Natural Products

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A Short Formal Total Synthesis of Strychnine with a Samarium Diiodide Induced Cascade Reaction as the Key Step**

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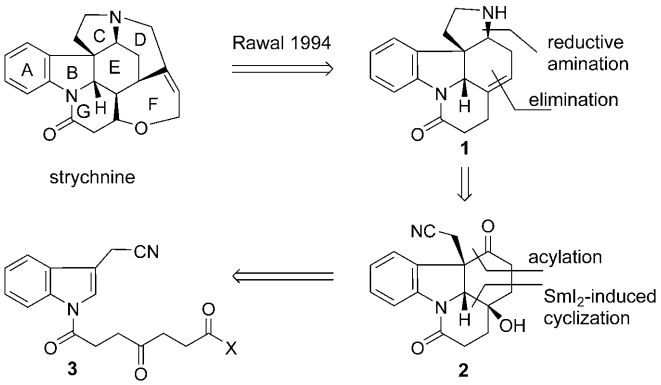
Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

The family of *Strychnos* alkaloids[1] with strychnine[2] as the most prominent example constitutes one of the most intriguing classes of natural products. Since the structure elucidation of strychnine by Robinson et al.[3] the high level of complexity of this molecule has continued to attract synthetic chemists. It possesses seven fused rings and six asymmetric centers and is hence one of the most complex natural products of this size. More than 30 years after its first total synthesis by Woodward et al.,[4] a scientific milestone in the field of organic chemistry, a number of other research groups have reported successful syntheses of the racemic[5,6] or enantiopure compound.[7] Each of the described syntheses featured novel strategies and methods designed to increase the synthetic efficacy. The shortest approach to date appears to be the formal total synthesis reported by Bodwell and Li[6] which employs an elegant transannular Diels–Alder reaction with inverse electron demand as a crucial step. Here we describe our even shorter formal total synthesis of (racemic) strychnine. The new key step is a samarium diiodide induced cascade reaction.[8] Furthermore, we correct the relative configuration of the key compound reported by Bodwell and Li.[6]

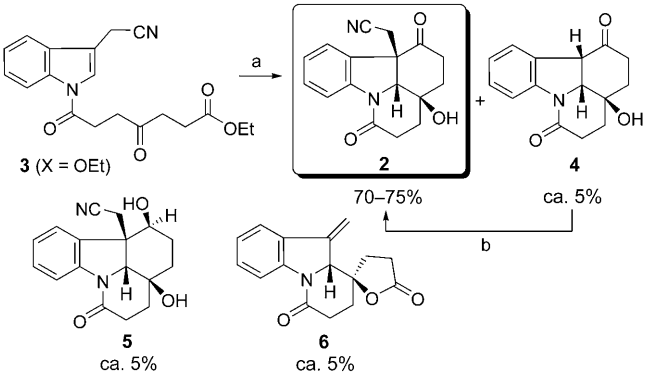
Our retrosynthetic analysis led to the pentacyclic strychnine precursor **1**, first described by Rawal in 1994,[5c] and then to the tetracyclic compound **2** (Scheme 1). We anticipated that this key intermediate should be directly available by a samarium diiodide induced cascade process starting from the simple indole derivative **3**. The ketyl cyclization of **3** should be followed by an intramolecular acylation reaction, thus forming two new rings and three stereogenic centers, including a quarternary carbon, in one step.[9] Most remarkably, precursor **3** already contains all the atoms required for the construction of the skeleton of target compound **1**.



Scheme 1. Retrosynthetic analysis of strychnine based on Rawal's key building block **1** and a samarium diiodide induced cascade reaction of precursor **3** leading to the crucial intermediate **2**.

Precursor **3** (X = OEt) was readily prepared in multigram scale by smooth acylation of commercially available 3-indolylacetonitrile with 4-oxopimelic acid monoester.[10] When **3** was subjected to 2.4 equivalents of samarium diiodide in the presence of HMPA[11] the cyclization and subsequent acylation readily occurred and the desired tetracycle **2** was isolated as the major product in diastereomerically pure form (Scheme 2). The cascade reaction apparently proceeded within seconds as indicated by the decolorization of SmI_2.

As a by-product, compound **4** was isolated in low yield; it was probably formed by the reductive fragmentation of compound **2** into an X_2SmCH_2CN species and the samarium-



Scheme 2. SmI_2-induced reaction of precursor **3** leading to the tetracyclic product **2**. Reagents and conditions: a) 2.4 equiv SmI_2, 10.0–12.0 equiv HMPA, THF, RT, 5 min; b) addition of 1.0–3.0 equiv bromoacetonitrile, 12 h. HMPA = hexamethylphosphoric acid triamide.

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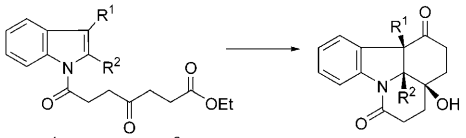
(III) enolate of **4**.[8f] Fortunately, this species could be reconverted in situ into product **2** by the addition of bromoacetonitrile to the reaction mixture, thus improving the overall yield to 75–80%. Two other products each isolated in roughly 5% yield were diol **5**, formed by the SmI_2-induced reduction of **2**, and the elimination product **6**.[12]

It should be emphasized that the intermediate organosamarium species is not stabilized by acceptor groups as in our earlier published examples,[13] and hence the efficacy of the intramolecular acylation step is without precedence. We briefly examined the scope of this new cascade process by varying the substitution pattern at the indole moiety (Table 1). When compound **7**, which strongly resembles **3**, was subjected to the standard reaction conditions tetracyclic derivative **8** was obtained in 18% yield together with spirolactone **9** (20%) and the major product pentacyclic ketal **10** (39%; Table 1, entry 1). Addition of 5.2 equiv *t*BuOH to the reaction mixture partially hampered the formation of ketal **10** and the desired product **8** was now isolated in 56% yield.[10] Similar to cyclization of **3**, traces (<5%) of dealkylated compound **4** could be isolated.

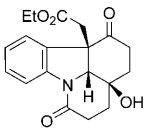
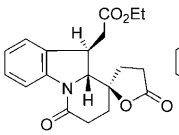
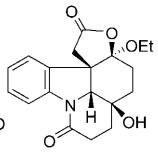
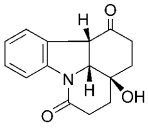
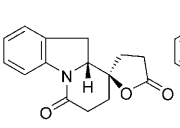
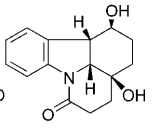
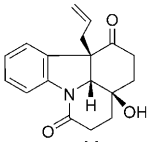
The unsubstituted indole derivative **11** (Table 1, entry 2) furnished the expected tetracycle **4** in good yield together with spirolactone **12** (19%) and traces of diol **13** (2%). By subsequent addition of allyl iodide to the reaction mixture, tetracyclic compound **4** was nearly quantitatively converted into the C-allylated product **14** under the given basic conditions (Table 1, entry 3). Overall, the examples in Table 1 show that several highly functionalized tetracyclic indole derivatives are stereoselectively available by this samarium diiodide induced ketyl–aryl coupling/acylation sequence. This new method again demonstrates the synthetic value of the addition of samarium ketyls to aromatic units—a reaction discovered by our group several years ago and successfully applied to a broad range of substrates.[13,14]

Starting from the tetracyclic intermediate **2**, all atoms required for the rapid construction of Rawal's key building block **1** were already present in the molecule. A straightforward series of functional-group conversions should lead to pentacycles similar to those described by Bodwell and Li[6] and finally result in a formal total synthesis of strychnine (Scheme 3). Raney nickel under a hydrogen atmosphere was used to reduce the nitrile moiety of intermediate **2** to the primary amine, which was instantaneously converted into the pentacyclic imine **15**; this could be isolated in nearly quantitative yield upon filtration. Treatment of **15** with either mesyl chloride[15] or methyl chloroformate under basic conditions furnished the protected enamines **16** and **17** in yields of 70% and 76%, respectively. In the mesylation reaction notable amounts of the O-mesylated compound and the desired diene **18** were isolated. The tertiary hydroxy groups of **16** and **17** were subsequently removed by elimination, either by reaction with MsCl/DBU or with the Burgess reagent, and the newly generated double bond was directed to the correct position. The reaction of **16** using the

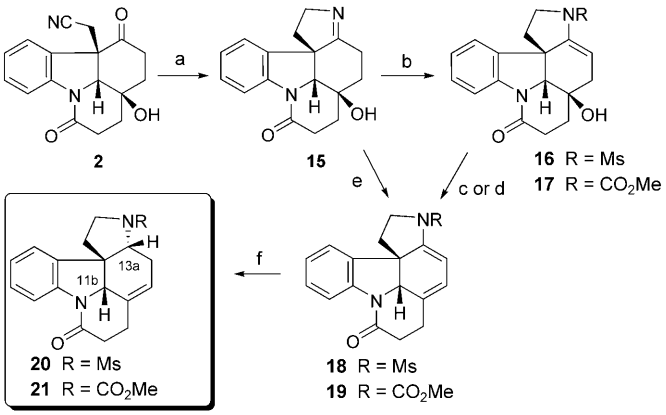
Table 1: Cascade reactions of differently substituted N-acylated indole precursors.[a,b]



7 $R^1 = CH_2CO_2Et$, $R^2 = H$
11 $R^1 = R^2 = H$

Entry	Starting material	Product		
1	**7**	 **8** (18%) 56%[c]	 **9** (20%) 16%[c]	 **10** (39%) 8%[c]
2	**11**	 **4** 57%	 **12** 19%	 **13** 2%
3[d]	**11**	 **14** 56%	**12** 20%	**13** 6%

[a] Conditions: 2.2–2.4 equiv SmI_2, 10.0–12.0 equiv HMPA, THF, RT, 2 h. [b] Yield of isolated compounds. [c] Addition of 5.2 equiv *t*BuOH. [d] After cyclization (5 min), addition of 1.8 equiv allyl iodide, 16 h.



Scheme 3. First attempts toward the synthesis of Rawal's strychnine precursor **1**. Reagents and conditions: a) Raney Ni, H_2, 1 day, MeOH, 96%; b) to **16:** MsCl, DMAP, TEA, CH_2Cl_2, 12 h (70%+8% of **18**); to **17**: $ClCO_2Me$, DMAP, TEA, CH_2Cl_2, 12 h (76%); c) Burgess reagent, toluene, 70°C, 2 h: **18**: (83%), **19**: (85%); d) MsCl/DBU protocol: 1. MsCl, DMAP, TEA, CH_2Cl_2, 12 h, 2. DBU, 24 h: **18** (90%), **19** (86%); e) one-pot procedures: to **18**: 1. MsCl, DMAP, TEA, 12 h, 2. DBU, 24 h (78%); to **19**: 1. $ClCO_2Me$, DMAP, TEA, CH_2Cl_2, 16 h, 2. MsCl, DMAP, TEA, 16 h, 3. DBU, 24 h (66%); f) $NaCNBH_3$, MeOH CH_2Cl_2 (pH ≈ 1, by addition of sat. methanolic HCl), 4 h: **20** (40%+25% **18**), **21** (78%+10% **19**). MsCl = mesyl chloride, DMAP = *N*,*N*-dimethyl-4-aminopyridine, TEA = triethylamine, Burgess reagent = methyl *N*-(triethylammoniumsulfonyl)carbamate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

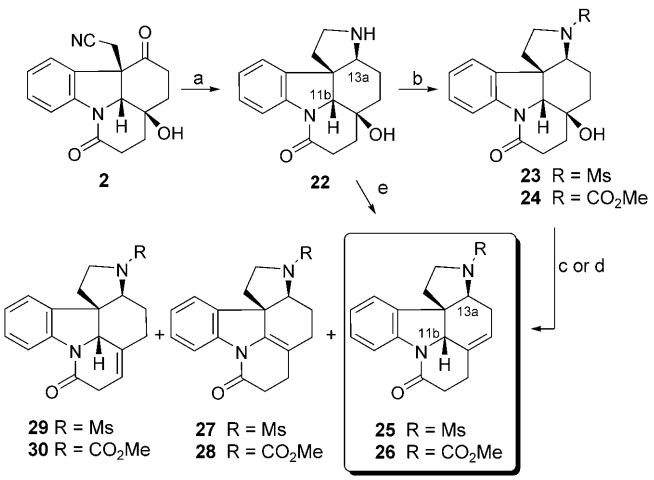
MsCl/DBU protocol proceeded in 90% yield, whereas the Burgess reagent led to 83% yield. Analogously, carbamate **19** was prepared by application of either the MsCl/DBU protocol or the Burgess reagent in good yield. Dienes **18** and **19** were also synthesized in comparable yield by employing one-pot procedures starting from imine **15** by subsequent addition of the required reagents. In the next step, the activated enamine double bond was reduced regio- and stereoselectively under acidic conditions with sodium cyanoborohydride furnishing the mesyl-protected pentacyclic amine **20** in only 40% yield, but the carbamate **21** was isolated in 78% yield.

The ^{1}H NMR and ^{13}C NMR data of our compound **21** were identical with those reported by Bodwell and Li.[6] Remarkably, NOE experiments of both **20** and **21** revealed that the bridgehead protons (11b-H and 13a-H) are *cis* positioned as depicted in Scheme 3.[16] This configuration, which would be wrong for the synthesis of strychnine, can be rationalized by considering the fairly flat geometry of dienamines **18** and **19** and the resulting iminium species. An attack of the hydride source occurs more likely from the less hindered convex top face, rather than from the more shielded bottom side.[17] With these results we had unexpectedly demonstrated that the sequence as described by Bodwell and Li leads to the wrong configuration at C-13a, and hence our first approach to key intermediate **1** had also failed.

In a second attempt we therefore decided to reduce the tetracyclic building block **2** with Raney nickel to approach pentacycle **22** directly by in situ formation of imine **15** and its subsequent reduction (Scheme 4).[17] Gratifyingly, we isolated pentacyclic amine **22** as a single diastereomer, now bearing the correct configuration at C-13a, in almost quantitative yield. Presumably, owing to the steric hindrance because of the tertiary hydroxy group, the attack of the reducing agent occurs exclusively from the bottom face of the molecule.[17a] Without further purification secondary amine **22** was either mesylated or acylated yielding **23** or **24** in good to very good yields. NOE and NOESY experiments on amine **22** and protected amines **23** and **24** indicated that the bridgehead protons 11b-H and 13a-H are now *trans* positioned as required.[16]

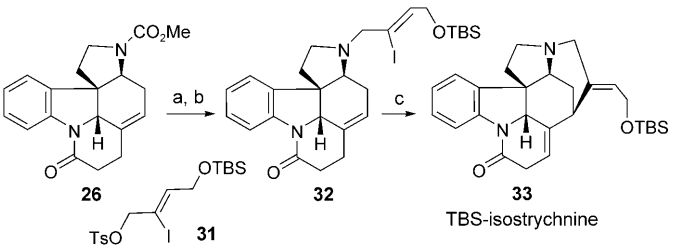
Subsequently, we attempted the regioselective conversion of the tertiary alcohols **23** and **24** into the desired alkenes **25** and **26**. In first attempts for elimination we employed the Burgess reagent which, unfortunately, furnished for both series mixtures of the three possible alkenes (roughly 2:1:1, compounds **25** to **30**) as depicted in Scheme 4. Fortunately, treatment of either **23** or **24** with MsCl/DBU at room temperature afforded the desired key building blocks **25** and **26** as the major products in good selectivity (5:1:1 ratio), which could easily be isolated by column chromatography. We also developed one-pot procedures for compounds **25** and **26** starting from amine **22**. However, as a result of longer reaction times and partial decomposition, the overall yields of **25** and **26** were lower than those achieved in the two-step protocol. 2D NMR experiments (COSY, HMQC, NOESY) on compounds **25** and **26** clearly indicated the correct relative configuration as depicted in Scheme 4.[16]

We then converted carbamate **26** by TMSI-induced deprotection into the pentacyclic amine **1**.[18] Subsequent



Scheme 4. Synthesis of protected strychnine precursors **25** and **26**. Reagents and conditions: a) Raney Ni, H_2, 3 d, MeOH, 97%; b) to **23**: MsCl, DMAP, TEA, CH_2Cl_2, 2 h (92%); to **24**: $ClCO_2Me$, DMAP, TEA, CH_2Cl_2, 4 h (87%); c) to **25**, **27**, **29**: Burgess reagent, toluene, 70°C, 2 h (ratio ≈ 2:1:1: Σ = 77%); d) 1. MsCl, DMAP, TEA, 16 h, 2. DBU, 24 h: to **25**, **27**, **29**: (ratio ≈ 5:1:1, Σ = 89%), to **26**, **28**, **30**: (ratio ≈ 5:1:1, Σ = 88%); e) one-pot procedure to **25**, **27**, **29**: 1. MsCl, DMAP, TEA, CH_2Cl_2, 24 h, 2. DBU, 24 h (ratio ≈ 5:1:1, Σ = 70%); to **26**, **28**, **30**: 1. $ClCO_2Me$, DMAP, TEA, CH_2Cl_2, 4 h, 2. MsCl, DMAP, TEA, CH_2Cl_2, 12 h, 3. DBU, 24 h (ratio ≈ 5:1:1, Σ = 62%).

alkylation of this secondary amine with tosylate **31**[5c,10] furnished the known strychnine precursor **32** in similar yield to that reported by Rawal[5c] (Scheme 5). Finally, we subjected



Scheme 5. Synthesis of TBS-protected isostrychnine **33**. Reagents and conditions: a) 1. TMSI, $CHCl_3$, 60°C, 2 h, 2. MeOH, 60°C, 1 h; b) 1.2 equiv **31**, K_2CO_3, nBu_4NI, CH_3CN (65% for two steps); c) Pd-$(OAc)_2$, K_2CO_3, nBu_4NCl, DMF, 70°C, 3 h (68%). TMSI = iodotrimethylsilane.

compound **32** to the published Heck reaction which gave the hexacyclic TBS-protected isostrychnine **33** in 68% yield. The NMR data for compounds **32** and **33** are in complete agreement with the previously published data and allowed further unambiguous proof of our configurational assignments.

In conclusion, with this formal total synthesis of strychnine we could demonstrate the power of SmI_2-induced cascade reactions. Starting from simple indole precursors, the novel process allowed the generation of two new rings and three stereogenic centers, including a quaternary carbon atom, in one step. Moreover, the key building block **26** was obtained from commercially available indolylacetonitrile in

just five steps in an overall yield of 33% (the abbreviated four-step protocol provided 27% yield). Further transformations of compound **26** into Rawal's key building block **1** completed the formal total synthesis establishing the shortest route yet reported towards (±)-strychnine. We want to emphasize that only one protective group was necessary in the reaction sequence highlighting the efficacy of this approach. In the course of our studies we could correctly assign the configuration of the pentacyclic amine **21**, which was reported earlier by Bodwell and Li and incorrectly assigned to structure **26**. Hence we show that this previous approach does not constitute a formal total synthesis of strychnine.[6] In the future we will try to generalize our concept for the preparation of natural products and their analogues, and we will also search for enantioselective versions of the crucial cascade step.

Experimental Section

Typical procedure for the SmI_2-induced reaction of indole derivative **3**: Indole derivative **3** (680 mg, 2.00 mmol, 1.0 equiv) was dissolved in THF (20 mL), and argon was bubbled through the solution for 10–20 min. The resulting solution was rapidly added in one portion to a vigorously stirred solution of SmI_2 (4.80 mmol, 2.4 equiv in 48.0 mL THF) and HMPA (4.00 mL, 22.3 mmol, 11.2 equiv). After the solution color had turned brownish yellow, bromoacetonitrile (300 mg, 2.50 mmol, 1.25 equiv) was added. The reaction mixture was stirred for 16 h and quenched with aq. sat. $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted three times with diethyl ether. The combined ether extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The obtained residue was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1, 1:3, ethyl acetate) affording compound **2** (460 mg 77%), diol **5** (30 mg, 6%), and spirocycle **6** (25 mg, 4%) as colorless solids.

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[13] For the intramolecular addition of samarium ketyls to indole and pyrrole moieties, see: a) S. Gross, H.-U. Reissig, *Org. Lett.* **2003**, *5*, 4305–4307; b) C. Beemelmanns, V. Blot, S. Gross, D. Lentz, H.-U. Reissig, *Eur. J. Org. Chem.* **2010**, 2716–2732; also see Ref. [12].

[14] For selected publications on the intramolecular additions of samarium ketyls to aryl groups, see: a) C. U. Dinesh, H.-U. Reissig, *Angew. Chem.* **1999**, *111*, 874–876; *Angew. Chem. Int. Ed.* **1999**, *38*, 789–791; b) F. Aulenta, M. Berndt, I. Brüdgam, H. Hartl, S. Sörgel, H.-U. Reissig, *Chem. Eur. J.* **2007**, *13*, 6047–6062; c) U. K. Wefelscheid, M. Berndt, H.-U. Reissig, *Eur. J. Org. Chem.* **2008**, 3635–3646, and cited therein.

[15] In initial experiments imine **15** was converted into mesylate **16** with the intent to develop a one-pot elimination to give diene **18**.

The mesyl compounds proved to be very helpful in the determination of the relative configurations, since in the NMR spectra the signals of rotamers (visible in the spectra of the related carbamates) were not evident. In this way the ^{1}H and ^{13}C NMR spectra could be assigned unambiguously.

[16] For copies of ^{1}H and ^{13}C NMR spectra and descriptions of NOE and NOESY experiments, see the Supporting Information.

[17] For similar results for the stereoselective reduction of imines in tri- and tetracyclic indole derivatives, see a) A. Azzouzi, B. Perrin, M.-E. Sinibaldi, J.-C. Gramain, C. Lavaud, *Tetrahedron Lett.* **1993**, *34*, 5451 – 5454; b) G. A. Kraus, D. Bougie, *Tetrahedron* **1994**, *50*, 2681 – 2690; c) O. Callaghan, C. Lampard, A. R. Kennedy, J. A. Murphy, *J. Chem. Soc. Perkin Trans. 1* **1999**, 995 – 1001.

[18] Removal of the mesyl protecting group of compound **25** was not possible; even treatment of **28** with SmI_2 did not show significant conversion to **1**.

