manifested in diastereoselective Grignard additions[13] and double Michael reactions,[14] respec-

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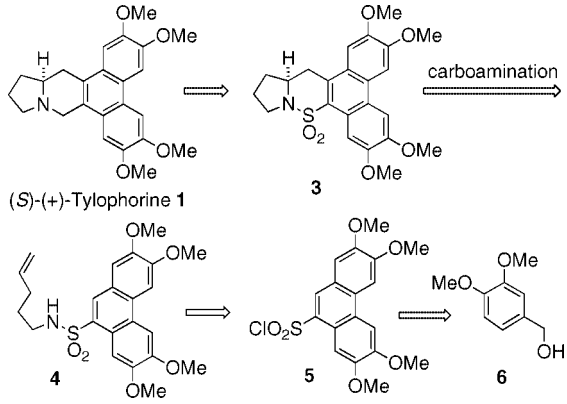
SCHEME 1. Retrosynthetic Analysis

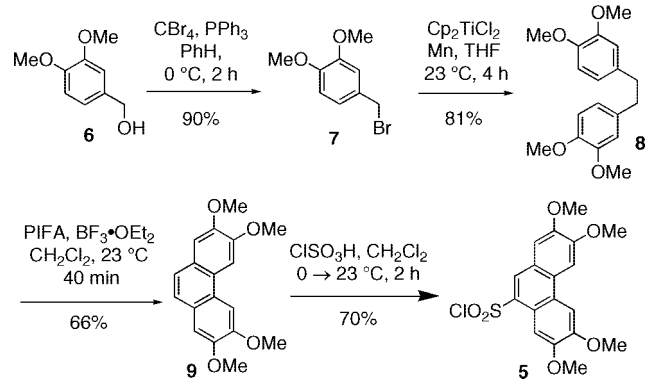


tively. Reported enantioselective syntheses of antofine make use of either the chiral pool (proline,[10b,7b] pyroglutamate,[15] methyl lactate[16]) or asymmetric catalysis (phase transfer alkylation).[17] In the former case,[7b] however, epimerization of the indolizidine stereocenter is sometimes observed, while in the latter case the synthesis is somewhat lengthy.[17] Although a considerable amount of synthetic effort has been exerted toward these targets, we believed we could contribute uniquely to this area of research. We sought to develop a concise, convergent, and enantioselective route to these compounds that would be amenable to the synthesis of substituted indolizidine analogs where both the relative and absolute stereochemistry could be predictably installed. Herein is described our enantioselective synthesis of (*S*)-tylophorine, which uses a catalytic asymmetric carboamination reaction to install the required indolizidine stereocenter.

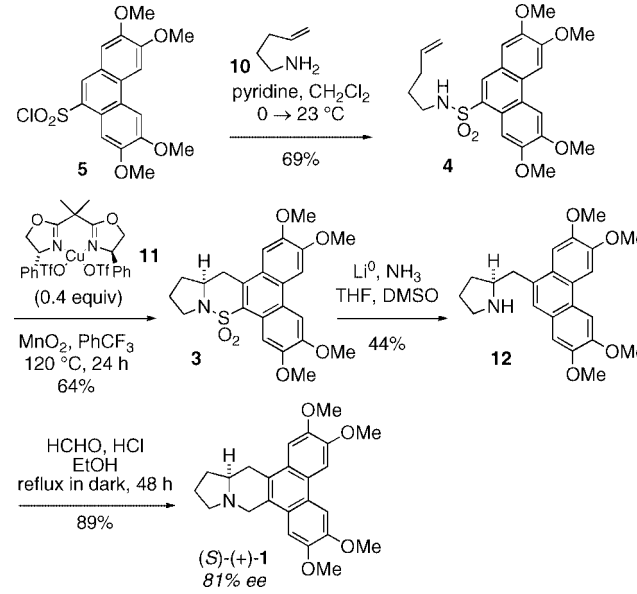
We have recently reported the use of copper(II) complexes in the efficient intramolecular carboamination of terminal alkenes.[18] These reactions result in the formation of polycyclic aromatic nitrogen heterocycles and can be performed both diastereoselectively[18b] and enantioselectively.[18c] We saw the carboamination disconnection in tylophorine, wherein sulfonamide **4** could undergo enantioselective carboamination to provide sultam **3**, which could be processed in short order to tylophorine (**1**) (Scheme 1). The sulfonamide serves a dual purpose in this reaction, both in increased reactivity (compared to the corresponding amide) and as a handle for enantioinduction (we have not been able to render the carboamination reactions of γ-alkenyl amides asymmetric yet).

Sulfonamide **4** is convergently synthesized from commercially available 3,4-dimethoxybenzyl alcohol. Conversion of 3,4-dimethoxybenzyl alcohol (**6**) to the bromide **7** followed by radical-induced dimerization[19] provided dimer **8** (Scheme 2). Oxidative cyclization and aromatization with phenyliodine(II-I)bis(trifluoroacetate) (PIFA) provided the known phenanthrene **9**.[20] Monosulfonylation with chlorosulfonic acid provided the

SCHEME 2. Phenanthrene Synthesis



SCHEME 3. Completion of (*S*)-Tylophorine



necessary arylsulfonyl chloride **5**.[21] Careful control of the reaction temperature and equivalents of chlorosulfonic acid was necessary to avoid disulfonylation.

Coupling of 3-pentenyl amine (**10**) with arylsulfonyl chloride **5** provided sulfonamide **4** (Scheme 3). Enantioselective carboamination, promoted by substoichiometric (0.4 equiv) copper(II)-(*R*)-Ph-Box **11**, provided sultam **3** in 64% yield. Because of the poor solubility properties of this compound in the HPLC solvents hexanes/isopropanol, the enantiomeric excess was not measured at this point. Removal of sulfur dioxide under dissolving metal conditions (Li/NH_3/DMSO) provided the known[10a] pyrrolidine **12**. The yield of this step is modest because removal of aryl methoxy groups also occurred under these conditions.[22] A range of reduction conditions were explored as alternative (Raney nickel, $Ni(acac)_2$/*i*-Pr_2Mg,[23] Mg/MeOH,[24] Na/NH_3), but no superior conditions were identified. Pictet–Spengler reaction with formaldehyde closed the indolizidine

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ring,[10a] thereby providing synthetic (*S*)-tylophorine (**1**). The enantiomeric excess was measured to be 81% on chiral HPLC (Chiralcel AD-H). The NMR spectra of synthetic tylophorine matched the reported values,[10] and the optical rotation of (*S*)-(+)-**1**, $[\alpha]^{23}_D = +62.1°$ (*c* 1.0, $CHCl_3$) is in agreement with that reported previously, $[\alpha]^{21}_D = +73.0°$ (*c* 0.7, $CHCl_3$).[10a]

In summary, we have described a concise and convergent enantioselective synthesis of (*S*)-tylophorine. This route is amenable to the synthesis of either enantiomer of tylophorine from a common advanced intermediate and is also applicable to the synthesis of substituted indolizidine analogs via coupling of arylsulfonyl chloride **5** with a number of functionalized terminal γ-alkenyl amines. Structure−activity relationship studies of indolizidine-substituted analogs of tylophorine are in progress and will be reported in due course.

Experimental Section

Procedure for the Carboamination. (*S*)-2,3,6,7-Tetramethoxy-11,12,12a,13-tetrahydro-10*H*-9-thia-9a-aza-cyclopenta[*b*]triphenylene-9,9-dioxide (3). $Cu(OTf)_2$ (10.0 mg, 0.028 mmol, 0.4 equiv), 2,2-bis[(4*R*)-4-phenyl-2-oxazolin-2-yl]-propane (9.2 mg, 0.028 mmol, 0.4 equiv), and 2.5 mL of $PhCF_3$ were combined in a pressure tube equipped with a stir bar under Ar, and the mixture was stirred at 45−50 °C for 1 h to make the Cu(II) salt coordinate with the ligand completely. This mixture was then treated with K_2CO_3 (9.5 mg, 0.069 mmol, 1 equiv), MnO_2 (18.0 mg, 0.206 mmol, 3 equiv), and 2,3,6,7-tetramethoxyphenanthrene-9-sulfonic acid pent-4-enylamide (**4**) (30.6 mg, 0.069 mmol, 1 equiv), and then the tube was refreshed with Ar for 5 min, sealed, and heated at 120 °C in an oil bath for 24 h. Upon cooling to room temperature, the mixture was diluted with $CHCl_3$ (2.0 mL) and stirred for about 5 min. Filtration of the cooled solution and removal of the solvent in vacuo afforded a crude residue. Successive chromatography on SiO_2 (EtOAc/hexane, 3:1; $CHCl_3$/EtOAc, 20:1) afforded purified sultam **3** (20.0 mg, 64%) as a light yellow solid. This reaction was performed on 0.344 mmol (0.153 g) of **4** as well, and a 61% yield was obtained. Mp 289−291 °C (decomposed); $[\alpha]^{23}_D = +47.1$ ° (*c* 2 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1 H), 7.79 (s, 1 H), 7.77 (s, 1 H), 7.30 (s, 1 H), 4.40−4.25 (m, 1 H), 4.14 (s, 3 H), 4.12 (s, 3 H), 4.10 (s, 3 H), 4.06 (s, 3 H), 3.80−3.70 (m, 1 H), 3.51−3.39 (m, 2 H), 3.20 (dd, J = 16.0, 8.0 Hz, 1 H), 2.52−2.40 (m, 1 H), 2.13−2.08 (m, 2 H), 2.00−1.90 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.3, 150.0, 149.8, 149.7, 130.1, 129.6, 127.0, 125.0, 123.9, 120.9, 107.0, 105.3, 103.7, 103.4, 56.9, 56.5, 46.6, 33.2, 31.3, 23.0. IR (neat): 2959, 2938, 2253, 1619, 1533, 1515, 1476, 1466, 1421, 1278, 1264, 1247, 1213, 1199, 1147, 1044, 1005, 728, 607 cm^{-1}. HRMS (EI) calcd for $[M]^+$ $C_{23}H_{25}NO_6S$ 443.1397, found 443.1407.

Sulfonamide Reduction. (*S*)-2-(2,3,6,7-Tetramethoxyphenanthren-9-ylmethyl)-pyrrolidine (12). The desulfonylation was performed by modification of the procedure reported by Evans.[22] Ammonia (10.0 mL) was condensed in a volume-marked two-neck flask containing sultam **3** (22.5 mg, 0.051 mmol) and dry THF/DMSO (1.0 mL, 1: 2) at −78 °C under Ar. Lithium metal (3.0 mg, 0.43 mmol, 8.4 equiv) was added over 15 min (1.0 mg of lithium per 5 min was added). After the mixture was stirred at −78 °C under Ar for 30 min, solid NH_4Cl (1.0 g) was added, and the solution was warmed to room temperature and allowed to evaporate overnight. EtOAc (10 mL) and aqueous KOH (20%, 10 mL) were added to the resulting residue. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4. The solvents were removed in vacuo, and flash chromatography of the resulting crude oil on SiO_2 using CH_3OH/aqueous 37% NH_4OH (3: 0.1) as eluent afforded 8.5 mg (44%) of (*S*)-2-(2,3,6,7-tetramethoxyphenanthren-9-ylmethyl)-pyrrolidine (**12**) as a light yellow oil, whose NMR spectrum was identical to that previously reported for **12**.[10a] $[\alpha]^{23}_D = +3.5°$ (*c* 0.94, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1 H), 7.77 (s, 1 H), 7.48 (s, 1 H), 7.44 (s, 1 H), 7.19 (s, 1 H), 4.12 (s, 3 H), 4.11 (s, 3 H), 4.05 (s, 3 H), 4.03 (s, 3 H), 3.60−3.50 (m, 1 H), 3.19 (d, 2 H, J = 6.8 Hz), 3.18−3.08 (m, 1 H), 2.90−2.80 (m, 1 H), 1.91−1.88 (m, 2 H), 1.78−1.73 (m, 2 H), 1.60−1.50 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 149.1, 132.4, 126.9, 126.1, 125.5, 125.2, 124.2, 108.6, 105.5, 104.0, 103.4, 59.2, 56.7, 56.6, 56.5, 56.4, 46.8, 40.8, 32.3, 25.5.

(*S*)-(+)-Tylophorine (1). The Pictet−Spengler reaction was performed by a modification of the procedure as reported by Njoroge.[10a] To a solution of amine **12** (7.3 mg, 0.02 mmol) in EtOH (0.50 mL) were added 37% formaldehyde (0.11 mL) and concentrated HCl (11.0 μL). The reaction mixture was refluxed for 2 days in the dark and then concentrated to dryness under reduced pressure. The residue was treated with 20% KOH (1 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic layers were washed with water and brine and dried over Na_2SO_4. Filtration and concentration in vacuo afforded the crude oil, which was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to afford (*S*)-tylophorine (**1**) (6.7 mg, 89%) as light yellow solid. Mp 283−285 °C (lit. mp 282−284 °C,[11] 284−286 °C[10a]). $[\alpha]^{23}_D = +62.1°$ (*c* 1.0 in $CHCl_3$). Lit.[10] $[\alpha]^{21}_D = +73°$ (*c* 0.7 in $CHCl_3$), ee = 81%, determined by HPLC analysis [Chiralcel AD-H, 15% IPA/hexane, 0.70 mL/min, λ = 254 nm, t_R (major) = 22.50 min, t_R (minor) = 34.54 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 2 H), 7.29 (s, 1 H), 7.14 (s, 1 H), 4.61 (d, 1 H, J = 16 Hz), 4.11 (s, 6 H), 4.05 (s, 6 H), 3.66 (d, 1 H, J = 14.4 Hz), 3.51−3.41 (m, 1 H), 3.34 (d, 1 H, J = 17.2 Hz), 2.90 (t, 1 H, J = 11.2 Hz), 2.48−2.46 (m, 2 H), 2.31−2.20 (m, 1 H), 2.10−2.00 (m, 1 H), 2.00−1.80 (m, 1 H), 1.80−1.70 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 147.5, 147.4, 125.3, 124.8, 123.3, 122.6, 122.4, 103.0, 102.5, 102.3, 102.1, 59.2, 55.0, 54.9, 54.1, 52.9, 32.7, 30.2, 20.6. IR (neat): 2957, 1717, 1602, 1535, 1515, 1472, 1441, 1425, 1416, 1262, 1249, 1213, 1195, 1150, 1016, 840, 770 cm^{-1}. HRMS (EI) calcd for $[M]^+$ $C_{24}H_{27}NO_4$ 393.1935, found 393.1933. These data were in agreement with those reported.[10−13]

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Supporting Information Available: Procedures and characterization data and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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