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AN ENANTIOSPECIFIC SYNTHESIS OF (+)- AND (-)-20-EPI-IBOPHYLLIDINE VIA AN *INTRAMOLECULAR DIELS-ALDER TYPE CYCLIZATION* †

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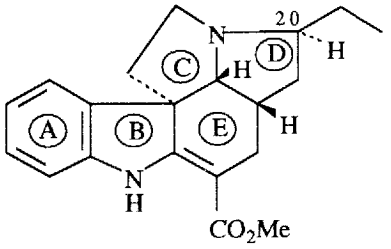
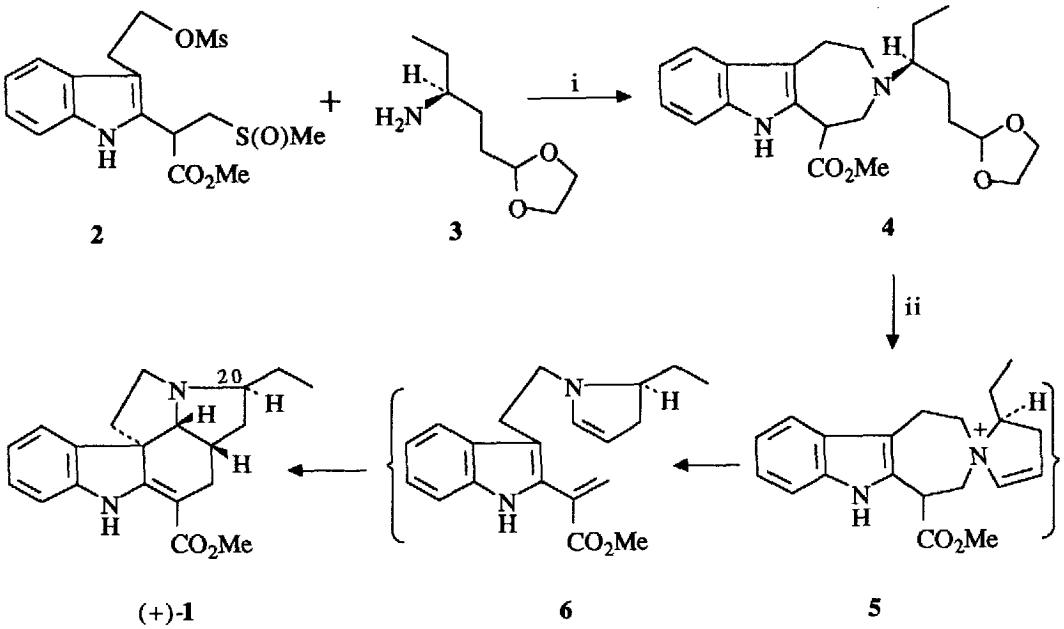
Abstract: An enantiospecific synthesis of the pentacyclic pseudo-*Aspidosperma* alkaloid (+)-20-epi-ibophyllidine **1** as well as of its (-)-enantiomer has been achieved via an intramolecular Diels-Alder type cycloaddition of a transient secodine-like intermediate **6** formed by condensation of the indole-2-acrylate precursor **2** and the appropriate chiral amine **3** followed by acidic treatment.

In an earlier communication[1] we described an expeditious route toward the construction of the pentacyclic skeleton of several *Aspidosperma*/pseudo-*Aspidosperma* type indole alkaloids in a stereoselective but racemic mode. Among the target compounds was the alkaloid 20-epi-ibophyllidine, the natural (+)-enantiomer of which has the absolute stereochemistry depicted in structure **1**.[2] A stereoselective synthesis of (±)-20-epi-ibophyllidine was also reported by Kuehne *et al.*[3] Our synthesis, outlined in Scheme 1, consisted essentially of the condensation of the previously prepared indole-2-acrylic ester precursor **2**[4] with the amine-acetal **3** (racemic) giving access to the tertiary amine **4**. Release of the aldehyde function by acidic hydrolysis led to (±)-20-epi-ibophyllidine in 35% overall yield from **2**. The formation of the target molecule presumably proceeded through the enammonium ion **5**, its fission to the transient secodine-like intermediate **6** followed by an intramolecular Diels-Alder type cyclization.



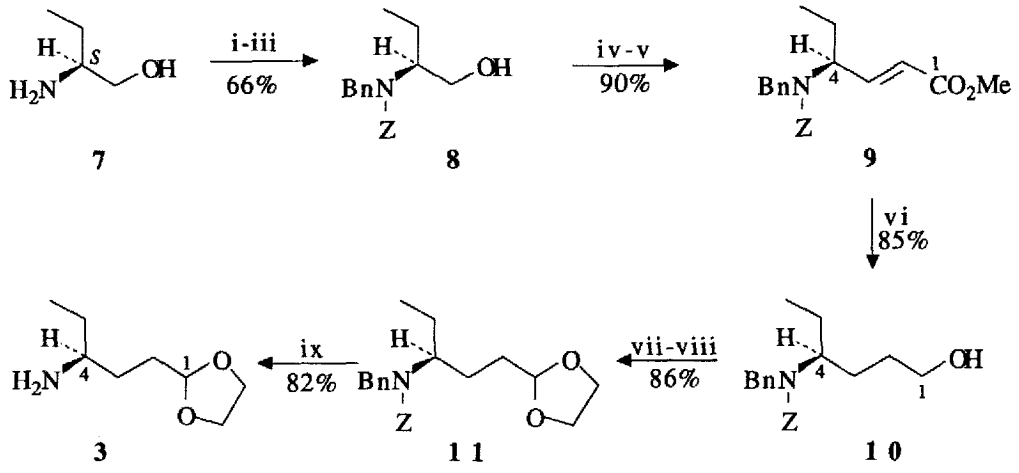
(+)-20-epi-ibophyllidine **1**

† Dedicated to the memory of Professor Edgar Lederer.



2 3 4

Scheme 1: i. K_2CO_3, NaI, pyridine, 25°C, 48h; ii. THF (HCl 10%), 25°C, 2h.



7 8 9 10 11 3

Scheme 2 : i. PhCHO, $MgSO_4$, CH_2Cl_2, 25°C; ii. $NaBH_4$, MeOH, at 0°C and then 2h at room temperature; iii. $PhCH_2OCOCl$, NaOH, H_2O-dioxan (1:1); iv. Me_2SO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78°C; v. $Ph_3P{=}CHCO_2Me$, THF, 25°C; vi. $NaBH_4$-LiCl (1:1), EtOH-THF (4:3), 25°C; vii. PCC, CH_2Cl_2, molecular sieves, 4Å, 25°C; viii. $HO(CH_2)_2OH$, TsOH, PhH, reflux; ix. HCO_2NH_4, 10% Pd-C, MeOH, reflux, 1min.

By using the amine-acetal **3** in its appropriate chiral form [*S* or *R*], we now show that this synthetic approach can lead to (+)- or (-)-enantiomer of 20-epi-ibophyllidine, respectively. The chiral center bearing the ethyl group in the intermediate **6** thus fully controls the enantiospecificity of the intramolecular cyclization thereby defining the configuration of the newly formed bridge-head chiral centers of the rings C, D and E of the resulting 20-epi-ibophyllidine.

The chiral amine-acetal (4*S*)-**3**, required for the synthesis of (+)-20-epi-ibophyllidine **1**, was prepared from the commercially available (*S*)-(+)-2-amino-1-butanol **7** through the reaction steps outlined in Scheme 2. The amino group was successively protected with a benzyl (Bn) and a benzyloxycarbonyl (Z) group to give the alcohol **8**. Swern oxidation[5] of **8** led to the corresponding aldehyde which, without purification, was subjected to Wittig olefination yielding *E* α,β–unsaturated ester **9**. Reduction of the conjugated ester group of **9** with sodium borohydride in the presence of lithium chloride[6] provided the saturated alcohol **10**. The aldehyde obtained by the pyridinium chlorochromate (PCC)[7] oxidation of **10** was converted into the acetal **11** which, when treated with ammonium formate in the presence of 10% Pd-C in refluxing methanol[8] under nitrogen, afforded the amine-acetal (4*S*)-**3**.

Pure (+)-20-epi-ibophyllidine **1** was obtained by reacting the amine-acetal (4*S*)-**3** with the indole derivative **2** (Scheme 1). Similarly, the use of the (4*R*)-epimer of **3**, prepared from (*R*)-(-)-2-amino-1-butanol, afforded (-)-20-epi-ibophyllidine. Naturally occurring (+)-ibophyllidine and (+)-20-epi-ibophyllidine could be distinctly separated by HPLC. Under similar conditions, no ibophyllidine was detected in our synthetic specimens of either (+)- or (-)-20-epi-ibophyllidine described here. Previously, we erroneously reported[1] the formation of (±)-ibophyllidine in the course of the synthesis of (±)-20-epi-ibophyllidine.

The synthetic (+)- and (-)-**1** had identical spectral data which fully matched those previously reported.[2] Their enantiomeric homogeneity was established through the measurements of their 400 MHz ^{1}H n.m.r. spectra using different concentrations of the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(-)-camphorato]-europium(III). Moreover, the enantiomeric purity (e.e. > 95%) of the (4*S*)- and (4*R*)-epimers of the amine-acetal **3** was ensured by the 400 MHz ^{1}H n.m.r. analysis of their (*S*)-(-)-α-methoxy-α–(trifluoromethyl)phenylacetyl derivatives (Mosher amides).[9,10]

The enantioselective formation of either (+)- or (-)-20-epi-ibophyllidine as a single isomer in the course of our reaction sequence confirms the previously proposed mechanism according to which the 2-ethyl-2,3-dihydropyrrole ring of the transient secodine-like intermediate **6** reacted with the acrylic ester system entirely from the face of the five-membred ring opposite the ethyl chain.[3]

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   Mosher amides were prepared directly with commercial (*S*)-(-)-(α)-methoxy(trifluoromethyl)phenylacetic acid following the procedure described by P. Garner and J. M. Park, *J. Org. Chem.*, 52, 2361, 1987.
10. All reported yields are for purified materials isolated from column chromatography and all compounds gave spectroscopic data in agreement with the assigned structures. Selected physical data include the following.

    9: ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.80 (t, 3H, J 7,5 Hz, 3H-6), 1.36-1.87 (m, 2H, 2H-5), 3.65 (s, 3H, CO_2Me), 4.40 (m, 3H, H-4 and CH_2Ph), 5.14 (s, 2H, CO_2CH_2Ph), 5.72 (d, 1H, $J_{2,3}$ 16 Hz, H-2), 6.81(dd, 1H, $J_{3,2}$ 16 Hz, $J_{3,4}$ 6 Hz, H-3), 7.17 and 7.28 (2s, 10H, Ar); EIMS m/z 367 ($M^{+}\cdot$); $[\alpha]_D$ -27° (c 3, EtOH) for (*S*)-**9**; $[\alpha]_D$ +27° (c 3, EtOH) for (*R*)-**9**.

    10: ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.78 (t, 3H, 3H-6), 1.17-1.75 (m, 7H, 2H-2, 2H-3, 2H-5, OH), 3.40 (m, 2H, 2H-1), 3.90 (m, 1H, H-4), 4.34 (s, 2H, CH_2Ph), 5.12 (s, 2H, CO_2CH_2Ph), 7.27 (m, 10H, Ar); EIMS m/z 341 ($M^{+}\cdot$); $[\alpha]_D$ +8° (c 3.9, $CHCl_3$) for (*S*)-**10**; $[\alpha]_D$ -7° (c 3.5, $CHCl_3$) for (*R*)-**10**.

    3: ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.96 (t, 3H, J 7Hz, 3H-6), 1.30-1.90 (m, 6H, 2H-2, 2H-3, 2H-5), 2.87 (m, 1H, H-4), 3.86 (m, 4H, OCH_2CH_2O), 4.35 (br s, 2H, NH_2), 4.82 (t, 1H, J 4Hz, H-1); CIMS m/z 160 (MH^+); $[\alpha]_D$ +4° (c 1.46, MeOH) for (*S*)-**3**; $[\alpha]_D$ -4° (c 2, MeOH) for (*R*)-**3**.

    1: The observed $[\alpha]_D$ values (in $CHCl_3$) of (+)-1 and (-)-1 were +268° (c 1) and -271° (c 1), respectively. Since literature precedent,[2] $[\alpha]_D$ +528° (c 0.3, $CHCl_3$), was significantly different, a sample of the natural alkaloid kindly provided by Dr. (Mrs.) C. Kan was repurified and its recorded $[\alpha]_D$ +322° (c 1.3) was much closer to that found for the synthetic specimen.

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