First enantiocontrolled syntheses of (+)-uleine and (+)-dasycarpidone

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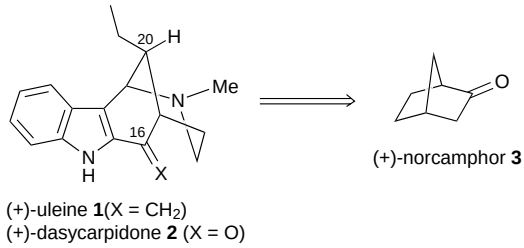
Stereocontrolled syntheses of (+)-uleine and (+)-dasycarpidone are achieved for the first time in an enantiocontrolled way starting from (+)-norcamphor.

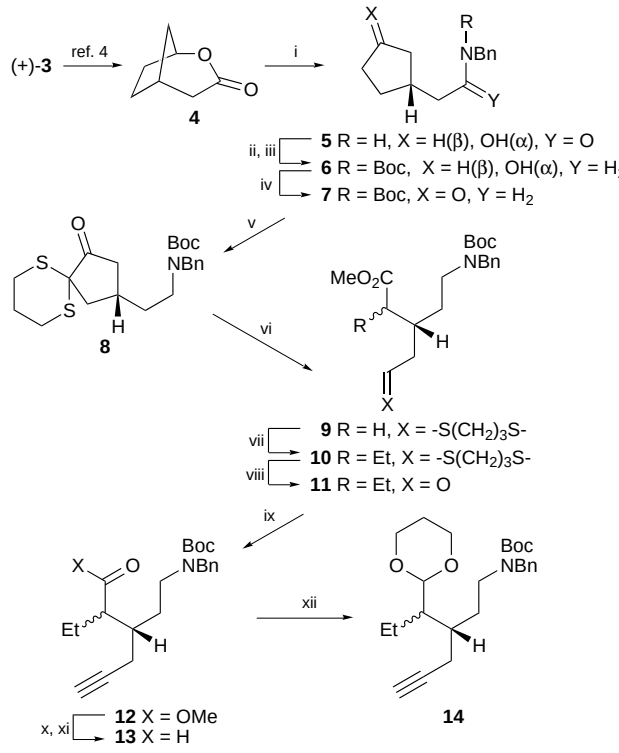
Although a number of racemic syntheses of the uleine type indole alkaloids have been reported,[1] no enantiocontrolled synthesis has been disclosed to date. We report here the first stereo- and enantio-controlled construction of the representatives of this group, (+)-uleine **1** and (+)-dasycarpidone **2**, using (+)-norcamphor **3** as starting material (Scheme 1).[2]

(+)-Norcamphor **3**† was first transformed into the δ-lactone **4**[3a] which was then condensed with benzylamine to give the amide alcohol **5**,‡ mp 94–95 °C, $[\alpha]_D^{33}$ −1.95 (*c* 0.55, $CHCl_3$), in 75% yield. Hydride reduction of **5** followed by *N*-carbamoylation of the resulting amine yielded the carbamate **6**, $[\alpha]_D^{27}$ −0.76 (*c* 1.0, $CHCl_3$), which was oxidized to give the cyclopentanone **7**, $[\alpha]_D^{30}$ +58.0 (*c* 0.9, $CHCl_3$), in 90% overall yield. Transformation of **7** into the α-diketone monothioketal[3,4] **8**, mp 72–74 °C, $[\alpha]_D^{29}$ −43.5 (*c* 0.742, $CHCl_3$), followed by alkaline cleavage[3–5] yielded the acyclic methyl ester **9**, $[\alpha]_D^{31}$ +43.1 (*c* 0.3, $CHCl_3$), in 59% overall yield after treatment of the resulting acid with diazomethane. Exposure of **9** to iodoethane in the presence of sodium hexamethyldisilazide in THF containing HMPA at −78 °C afforded the α-ethyl ester **10** in 73% yield as an inseparable epimeric mixture with recovery of 14% of the starting material. The dithiane group of **10** was hydrolysed to give the aldehyde **11** in 92% yield which was treated with dimethyl 1-diazo-2-oxopropylphosphonate[6] in the presence of potassium carbonate to furnish the terminal acetylene **12** in 90% yield. Compound **12** was then converted into the 1,3-dioxane **14** in 72% overall yield *via* the aldehyde **13** by sequential reduction, oxidation and acetalization[7] (Scheme 2).

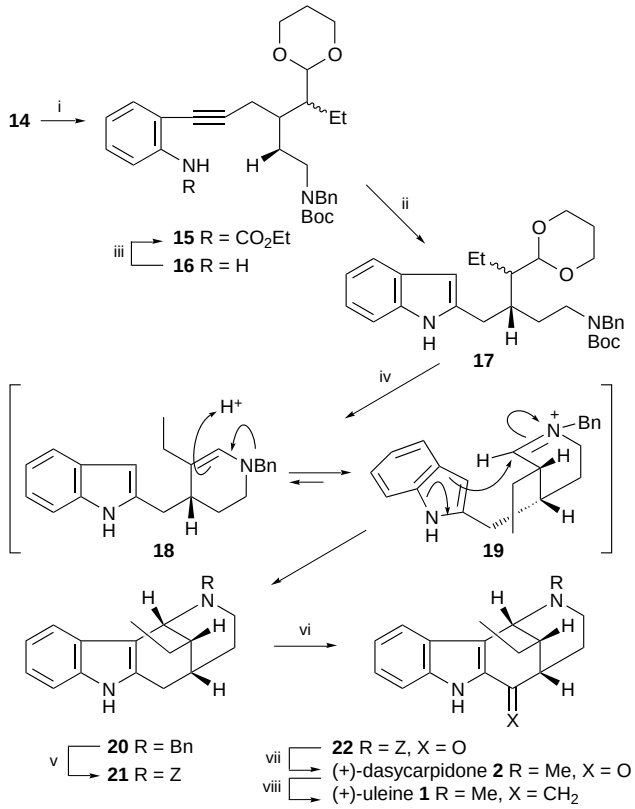
To construct the indole framework,[8,9] the acetylene **14** was first coupled with ethyl (2-iodophenyl)carbamate in the presence of dichlorobis(triphenylphosphine)palladium(ii) [$PdCl_2(PPh_3)_2$] and copper(i) iodide in triethylamine[10] to give the arylacetylene **15** in 86% yield. Cyclization was then carried out by treating **15** with sodium ethoxide in ethanol[8,9] at reflux to furnish the indole **17** in 64% yield accompanied by 31% of the de-*N*-acylated product **16** which, after separation, was treated with ethyl chlorocarbonate in pyridine to recover the carbamate **15** in 81% yield. The indole **17**, on reflux with TFA, afforded stereoselectively the tetracyclic amine **20**, $[\alpha]_D^{29}$ −155.3 (*c* 0.7, $CHCl_3$), in 54% yield accompanied by the readily separable 20-epimer (4%) by spontaneous deacetalization, decarbamoylation and stereoselective cyclization. The observed stereoselectivity may be rationalised by intervention of the enamine intermediate **18** which allowed epimerization of the C-20 stereogenic centre and stereoselective generation of the iminium intermediate **19** followed by its stereoselective cyclization[2a,b,d] under the conditions. Since the amine **20** was found to be unstable under the oxidation conditions, it was first transformed into the carbamate **21**, $[\alpha]_D^{28}$ +89.4 (*c* 0.4, $CHCl_3$), in 74% overall yield by sequential catalytic debenzylation and carbamoylation.[2d] The resulting carbamate **21** was then treated with pyridinium dichromate (PDC) on Celite in the presence of *tert*-butyl hydroperoxide (TBHP)[11] in benzene to afford the 16-ketone **22**, $[\alpha]_D^{28}$ +231.8 (*c* 0.2, $CHCl_3$), in 54% yield. Concurrent *N*-deprotection and *N*-methylation of **22** under the reductive conditions[2d] in the presence of 37% formalin afforded (+)-dasycarpidone **2**, $[\alpha]_D^{30}$ +63.1 (*c* 0.7, $CHCl_3$) [natural: $[\alpha]_D^{26}$ +64.7 (*c* 1.02, $CHCl_3$)],[12] in 83% yield. By following the established procedure,[2a,b] (+)-dasycarpidone **2** obtained was transformed into (+)-uleine **1**, $[\alpha]_D^{27}$ +18.2 (*c* 0.3, $CHCl_3$) [natural: $[\alpha]_D^{25}$ +16.5 (*c* 0.91, $CHCl_3$);[12] $[\alpha]_D^{27}$ +20 (*c* 0.94, $CHCl_3$)[13]], in 71% overall yield on treatment with methyl-



Scheme 1



Scheme 2 *Reagents and conditions*: i, $BnNH_2$, 180 °C (75%); ii, LAH, THF, reflux; iii, Bo_2O, aq. NaOH room temp. (95%); iv, pyridinium chlorochromate (PCC), NaOAc, CH_2Cl_2 (95%); v, pyrrolidine, benzene, reflux, then $TsS(CH_2)_3STs$, Et_3N, MeCN (59%); vi, KOH, Bu^{t}OH, 60 °C, acid workup, then CH_2N_2 (99%); vii, $NaN(SiMe_3)_2$, EtI, THF, HMPA, −78 °C (73%, recovery of 14% of **9**); viii, $Hg(ClO_4)_2$, $CaCO_3$, 20% aq. THF (92%); ix, $AcC(=N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, room temp. (90%); x, LAH, THF; xi, Swern oxidation (87%); xii, $Me_3SiO(CH_2)_3OSiMe_3$, Me_3SiOTf (cat.), THF, −78 °C (83%)



Scheme 3 *Reagents and conditions*: i, $PdCl_2(PPh_3)_2$ (10 mol%), CuI (10 mol%), 2-$IC_6H_4NHCO_2Et$, Et_3N, reflux (86%); ii, NaOEt, EtOH, reflux (**16**: 31% and **17**: 64%); iii, $ClCO_2Et$, pyridine (81%); iv, TFA, reflux (54%; 20-epimer 4%); v, 10% Pd–C, HCO_2NH_4, MeOH, reflux, then $ClCO_2Bn$, K_2CO_3, CH_2Cl_2 (74%); vi, PDC–Celite, TBHP, benzene, room temp. (54%); vii, H_2, 10% Pd–C, 37% formalin, MeOH (83%); viii, MeLi, THF, then neutral Al_2O_3 (activity I), 120 °C (71% overall)

lithium followed by dehydration of the resulting tertiary alcohol with neutral alumina.

Footnotes

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† Prepared from (+)-*endo*-norborneol (*ca.* 95% ee) kindly provided by Chisso Corporation, Japan.

‡ Satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, ^1H NMR, and MS) data were obtained for all new isolable compounds.

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