DOI: 10.1002/ejoc.200600922

Total Synthesis of (±)-Decursivine

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Keywords: Decursivine / Diels–Alder / Indole / Total synthesis / Boron aldol

The first preparation of the antimalarial natural product decursivine is described. A Diels–Alder/Plieninger indolization protocol allows convenient preparation of the indole **15** which, in turn is a suitable substrate for a boron–enolate aldol reaction with piperonal (**16**). The resulting adduct **14** is transformed efficiently to the natural product.

Introduction

The natural product decursivine (**1**) was isolated in 2002 from *Rhaphidophora decursiva*, a plant found in the Cuc Phuong National Park in Vietnam after fractions containing it displayed activity against the malaria-causing parasite *Plasmodium falciparum*.[1] Upon isolation of decursivine, the spectroscopic data showed a remarkable resemblance to the natural product serotobenine (**2**) which was first isolated in 1985[2] and later in 1997[3] under the name moschamindole. Serotobenine, unlike decursivine, exhibits no activity against *Plasmodium falciparum*.[2] The only structural difference between decursivine and serotobenine results from the fact that the methyl group in the latter is present in a higher oxidation state as a methylenedioxy unit in the former. This minor difference would thus indicate the methylenedioxy unit is vital to the biological activity of decursivine. Both decursivine and serotobenine also likely share a common biosynthesis involving a cinnamide composed of serotonin and an appropriately substituted cinnamic acid. This is implied by the fact that moschaminindolol (**3**) and moschamine (**4**) were co-isolated with serotobenine (moschamindole). If the cinnamide (such as **4**) is derived from tryptamine rather than serotonin, the biogenetic outcome appears to be cyclization onto the indole 2-position resulting in compounds such as balasubramide (**5**) (isolated from *Clausena indica*), see Figure 1.[4]

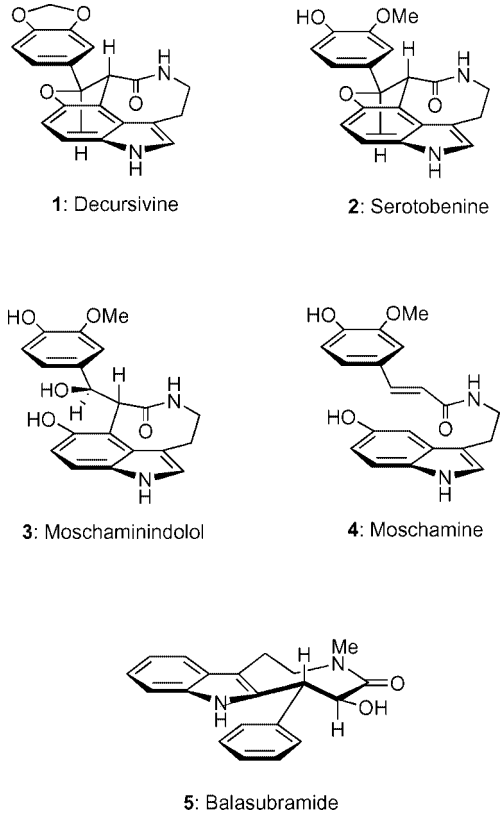

Figure 1. Decursivine and related alkaloids.

To date, there are no synthetic activities published towards decursivine or related compounds. While small by most synthetic standards, decursivine poses significant synthetic challenges, namely the functionalization of the 3-, 4-, and 5-positions of the indole, the sensitivity of the electron-rich indole to oxidation, and the stereogenic centres on the dihydrobenzofuran. Herein, we report the first synthesis of decursivine.

Our initial synthetic plan is illustrated in Scheme 1. Our final transformation was envisaged to be a simple lactamization which would require a one-carbon homologation of intermediate **6**. The addition of a methylenedioxyphenyl-derived organometallic reagent to the aldehyde **7** followed by etherification would secure **6**. A Plieninger indolization[5] involving the dihydronaphthalene **8** would in turn furnish

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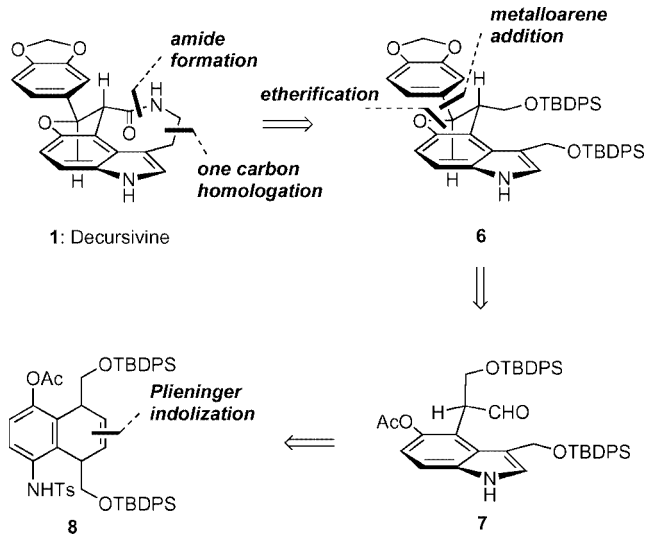
7.[6] The preparation of **8** would be accomplished by our recently described Diels–Alder reaction of a quinone monoimine with a suitable 1,3-butadiene.[7]

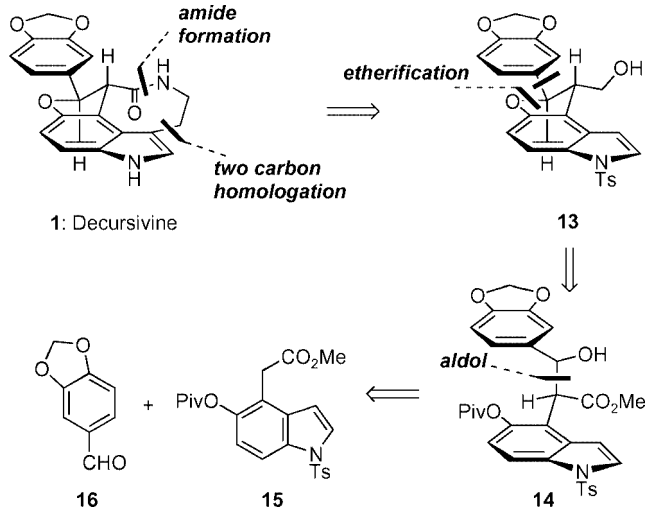


Scheme 1. Initial retrosynthesis of decursivine.

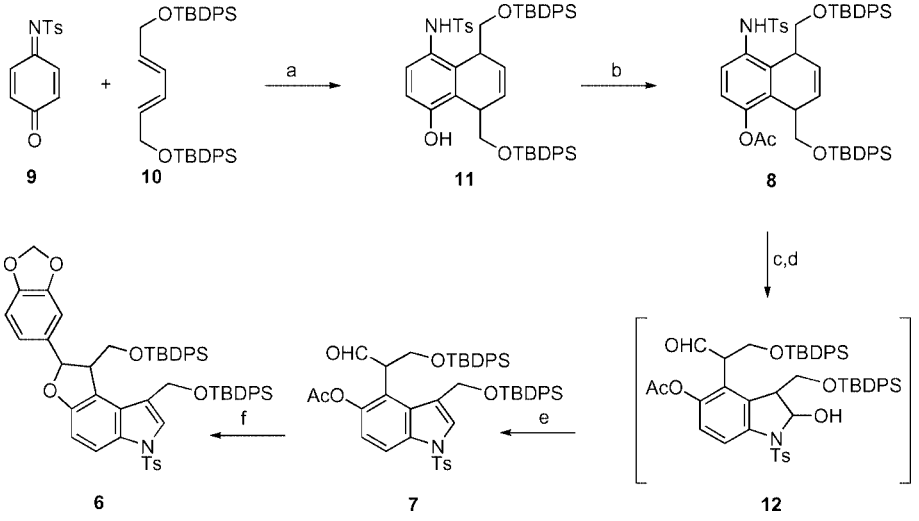
Our synthetic efforts commenced with the Diels–Alder cycloaddition of the quinone monoimine **9** with the diene **10**. The cycloaddition reaction proceeded to produce **11** in an acceptable yield of 55% under hyperbaric conditions (13 kbar). Acetylation of the phenolic hydroxy group gave **8**, which was a suitable substrate for Plieninger indolization through dihydroxylation with OsO_4 and periodate cleavage. The result was the formation of an unusually stable hemiaminal **12** which, in contrast to our normal indolization protocol, did not undergo aromatization under acidic conditions. Instead, treatment of **12** with methanesulfonyl chloride and triethylamine gave the requisite indole **7**.

We were pleasantly surprised to observe that treatment of **7** with a variety of metalloaryl species gave not the expected benzylic alcohol, but the dihydrobenzofuran **6** directly in varying yields. Conditions included the aryllithium and the chloromagnesio derivative. The best yields involved the lithio species with the addition of a stoichiometric quantity of ceric chloride.[8] The low yield was felt to be related to the undoubtedly high enolizability of **7**. The yield of **6** shown in Scheme 2 represents reactions done on a small scale (100 mg). Attempts to scale this even to 250 mg resulted in a precipitous drop in yield to about 25%. With the inability to advance sufficient synthetic material, this route was abandoned, a frustrating development considering the rapid formation of the required dihydrobenzofuran unit. From this initial study, however, our spirits were buoyed by the apparent ease of formation of the dihydrobenzofuran ring from the putative dihydroxy compound.

A second generation retrosynthesis is illustrated in Scheme 3. Again, the final step of the synthesis would be an amide bond formation. We would also require the instal-



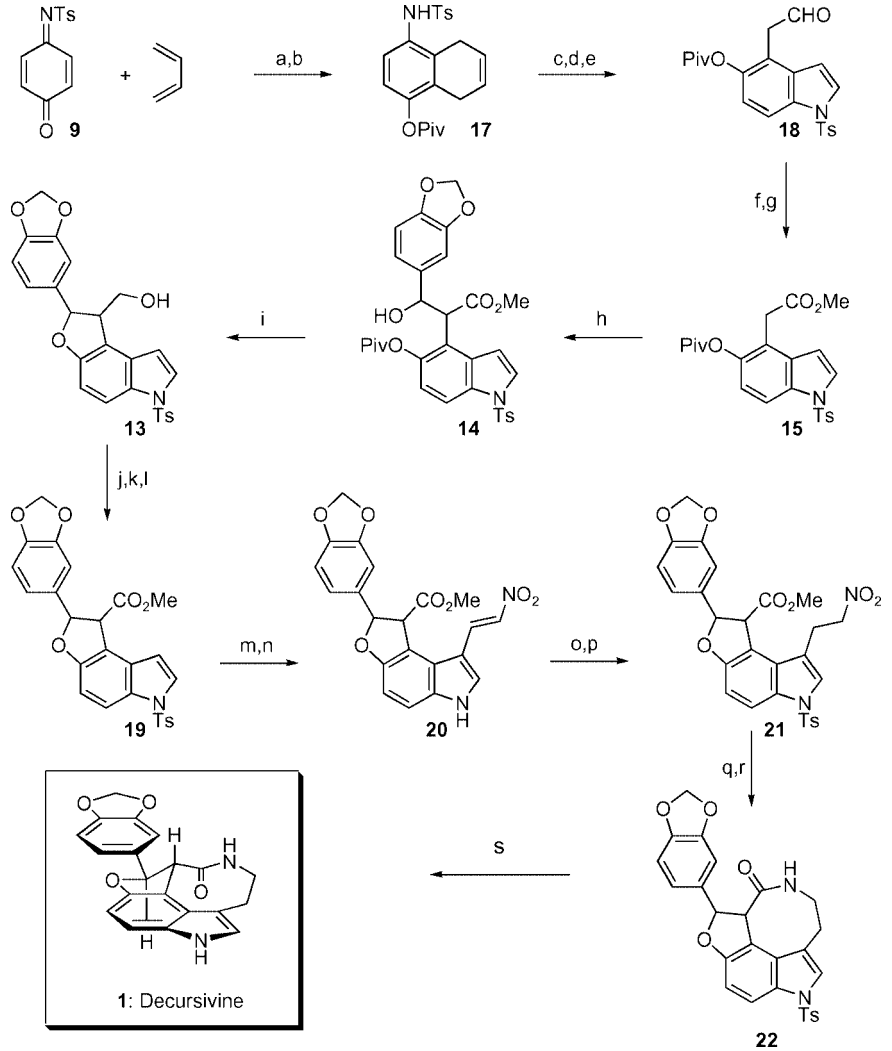
Scheme 3. Revised retrosynthesis of decursivine.



Scheme 2. Synthesis of an advanced benzofuran intermediate. a) CH_2Cl_2, 13 kbar, followed by DBU (55%); b) AcCl, Et_3N, THF (64%); c) OsO_4, NMO, THF, H_2O; d) $NaIO_4$, THF, H_2O; e) MsCl, Et_3N, THF (80%, 3 steps); f) 1-bromo-3,4-(methylenedioxy)benzene (3 equiv.), *t*BuLi (6 equiv.), $CeCl_3$ (1 equiv.), THF (40%). AcCl = acetyl chloride, MsCl = methanesulfonyl chloride.

lation of an aminoethyl appendage at the indole 3-position which would lead in a disconnective fashion to **13**. A facile etherification to the dihydrobenzofuran leads to **14** which is the aldol product of ester **15** and piperonal **16**.

Our revised synthetic strategy, illustrated in Scheme 4, began with a much simpler and more scalable Diels–Alder reaction, namely that of **9** with butadiene. Aromatization of the initially formed adduct with DBU and protection of the phenolic moiety as the pivaloyl ester gave **17** in an overall yield of 89%. Subjection of **17** to oxidative olefin cleavage and indolization yielded **18** in 84% overall yield. Oxidation[9] and treatment of the resulting carboxylic acid with $TMSCHN_2$ yielded methyl ester **15** in 90% yield over two steps. This ester was a willing participant in a boron enolate aldol reaction with piperonal **16** to produce **14** (76%).[10] We were unconcerned at this time with the relative stereochemistry of the aldol reaction since we would be relying on the enolizability of the resultant molecule (or a later stage intermediate) to ensure the required *trans* stereochemistry of the dihydrofuran. At this stage, simple deprotection of the phenol in **14** met with frustration as treatment with any acidic or basic reagent resulted in a retroaldol reaction pathway, often in near quantitative yields. Reductive removal of the pivaloate with $LiAlH_4$ or $LiBH_4$ also led to retroaldol products. Ultimately, it was determined that treatment with diisobutylaluminum hydride in large excess resulted in removal of the pivaloate, reduction of the ester (thereby avoiding retroaldol issues) and closure of the dihydrobenzofuran ring (on workup) to yield **13** in 70% yield. We were pleased to see that the propensity for formation of the dihydrofuran ring noted earlier was also the case in this synthetic sequence. With the dihydrobenzofuran intact (and retroaldols now impossible) the ester functionality was restored in a two step oxidation using the Dess–Martin



Scheme 4. Final synthetic route to decursivine a) CH_2Cl_2, sealed tube followed by DBU (95% overall); b) PivCl, THF, Et_3N (94%); c) OsO_4, NMO, THF, H_2O; d) $NaIO_4$, THF, H_2O; e) H_2SO_4, THF (84%, 3 steps); f) $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, 2-methyl-2-propene; g) $TMSCHN_2$, MeOH, benzene (90%, 2 steps); h) $(Chx)_2BI$, Et_3N, piperonal, CCl_4, CH_2Cl_2 (76%); i) DIBAL (12 equiv.), THF (70%); j) DMP, CH_2Cl_2 (83%); k) oxone, DMF; l) $TMSCHN_2$, MeOH, benzene (80%, 2 steps); m) Mg^0, NH_4Cl, MeOH, THF (83%); n) 2-(dimethylamino)-1-nitroethylene, TFA, CH_2Cl_2 (67%); o) TsCl, Et_3N, DMF (84%); p) $NaBH_4$, SiO_2, *i*PrOH, $CHCl_3$ (78%); q) Zn^0, HCl, THF; r) pyridine, microwave; s) Mg^0, NH_4Cl, MeOH, THF (43%, 3 steps). PivCl = trimethlyacetyl chloride, DMP = Dess–Martin periodinane, TFA = trifluoroacetic acid, TsCl = toluenesulfonyl chloride, $(Chx)_2BI$ = dicyclohexyl(iodo)borane.

periodinane[11] (83%) followed by oxone in DMF.[12] The resulting acid was converted into the methyl ester **19** with $TMSCHN_2$ (80% yield over two steps).

In order to functionalize the indole 3-position with the necessary aminoethyl side chain, the nucleophilicity of that position was increased by tosyl removal (83%) and treatment with 2-(dimethylamino)-1-nitroethylene to yield the nitroolefin **20** in 67% yield.[13] Retosylation followed by reduction of the styrenyl double bond[14] yielded **21** in % overall yield. The retosylation was found to be necessary in order to avoid decomposition in the ensuing transformations. Reduction of the nitro group followed by heating the resulting amino ester in pyridine under microwave irradiation produced the required lactam **22**. The natural product was then secured by removal of the tosyl group in 43% yield over three steps. The physical data for the synthetic material was identical in all respects with the published data except for optical rotation. We were pleased to find that the relative stereochemistry of the vicinal stereogenic centres were identical by comparison of coupling constants with the published data.

In summary we have succeeded in preparing for the first time the natural product decursivine in racemic form. The synthetic sequence involves 18 synthetic operations from **9** and produced the natural product in over 3% overall yield. Efforts are under way to explore the use of an asymmetric aldol for the formation of decursivine in optically pure form and to prepare other members of this fascinating class of natural products.

Supporting Information (see also the footnote on the first page of this article): Full experimental procedures and spectroscopic data for all new compounds.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada and Boehringer Ingelheim Canada for funding. We are grateful to Mr. Doug Hairsine for performing MS analyses. A.B. L. is the recipient of an NSERC CGSM postgraduate scholarship.

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Received: October 20, 2006
Published Online: November 27, 2006

