Natural Products

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Total Syntheses of Complanadines A and B**

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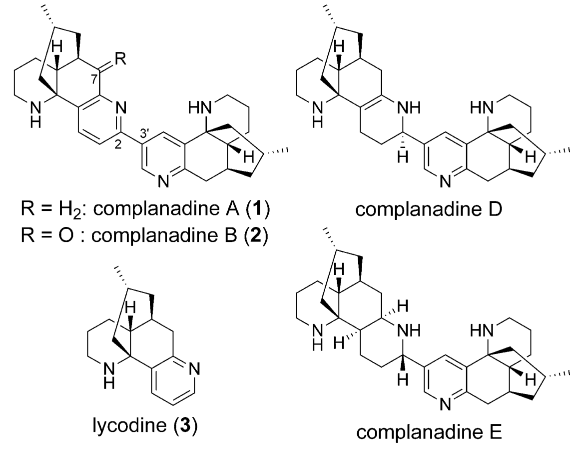
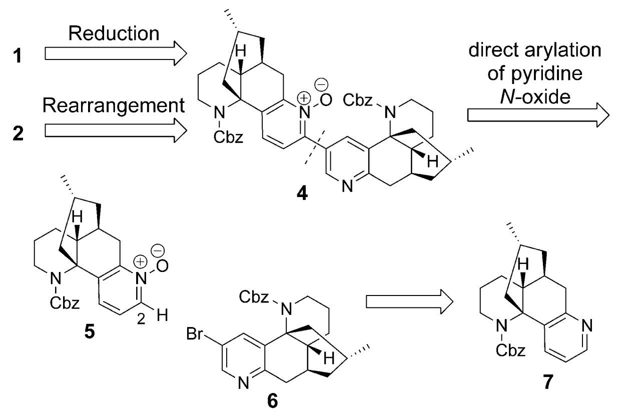
Naturally occurring dimeric alkaloids often show distinct and/or improved biological activities compared with those of their monomers. To investigate the details of their biogenesis and bioactivity, it is attractive to synthesize dimeric natural products from their monomers, in the same way as nature may do.[1,2] This approach is even more challenging when the dimer is unsymmetrical, because it requires position-controlled union of the two monomers.

Complanadines, isolated from the club moss *Lycopodium complanatum* by Kobayashi et al., are dimeric Lycopodium alkaloids (Scheme 1).[3,4] These compounds are unsymmetrical as a result of a C2–C3′ bipyridyl linkage and/or different oxidation levels of the lycodine units.[5,6] Complanadines A (**1**), B (**2**), D, and E have been reported to induce secretion of neurotrophic factors (NTFs) from 1321N1 human astrocytoma cells, thus they are lead compounds for the development of drugs for treating Alzheimer's disease.[3b–d] Because of their challenging unsymmetrical structures and intriguing biological activities, complanadines have attracted much attention from organic chemists.[2] Two groups reported a total synthesis of complanadine A in 2010.[7,8] In these pioneering studies, the 2,3′-bipyridyl framework was elegantly constructed, but there are still no reports of efficient and versatile ways of assembling unsymmetrical structures like that of complanadine B (**2**).[9] Herein, we report the total syntheses of **1** and **2** by straightforward coupling of the monomeric units, which were prepared from a single *N*-protected lycodine, and the subsequent correction of the reported specific rotation ($[\alpha]_D$) of natural complanadine A (**1**) to levorotatory.



Scheme 1. Complanadines A, B, D, and E, and lycodine.

Retrosynthetically, pyridine mono-*N*-oxide **4** could be a common intermediate for **1** and **2** (Scheme 2). Reduction of **4** would afford **1**. Regioselective benzylic oxidation using the *N*-oxide functionality would lead to ketone **2**. The mono-*N*-oxide **4** could be constructed by direct C2 arylation of pyridine *N*-oxide **5**[10,11] with 3-bromopyridine **6**. Enantiopure **5** and **6** could both be prepared by chemo- and regioselective functionalization of a single *N*-protected lycodine **7**. So far, there are no examples of the direct arylation of such a complex pyridine *N*-oxide system.[10,11] It was therefore essential to optimize the direct arylation reaction.



Scheme 2. Retrosynthesis of complanadines A and B. Cbz = benzyloxycarbonyl.

Our syntheses commenced with the preparation of **7** in enantiopure form. After a number of experiments, racemic ketone **8**[6c] was found to be readily resolved on an amylose chiral column (Daicel Chiral-Pak AS) when a mixture of

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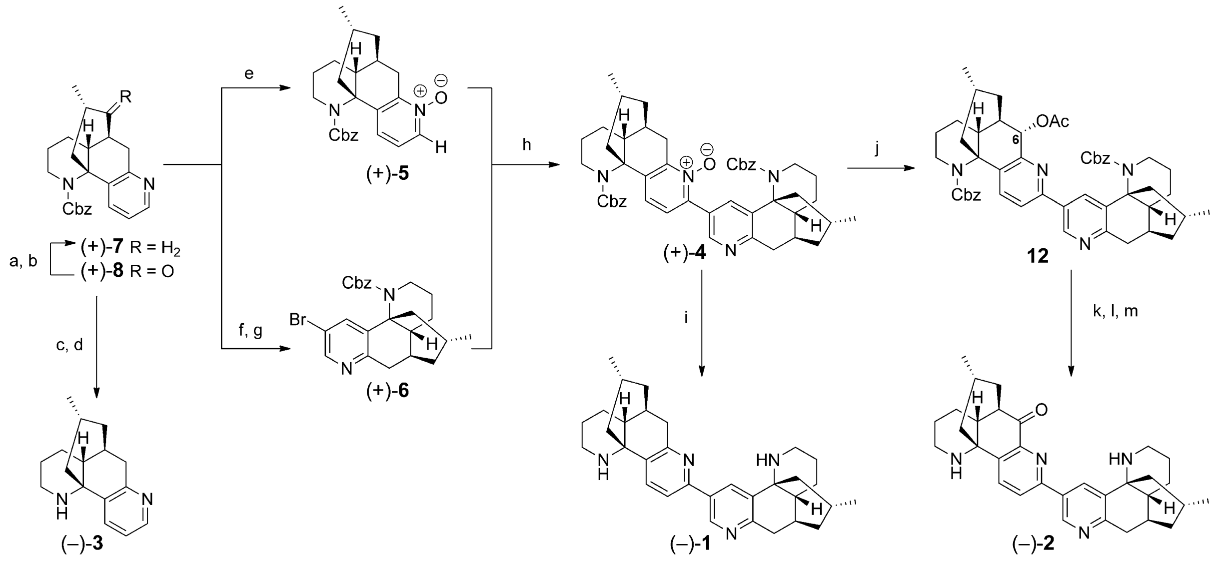


Scheme 3. Total syntheses of (−)-lycodine and (−)-complanadines A and B. Reaction conditions: a) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 88%; b) Ph_3SnH, AIBN, toluene, 110 °C, 86%; c) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; d) Raney Ni (W-2), EtOH, reflux, 70% (2 steps); e) *m*CPBA, CH_2Cl_2, 0 °C to RT, 92 %; f) [{Ir(cod)(OMe)}$_2$], *t*Budpy, [B(pin)]$_2$, THF, reflux; g) $CuBr_2$, MeOH/H_2O (1:1), reflux, 60% (2 steps); h) Pd(OAc)$_2$, *t*BuDavePhos, Cs_2CO_3, pivalic acid, mesitylene, 130 °C, 62% (see text for details and optimization of the reaction conditions); i) Pd(OH)$_2$/C, HCO_2NH_4, MeOH, 67%; j) Ac_2O, 125 °C, d.r. = 3:1; k) K_2CO_3, MeOH; l) DMP, CH_2Cl_2, 76%, (3 steps) ; m) 6 M aq. HCl, 70 °C, 78%. AIBN = 2,2′-azobisisobutylnitrile, *t*Budpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl, [B(pin)]$_2$ = bis(pinacolato)diboron, Cbz = benzyloxycarbonyl, cod = cyclooctadiene, *m*CPBA = *meta*-chloroperbenzoic acid, DMP = Dess–Martin periodinane, pin = pinacolato, THF = tetrahydrofuran.

ethanol/*n*-hexane/diethylamine (5.8%/94%/0.2%) was used as the eluent (Scheme 3), thus providing (+)- and (−)-**8** in 48% and 47% yields, respectively. Thioketalization of (+)-**8**, and subsequent treatment with Raney nickel, afforded (−)-lycodine (**3**). The ^1H and ^{13}C NMR data and specific rotation of the synthetic sample are fully consistent with those of the natural product.[5a,c]

Furthermore, the absolute configuration of (−)-**3** was unambiguously determined by X-ray crystallography of synthetic HBr salt of (−)-**3** (Figure 1). To our knowledge, the absolute configuration of natural (−)-lycodine (**3**) was directly and rigorously established for the first time.[12a,b]

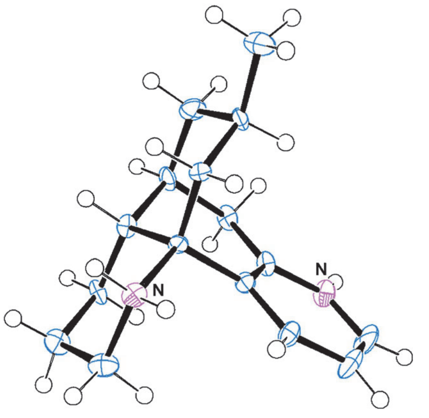
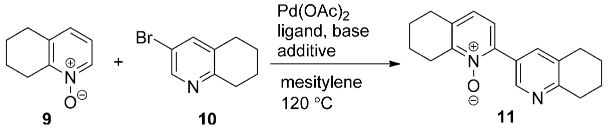


Figure 1. X-ray structure of HBr salt of (−)-**3**. Counter-anions are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.[12c]

With the enantiodefined and enantiopure (−)-**3** and (+)-**7**[13] in hand, we could synthesize (+)-*N*-Cbz-lycodine *N*′-oxide (**5**) and (+)-*N*-Cbz-bromolycodine (**6**) and investigate the assembly of the unsymmetrical dimer by a Pd-catalyzed coupling reaction (Scheme 3).[13,14] Before conducting the direct arylation of these complex molecules, we examined the reaction between model compounds **9** and **10** (Table 1). When **9** and **10** were treated with a catalytic amount of Pd(OAc)$_2$, *t*Bu$_3$P·HBF$_4$, and potassium carbonate in mesitylene at 120 °C, according to the method reported by Fagnou and co-workers,[10a,c,e] bipyridine mono-*N*-oxide **11** was formed in 33% yield (entry 1). With the sterically more-demanding phosphine ligand Cy$_3$P·HBF$_4$ a slightly higher yield was achieved (entry 2). The use of the more electron-rich and bulkier ligand, 2-di-*tert*-butyl-phosphino-2′-(*N*,*N*-

Table 1: Direct arylation of pyridine *N*-oxide **9** and bromopyridine **10**.



Entry	Ligand	Additive	Base	Yield [%][a]
1	*t*Bu$_3$P·HBF$_4$	None	K_2CO_3	33%
2	Cy$_3$P·HBF$_4$	None	K_2CO_3	37%
3	*t*BuDavePhos	None	K_2CO_3	41%
4	*t*BuDavePhos	PivOH	K_2CO_3	46%
5	*t*BuDavePhos	PivOH	Cs_2CO_3	56%

[a] Yield of the isolated product.

dimethylamino)biphenyl (*t*BuDavePhos),[15] increased the yield to 41 % (entry 3). Addition of pivalic acid (PivOH) resulted in an increased yield (46 %; entry 4).[10e,f] We found that using cesium carbonate as the base improved the yield to 56 % (entry 5).

(+)-*N*-Cbz-lycodine *N*′-oxide (**5**) was synthesized by *m*CPBA oxidation of (+)-**7**. Miyaura–Hartwig borylation[16] of (+)-**7**, which was carried out by using the procedure of Sarpong and Fischer,[7] and subsequent bromination with $CuBr_2$,[17] provided (+)-*N*-Cbz-bromolycodine (**6**) regioselectively. The optimized reaction conditions ($Pd(OAc)_2$ (20 mol %), *t*BuDavePhos (24 mol %),[15] Cs_2CO_3 (3 mol equiv) and pivalic acid (0.3 mol equiv) in mesitylene at 130 °C) were applicable the coupling of (+)-**5** and (+)-**6** to give the desired key intermediate (+)-**4** in 62 % yield.

The mono-*N*-oxide (+)-**4** was first converted into complanadine A (**1**). Reduction of the *N*-oxide and Cbz groups with ammonium formate in the presence of $Pd(OH)_2$ furnished (−)-complanadine A (**1**; Scheme 3).[13] The ^{1}H and ^{13}C NMR, and high resolution mass spectra of synthetic complanadine A were identical to those of the natural product. However, the specific rotation of the synthetic complanadine A purified by HPLC turned out to be levorotatory ($[\alpha]_{\mathrm{D}}^{25}=-16°$ ($c=0.16$, MeOH)), which was the opposite of that reported for the natural product ($[\alpha]_{\mathrm{D}}^{24}=+14°$ ($c=0.3$, MeOH))[3a,b] and those of synthetic samples reported by Siegel co-workers ($[\alpha]_{\mathrm{D}}^{24}=+14.5°$ ($c=0.3$, MeOH))[8] and by Sarpong and Fischer ($[\alpha]_{\mathrm{D}}=+22.2°$ ($c=0.85$, $CHCl_3$)).[7] We therefore re-examined the $[\alpha]_{\mathrm{D}}$ of natural complanadine A, which was gifted by Kobayashi and co-workers,[18] and found that the natural product purified by HPLC has $[\alpha]_{\mathrm{D}}^{25}=-16°$ ($c=0.04$, MeOH), which is consistent with that of our synthetic sample.[19] The reported $[\alpha]_{\mathrm{D}}$ values for complanadine A therefore need to be corrected.

The regioselective benzylic oxidation of (+)-**4** by prototropy and subsequent Claisen-type rearrangement of *O*-acetylated pyridine *N*-oxide, achieved by heating in acetic anhydride,[20] gave acetate **12** as a 3:1 epimeric mixture. Methanolysis of the acetate of **12**, subsequent oxidation using Dess–Martin periodinane,[21] and removal of the *N*-Cbz group under acidic conditions completed the first total synthesis of (−)-complanadine B (**2**). Its ^{1}H and ^{13}C NMR spectra, high resolution mass spectra, and $[\alpha]_{\mathrm{D}}^{25}$ of −28° ($c=0.11$, MeOH) are identical to those of the natural product ($[\alpha]_{\mathrm{D}}^{23}=-13°$ ($c=0.5$, MeOH).

In summary, we have accomplished the total syntheses of dimeric alkaloids complanadines A and B, the unsymmetrical motif of which was concisely constructed by Pd-catalyzed direct arylation of pyridine *N*-oxide with a bromopyridine derivative. We confirmed their absolute configurations, and, furthermore, the $[\alpha]_{\mathrm{D}}$ of complanadine A was corrected. The present synthetic strategy could be applied not only to the syntheses of other complanadine congeners that possess monomeric units with different oxidation levels, but also to the syntheses of other dimeric alkaloids. This synthesis strongly suggests an intermediacy of an mono-*N*-oxide, such as **4**, in the biosynthesis of dimeric alkaloids; this interesting finding requires further clarification. Investigation of the biological activities of the enantiomers of natural complanadines A and B will be reported in due course.

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Keywords: alkaloids · biomimetic synthesis · complanadine · direct arylation · total synthesis

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[13] We found that all N-Cbz protected lycodine derivatives synthesized from (−)-lycodine (**3**) become dextrotatory [(+)], and similarly that *N*-*N'*-bisprotection of (−)-complanadine A is likely to change the sign of specific rotation ($[\alpha]_D$) to dextrotatory (see below).

[14] As both enantiomers of lycodine are readily available, we performed the total syntheses of both enantiomers of complanadines A and B. Only the synthesis of (−)-complanadines from (−)-lycodine is described herein. Yields of each step of the synthesis of (+)-*ent*-enantiomer series are described in the Supporting Information.

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