41.55, H 5.23, N 20.42; found C 41.31, H 4.70, N 20.34; FTIR (KBr): $\tilde{\nu}$ = 2564 (B-H), 1722, 1634 cm^{-1} (C=O); $\lambda_{max}(CH_3CN, \varepsilon, м^{-1}cm^{-1})$: 378 (20).

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A Concise Formal Total Synthesis of (±)-Strychnine by Using a Transannular Inverse-Electron-Demand Diels–Alder Reaction of a [3](1,3)Indolo[3](3,6)pyridazinophane**

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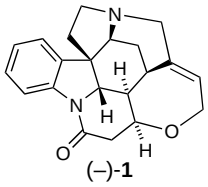
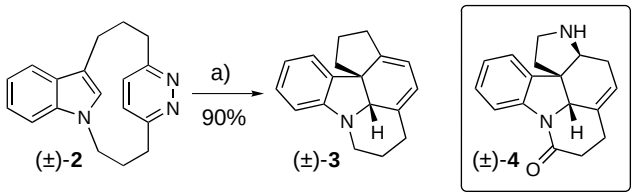
Owing to its level of complexity for its size, strychnine (**1**) presents a most formidable synthetic challenge.[1] The first total synthesis, one of the most significant achievements in the history of organic synthesis, was reported by Woodward[2] in 1954 and it wasn't until the early 1990s that a series of other successful syntheses, both racemic and enantioselective, began to appear. There are now ten reported total syntheses of strychnine[2–11] and each of them features an elegant application of one or more reactions that bring about a substantial increase in molecular complexity, for example, the Mannich reaction combined with a sigmatropic rearrangement (Overman and co-workers,[3] Kuehne et al.[4,5]), the intramolecular Diels–Alder reaction (Rawal et al.,[6] Martin and co-workers[7]), intramolecular Heck reactions (Rawal et al.,[6] Bonjoch, Bosch, and co-workers[8]), the cobalt-mediated [2+2+2] cycloaddition (Vollhardt and co-workers[9]), skeletal rearrangements (Stork,[10] and Martin and co-workers[7]) and transannular oxidative cyclization (Magnus et al.[11]). The shortest synthesis reported to date is that of Vollhardt (14 steps from propiolic acid), but the highest overall yield (10%) belongs to Rawal's synthesis.[6,12]



(–)-**1**

We recently reported the synthesis of cyclophane (±)-**2** and its efficient transannular inverse-electron-demand Diels–Alder (IEDDA) reaction to afford pentacycle (±)-**3** (Scheme 1).[13] The similarity of (±)-**3** to the key pentacyclic amine (±)-**4** (ABCEG rings of strychnine) described by Rawal[6] prompted us to attempt to apply our "cyclophane approach" to a formal total synthesis of (±)-strychnine.



(±)-**2** (±)-**3** (±)-**4**

Scheme 1. Conversion of (±)-**2** into (±)-**3**. Reagents and conditions: a) *N,N*-diethylaniline, Δ, 48 h.

The synthesis (Scheme 2) commenced with the reaction of the tryptamine **5** with 3,6-diiodopyridazine[14] to afford iodide **6** (100%). N-Allylation of the indole moiety yielded **7** (91%), which was subjected to a sequential hydroboration/intramolecular B-alkyl Suzuki-Miyaura cross-coupling reaction[15] to give cyclophane (±)-**8** (65%). The secondary amine was protected as a methyl carbamate and the resulting cyclophane (±)-**9** (96%) was heated in *N,N*-diethylaniline to induce the key transannular IEDDA reaction. Pentacycle (±)-**10**, the product of the transannular IEDDA reaction followed by the expulsion of N_2 from the initially formed adduct,[13] was obtained quantitatively. This very productive step resulted in the generation of two stereogenic centers (including the key quaternary center[1b]) with the correct relative stereochemistry[13] and the simultaneous construction of the C, E, and G rings.

Having rapidly constructed the ABCEG framework, a short series of functional group interconversions were required to prepare (±)-**4**. Reduction of (±)-**10** with $NaBH_4$/CF_3CO_2H occurred with complete chemo- and stereoselectivity to afford (±)-**11** (100%). The tertiary amine was then oxidized with PDC[16] to give the amide (±)-**12** (30%) and removal of the carbamate protecting group delivered Rawal's

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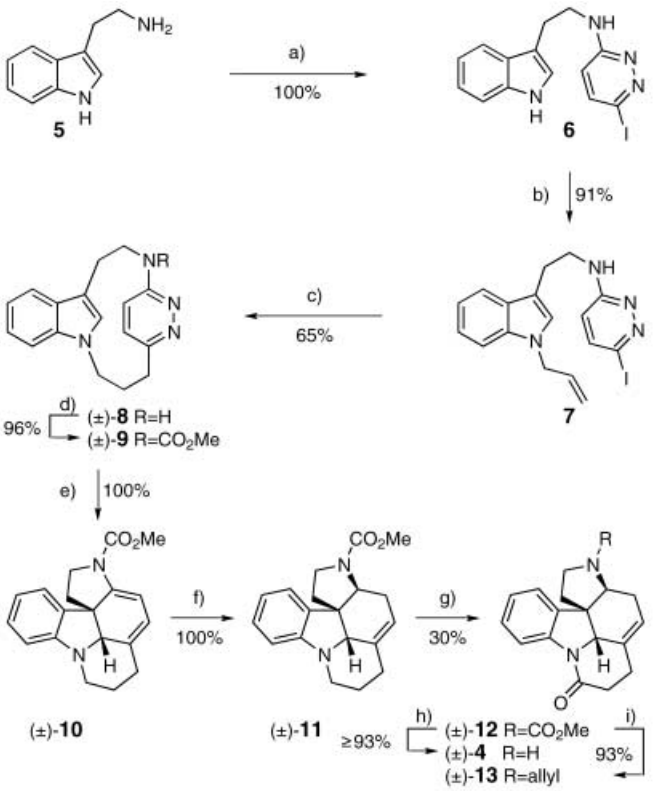
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Synthesis of Rawal's key intermediate (±)-**4**. Reagents and conditions: a) 3,6-diiodopyridazine, *sec*-butanol, Δ, 4 days; b) KOH, DMF, RT, 1 h, then allyl bromide, RT, 2 h; c) 9-BBN, THF, 0 °C→RT, 12 h, then $Pd(PPh_3)_4$, Cs_2CO_3, THF, Δ, 2 days; d) NaHMDS, THF, −78 °C, 1 h, then $ClCO_2Me$, −78 °C→RT, 3 h; e) *N,N*-diethylaniline, Δ, 1 h; f) $NaBH_4$, CF_3CO_2H, benzene, 0 °C→RT, 12 h; g) PDC, celite, CH_2Cl_2, RT, 3 d; h) TMSI, $CHCl_3$, Δ, 6 h; i) TMSI, $CHCl_3$, Δ, 6 h, then allyl bromide, Li_2CO_3, DMF, RT, 24 h. DMF = *N,N*-dimethylformamide, 9-BBN = 9-borabicyclo[3.3.1]nonane, PDC = pyridinium dichromate, TMS = trimethylsilyl.

key intermediate (±)-**4**. The crude yield of this latter reaction was typically over 100% and attempts to purify the product chromatographically led to substantial losses and little improvement in the quality of the NMR spectra. Rawal[6] also noted (in his Supporting Information) that this compound was not very stable. Consequently, he used the crude product immediately in the following step, which was the attachment of the side chain by N-alkylation of the secondary amine with an allylic bromide. Accordingly, the crude product of the reaction of (±)-**11** with TMSI was treated immediately with allyl bromide and Li_2CO_3. This reaction afforded (±)-**13** in 93% yield, which established a lower limit of 93% for the yield of (±)-**4**.

The overall yield of (±)-**4** from **5** is 15.8% over eight steps, with the majority of the losses occurring during the conversion of (±)-**11** into (±)-**12** (30% yield). All attempts to improve this yield have so far been unsuccessful, as have attempts to introduce the carbonyl group prior to the key transannular IEDDA reaction. Applying Rawal's yields[6] for the conversion of (±)-**4** into isostrychnine and Kuehne's yield[4] for the conversion of isostrychnine into strychnine, our formal overall yield of (±)-strychnine from tryptamine is 2.6% over 12 steps. Thus the synthesis described here is the shortest route to strychnine yet reported. However, the best overall yield still belongs to Rawal.[6]

Until recently, the use of cyclophanes in the synthesis of natural products was unheard of. The synthesis described above adds to the still small, but growing, number of syntheses that employ cyclophanes.[17] Future work in this area will be aimed at the modification of the existing synthesis to avoid the use of isostrychnine as an intermediate and development of an enantioselective route to strychnine.[18]

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