Alkaloid Total Synthesis

Enantioselective Total Synthesis of the Cyclotryptamine Alkaloid Idiospermuline**

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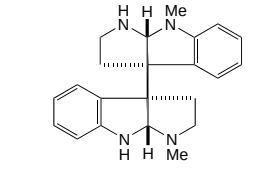
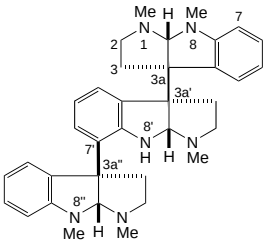
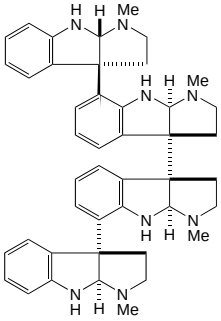
A remarkable group of alkaloids that link together up to eight pyrrolidinoindoline units has been isolated from higher plants.[1] (−)-Chimonanthine (**1**) is representative of the simplest of these. In higher order members of this group,



(–)-chimonanthine (**1**)



idiospermuline (**2**)



quadrigemine C (**3**)

exemplified by idiospermuline (**2**) and quadrigemine C (**3**), additional pyrrolidinoindoline units are attached at their benzylic quaternary stereocenters to *peri* positions of the aromatic ring of other pyrrolidinoindoline fragments. Stimulated by the unusual structures and varied biological activities of these cyclotryptamine alkaloids,[1] we have developed chemistry to access these complex, configurationally diverse alkaloids by stereocontrolled total synthesis.[2] We report herein the first total synthesis of the trispyrrolidinoindoline alkaloid idiospermuline (**2**), a naturally occurring cholinergic antagonist isolated recently from the seeds of *Idiospermum australiense*, a rare tree found in lowland rain forests of North Queensland, Australia.[3]

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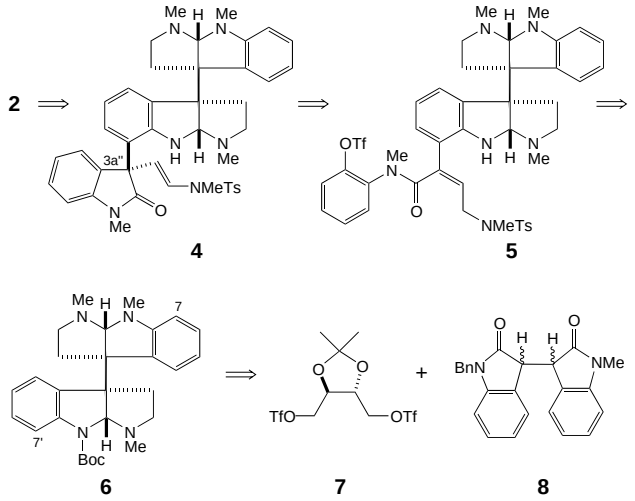
Idiospermuline (**2**) contains three all-carbon-substituted quaternary centers, two of which are vicinal (3a and 3a′) and the third (3a″), a diaryl-substituted quaternary carbon of the flanking pyrrolidinoindoline subunit. Two of the three indoline nitrogens (8 and 8″) carry methyl substituents, a structural feature that is rarely seen in polypyrrolidinoindoline alkaloids.[1] The synthesis plan we followed is outlined in antithetic format in Scheme 1. We envisaged forming the diaryl-substituted quaternary stereocenter by catalytic asym-

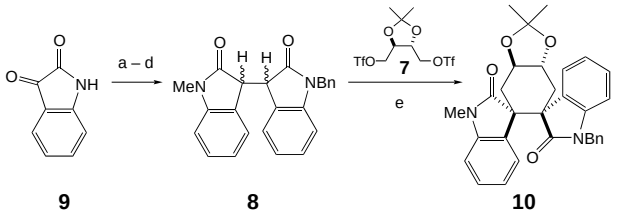


Scheme 1. Retrosynthesis of idiospermuline (**2**). Bn = benzyl, Boc = *tert*-butoxycarbonyl, Tf = trifluoromethanesulfonyl, Ts = toluenesulfonyl.

metric Heck cyclization of the heptacyclic triflate **5**.[4] This latter intermediate would be assembled from the (−)-chimonanthine congener **6**, whose contiguous quaternary carbons we saw as arising from the combination of tartrate-derived dielectrophile **7** and the lithium dienolate generated from dihydroisoindigo **8**.[2c] The asymmetric Heck cyclization step in this sequence would explore the utility of this transformation for appending a precursor of a pyrrolidinoindoline onto a chiral 3a,3a′-bispyrrolidinoindoline moiety.[5] The unsymmetrical methylation pattern of **2**, as well as the requirement to differentiate the two *peri* positions of **6** (7 and 7′), would be addressed expediently by simply beginning the synthesis with a dihydroisoindigo derivative having different substituents on the oxindole nitrogens.

This total synthesis endeavor commenced with the preparation of differentially functionalized dihydroisoindigo **8** (Scheme 2). Following a straightforward sequence, isatin (**9**) was *N*-benzylated[6] and then condensed with oxindole to provide the corresponding isoindigo. Methylation of this latter intermediate, followed by catalytic hydrogenation of the product over PtO_2 furnished **8** in 65% overall yield, and only one chromatographic purification was required in this four-step sequence.

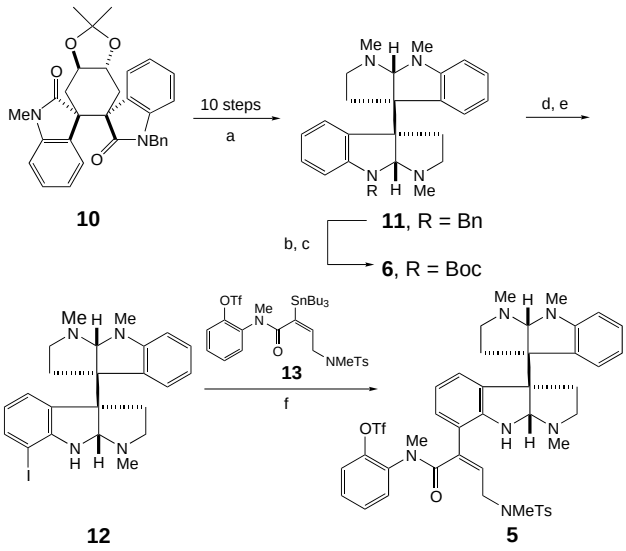
The first critical step in the synthesis was the combination of the lithium dienolate of dihydroisoindigo **8** with enantiopure ditriflate **7** (Scheme 2),[2c] a union that could produce four distinct C_1-symmetric dialkylation products. Detailed examination of this reaction revealed that solvent, temper-



Scheme 2. Reaction conditions: a) NaH, BnBr, DMF, RT; b) oxindole, AcOH, HCl, 110 °C (75%, 2 steps); c) Cs_2CO_3, MeI, DMF, RT; d) PtO_2, H_2, EtOAc, RT (87%,2 steps; e) 2 equiv LHMDS, 9:1 THF:HMPA, **7**, −40 °C (75%). DMF = dimethylformamide, HMPA = hexamethylphosphoramide, LHMDS = lithium bis(trimethylsilyl)amide, RT = room temperature.

ature, and concentration were all important factors in determining stereoselection.[7] The highest selectivity in generating the desired hexacyclic product **10** was realized by forming the lithium dienolate of **8** with LHMDS at −40 °C in a 9:1 mixture of THF/HMPA (0.05 M substrate concentration) and allowing this intermediate to react with **7** at this temperature.[8,9] These optimized conditions provided cyclohexanediol derivative **10** in 75% yield. Selective formation of **10** requires approach of the chiral dielectrophile from the *re* face of the prostereogenic dienolate, followed by cyclization of the resulting monoalkylated product without chelate organization.[2c,8]

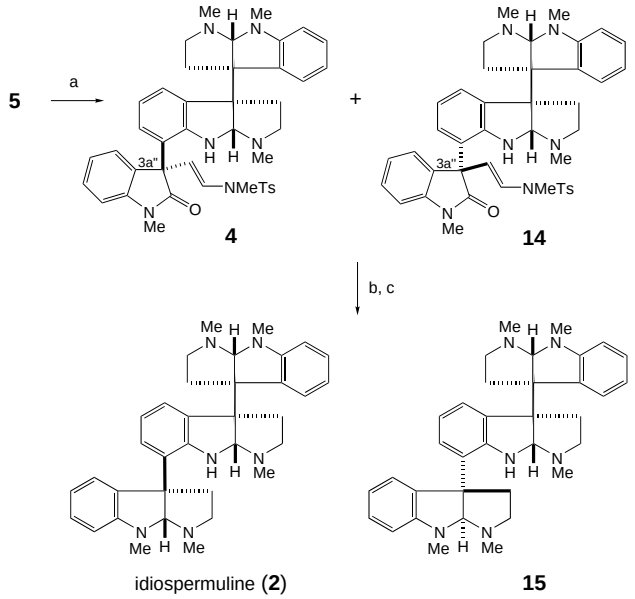
Elaboration of **10** by a ten-step sequence analogous to that developed in our earlier total syntheses of (−)- and (+)-chimonanthine[2b,c] provided enantiopure 3a,3a′-bispyrrolidinoindoline **11** in 49% overall yield (Scheme 3).[10] Removal of the benzyl group of **11** with Na/NH_3, followed by Boc



Scheme 3. Reaction conditions: a) for details of this sequence, see the Supporting Information (49% overall yield); b) Na, NH_3, THF, −78 °C (99%); c) Boc_2O, NaHMDS, THF, −78 °C (74%); d) 1) sBuLi, TMEDA, Et_2O, −78 °C; 2) diiodoethane, −78 to 0 °C (90%); e) TMSOTf, CH_2Cl_2, RT (94%); f) **13**, $Pd_2dba_3{\cdot}CHCl_3$, P(2-furyl)$_3$, CuI, NMP, RT (94%). dba = *trans*,*trans*-dibenzylideneacetone, NMP = 1-methyl-2-pyrrolidinone, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

protection of the resulting indoline, delivered **6** in 74% yield over the two steps. *ortho*-Lithiation of **6** with *s*BuLi at −78°C in pentane/TMEDA, quenching of the derived aryllithium intermediate with excess diiodoethane, and removal of the Boc group from the resulting product gave iodide derivative **12** in 85% yield.[11] The remaining carbon framework of idiospermuline was introduced by chemoselective Stille cross-coupling of **12** with the readily available stannyl butenanilide **13**[12] to furnish (*Z*)-butenanilide derivative **5** in 94% yield.[5,13]

With the Heck cyclization precursor in hand, we directed efforts toward construction of the 3a″ diaryl-substituted quaternary stereocenter. Substrate-controlled Heck cyclization of **5** using simple chelating diphosphane ligands such as bis(1,4-diphenylphosphanyl)butane (dppb) favored formation of the desired 3a″ *R* diastereomer **4**, albeit with poor selectivity (Scheme 4). Optimum stereoselection in forming **4** was realized with $Pd(OAc)_2$ as the precatalyst and (*S*)-Tol-BINAP ((*S*)-2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl) as the ligand (Table 1).[4b,14] With this catalyst, cyclization of **5** in acetonitrile at 80°C in the presence of excess 1,2,2,6,6-pentamethylpiperidine (PMP) provided epimers **4** and **14** in 97% yield and a 6:1 ratio. Identical cyclization using (*R*)-Tol-BINAP provided **4** and **14** in a 1:18 ratio, reflecting in this case a match of substrate and catalyst control.[15]



Scheme 4. Reaction conditions: a) 10 mol% $Pd(OAc)_2$, 20 mol% diphosphane ligand, PMP, MeCN, 80°C (see Table 1); b) $Pd(OH)_2$, 1500 psi H_2, 80°C, EtOH, (90%); c) 1) Red-Al, toluene, RT; 2) Na, NH_3, THF, −78°C, (a 6:1 mixture of **4** and **14** yields **2** (47%) and **15** (16%), 2 steps).

Table 1: Heck cyclizations of (*Z*)-butenanilide **5**.

Entry	Ligand	Yield [%]	**4**:**14**
1	dppb	90	2.5:1
2	*rac*-Tol-BINAP	97	1:1.8
3	(*S*)-Tol-BINAP	97	6:1
4	(*R*)-Tol-BINAP	99	1:18

The total syntheses of idiospermuline (**2**) and its 3a″,8a″ isomer **15** were completed as follows: As epimers **4** and **14** were not readily separated, the 6:1 mixture of these products produced by cyclization of **5** with the Pd/(*S*)-Tol-BINAP catalyst was advanced to the end of the synthesis where **2** and **15** could be separated readily by preparative HPLC. This conversion began with catalytic hydrogenation using palladium hydroxide on carbon at high hydrogen pressure to provide the corresponding saturated sulfonamides. The oxindole carbonyl group of these intermediates then was reduced with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene at room temperature,[16] and the resulting product was immediately exposed to excess sodium in ammonia at −78°C. After purification by preparative HPLC, idiospermuline (**2**), $[\alpha]_D = -267$ ($c = 0.85$ $CHCl_3$),[17] was isolated in 47% overall yield from the mixture of Heck products. Synthetic idiospermuline (**2**) was identical to a natural sample by comparison of ^1H NMR, ^{13}C NMR, CD, and HRMS data, as well as by HPLC coinjection.[18] An analogous sequence carried out with the 1:18 mixture of **4** and **14** generated from **5** with the Pd/(*R*)-Tol-BINAP catalyst gave 3a″,8a″-bisepiidiospermuline (**15**) in 57% yield.

The total synthesis of idiospermuline (**2**) described herein and that of hodgkinsine reported in the following communication[19] are the first total syntheses of trispyrrolidinoindoline alkaloids. Starting with isatin, idiospermuline was formed in 6% overall yield by way of 14 isolated and purified intermediates. This stereocontrolled total synthesis demonstrates for the first time the use of our dienolate dialkylation chemistry[2,8] for enantioselective preparation of unsymmetrical 3a,3a′-bispyrrolidinoindolines. It also provides another illustration of the ability of asymmetric intramolecular Heck reactions to generate compounds having congested quaternary carbon centers in high yield and the first demonstration of using such a transformation to elaborate a pyrrolidinoindoline unit at C7 of a chiral 3a,3a′-bispyrrolidinoindoline fragment.

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