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Special Issue

Account

Synthesis of Bis-*Strychnos* Alkaloids (–)-Sungucine, (–)-Isosungucine, and (–)-Strychnogucine B from (–)-Strychnine

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It was developed a concise synthetic route resulting in the first syntheses of bis-*Strychnos* alkaloids (–)-sungucine, (–)-isosungucine, and (–)-strychnogucine B from commercially available (–)-strychnine. Employing a highly convergent synthetic strategy, it was demonstrated that both *Strychnos* monomers could be efficiently prepared from commercially available (–)-strychnine. The venerable Mannich reaction was enlisted to join the two *Strychnos* monomers in a biomimetic fashion. Subsequent epimerization and olefin isomerization yielded (–)-strychnogucine B. Functional group manipulation transformed (–)-strychnogucine B into (–)-sungucine and (–)-isosungucine. Computational chemistry was employed to rationalize the regiochemical course of key steps *en route* to the bis-*Strychnos* targets.

Keywords: bis-*Strychnos* alkaloids, biomimetic synthesis, sungucine, Mannich

1. Introduction

Since the first isolation of the infamous indole alkaloid strychnine from the African plant *Strychnos icaja* by Sandberg *et al.*,[1] many other mono- and dimeric indole alkaloids have been isolated from the roots of this African *Strychnos* species.[2-6] Among them, the unsymmetric dimeric *Strychnos* alkaloids (–)-sungucine (**1**),[3,4] (–)-isosungucine (**2**),[4] and (–)-strychnogucine B (**3**)[5] captured our attention owing to their potential anticancer and antiplasmodial activities[4-9] in addition to structural complexity (Figure 1).

As part of our research program aimed at developing and applying novel synthetic methods for efficiently accessing complex indole alkaloids over the past decade,[10-20] we recently communicated the first enantiospecific syntheses of bis-*Strychnos* alkaloids **1**-**3**.[21] Herein, we provide a full account of our synthetic efforts, from failure to success, employed in the preparation of these unique natural products.

2. Results and Discussion

2.1. Synthetic strategy and retrosynthetic analysis

We proposed a semi-synthetic route to these bis-*Strychnos* alkaloids beginning with natural (–)-strychnine (**4**), which was purchased from Sigma-Aldrich for approximately $2 *per* gram. Our rationale for this, as opposed to a fully synthetic route, included the following reasons. First, it was reported that isostrychnine and strychnine were isolated from *S. icaja* along with **1**-**3**.[4,5] Moreover, it is reasonable to hypothesize strychnine is involved in the biosynthesis of these bis-*Strychnos* congeners due to structural similarity, particularly strychnogucine B whose Southern monomer is a C5-α-substituted strychnine unit! Third, strychnine is commercially available, inexpensive, and would greatly expedite any preparation of **1**-**3** since it represents an advanced intermediate. Finally, a semi-synthetic approach from (–)-**4** would guarantee an enantiospecific preparation of the targets, which is a prerequisite for biological evaluation.

The retrosynthetic analysis of **1**-**3** is shown in Scheme 1. We envisioned (–)-sungucine (**1**) and (–)-isosungucine (**2**) could be synthesized from (–)-strychnogucine B (**3**) via base-mediated ring-opening and deoxygenation at the C18 and C18' positions. For the retrosynthesis of (–)-**3**, we disconnected at the C23–C5' bond, which could arise from the late-stage biomimetic coupling of a Northern C23-anionic synthon with a Southern C5'-cationic synthon. Both synthons would ultimately be prepared from the putative biosynthetic precursor, (–)-strychnine (**4**).

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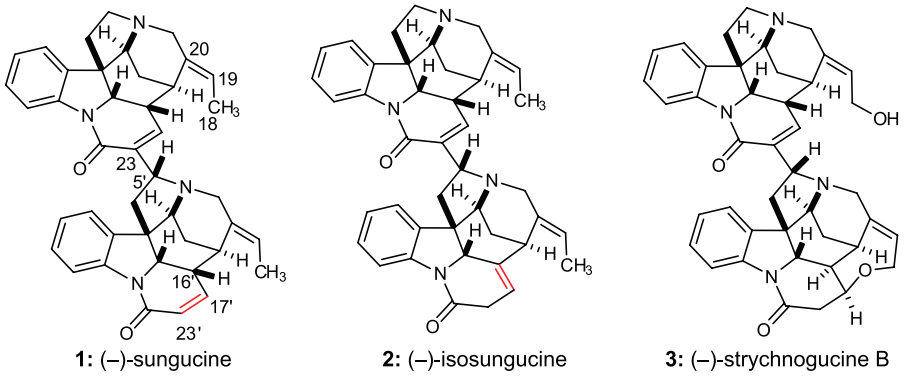
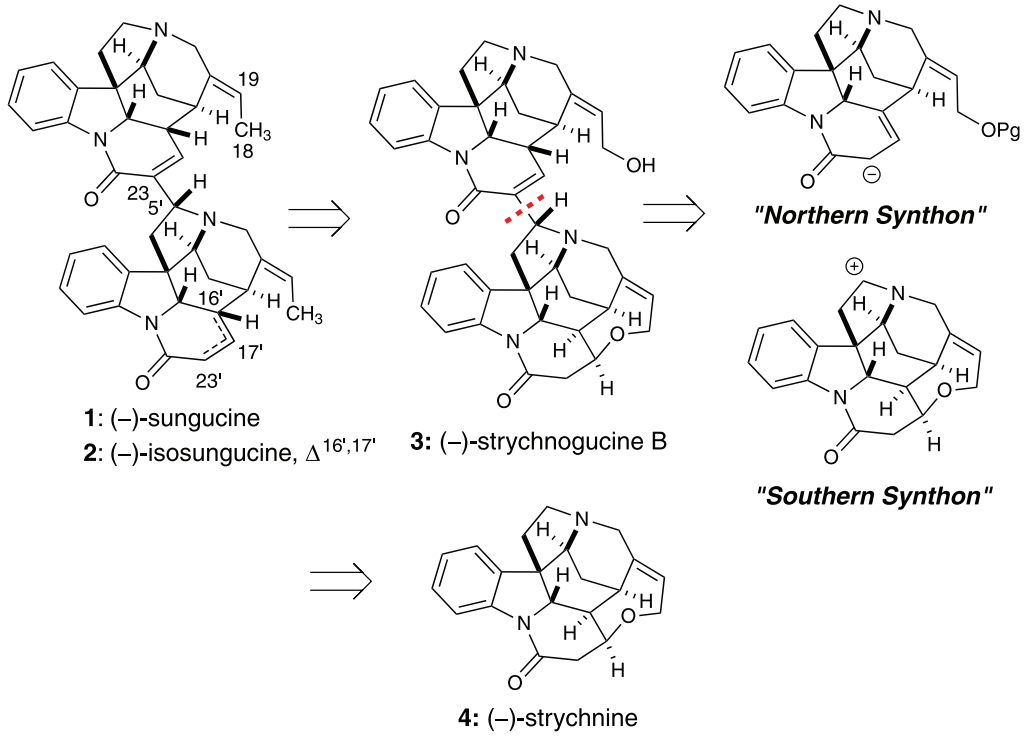


Figure 1. Structures of bis-*Strychnos* alkaloids (–)-sungucine (**1**), (–)-isosungucine (**2**), and (–)-strychnogucine B (**3**).



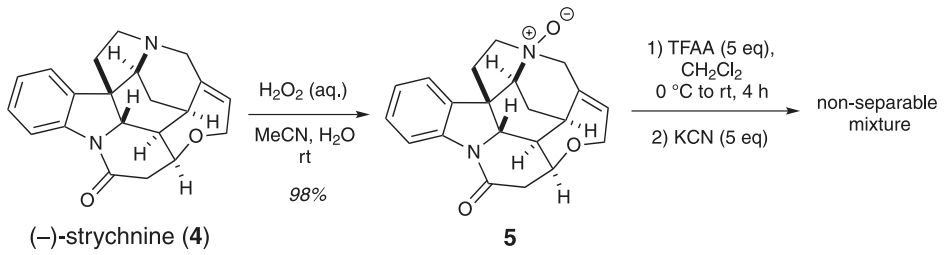
Scheme 1. Retrosynthetic analysis of (–)-**1**, (–)-**2** and (–)-**3** ultimately arriving at biosynthetic precursor (–)-strychnine (**4**).

2.2. Synthesis of the Southern fragment

For the synthesis of the Southern fragment, the main challenge to be addressed was the regioselective synthesis of the desired iminium ion from (–)-**4**. Even though the direct oxidation of amines to iminium ions seems attractive, most of the reported amine oxidation methods suffer from limited substrate scope, low functional group compatibility, high cost and toxicity.[22-24] On the other hand, the Polonovski-Potier reaction is a well-established method for the preparation of iminium ions via the activation of tertiary amine *N*-oxides with trifluoroacetic anhydride (TFAA).[25,26] Furthermore, the *in situ*-formed iminium ions are often trapped with cyanide to access the corresponding α-amino nitriles, which can be isolated and characterized. Subjection of these α-amino nitriles to Lewis or Brønsted acids regenerates the iminium ions, which can subsequently engage in reactions with suitable nucleophiles. Excellent examples include Husson and co-workers'[27-30] application of 2-cyano-Δ^3-piperidines in the synthesis of the corynanthe-type indole alkaloids and Lounasmaa's[31] synthesis of the indoloquinolizidine-type indole alkaloids.

To apply the Polonovski-Potier reaction in the synthesis of the Southern fragment, strychnine *N*-oxide (**5**) was first prepared from the hydrogen peroxide-mediated oxidation of (–)-strychnine (**4**). However, subjection of **5** to TFAA followed by trapping with KCN led to an intractable mixture of α-amino nitriles regioisomers (Scheme 2).

Activation of the mixture with Lewis acids (e.g., $AgBF_4$,[27,28,30,32,33] BF_3•OEt_2,[31,34] and $TiCl_4$)[35] or Brønsted acid

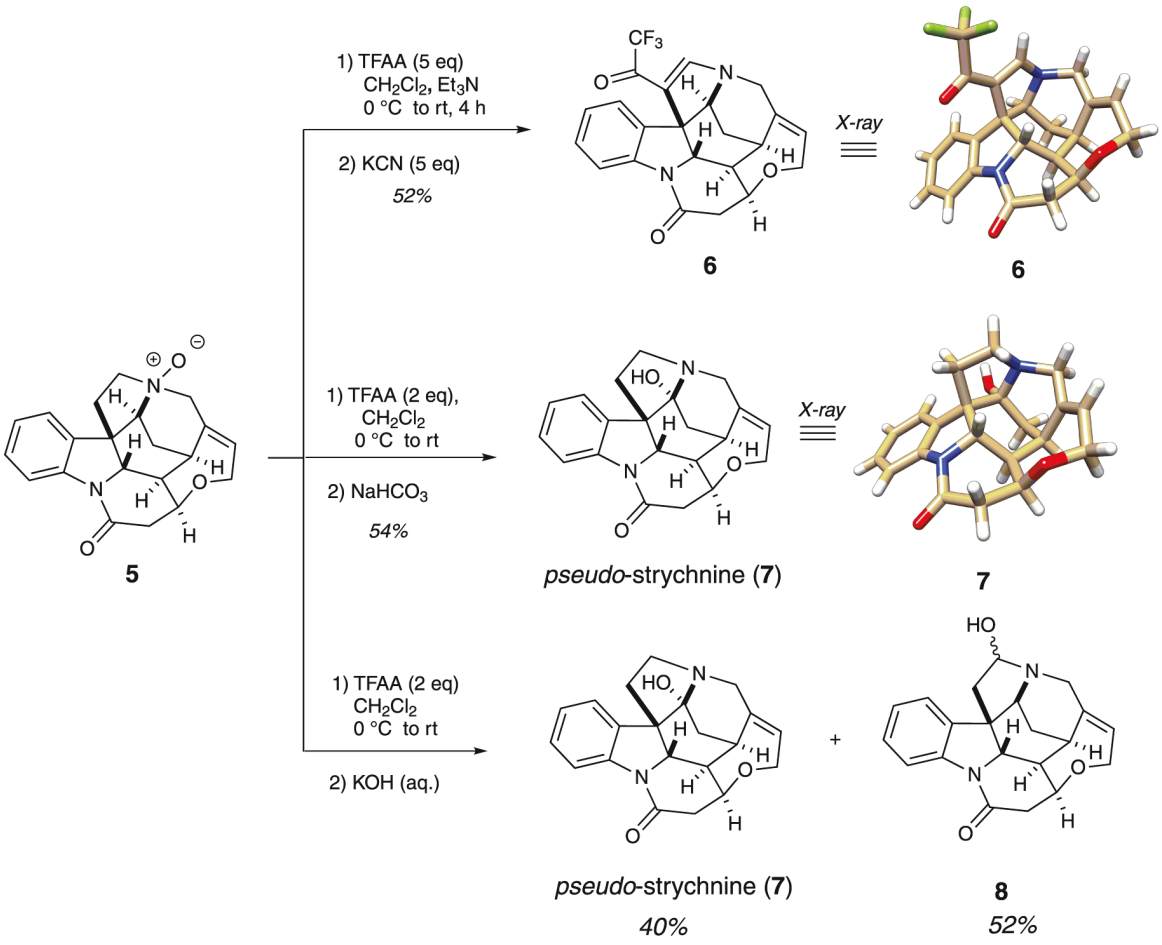


Scheme 2. The Polonovski-Potier reaction of *N*-oxide (**5**) and trapping with KCN.

(i.e., HCl),[36] followed by addition of various nucleophiles (e.g., Grignard reagents, silyl enol ethers, ketone enolates and amide enolates) yielded no coupling product. Likewise, all the efforts to directly apply the mixture as the Southern fragment for the next coupling step with various nucleophiles generated no satisfactory result.

While exploring the regioselectivity of the Polonovski-Potier reaction, we carried out the reaction in the presence of Et_3N. However, this led to the formation of the vinylogous trifluoromethyl amide **6**,[37,38] the structure of which was confirmed by single crystal X-ray analysis (Scheme 3). The formation of **6** presumably arises via a stepwise process including (*i*) regioselective C5–N_4 iminium formation; (*ii*) base-promoted imine-enamine tautomerism; (*iii*) nucleophilic attack of TFAA; and finally, (*iv*) elimination to furnish vinylogous trifluoroacetamide **6**.

At this juncture, we were aware that the iminium salt generated from the Polonovski-Potier reaction of **5** with TFAA might be stable enough to be isolated without being trapped with KCN. By following Lounasmaa and Hanhinen[31] procedure, the Polonovski-Potier reaction was carried out with $NaHCO_3$ workup. The crude product was then subjected to flash column chromatography on basic Al_2O_3 with EtOAc and hexanes as mobile phase solvents. The only isolated product from the reaction mixture was



Scheme 3. The fate of the Polonovski-Potier reaction of *N*-oxide (**5**) depending on the base employed.

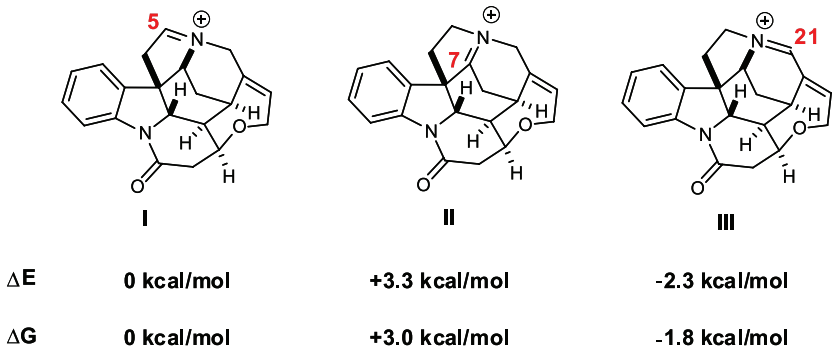


Figure 2. Relative DFT energies for iminium ions **I**-**III**.

pseudo-strychnine (**7**) whose structure was confirmed by single crystal X-ray analysis (Scheme 3).

Interestingly, when the Polonovski-Potier reaction of **5** was followed by addition of an aqueous solution of KOH, a more basic and nucleophilic base, the desired carbinolamine **8** was isolated in 52% yield as a mixture of two epimers at C5, together with regioisomeric *pseudo*-strychnine (**7**) in 40% yield (Scheme 3).

To rationalize the regiochemical course of the Polonovski-Potier reaction, density functional theory (DFT) analysis (mPW1PW91/cc-pvdz) was employed to determine relative free energies of the three iminium cations that may form upon trifluoroacetate elimination (Figure 2). It seems that the comparison of the relative calculated energies **I**-**III** cannot account for all the experimental results. For example, the carbinolamine derived from the lowest-energy iminium **III** was not obtained. However, the carbinolamine **7** derived from the highest-energy iminium **II** was isolated in 40% yield, as shown in Scheme 3. Other factors are believed to be at play to dictate the formation of the iminium ions. We then conducted further DFT analysis to determine the minimized structure of parent *N*-acyloxyammonium ion **IV**.[21] Based on the minimized structure of **IV**, C5–H_b bond and N4–O_{acyl} bond are closest to be *anti*-coplanar (i.e., H_b–C5–N_4–O dihedral = 148.3°), the prerequisite for the E2 reaction pathway. Thus, the formation of **8** may result from the elimination of **IV** to **I** via an E2-like mechanism.[21]

A natural population analysis (NPA)[39] of **IV** suggests that since the C7–H has the more positive charge (+0.30252) than those on C5 and C21, and it is *syn*-coplanar to the N–O_{acyl} bond, the iminium ion **II** is likely to be formed via the elimination of C7–H through an E1-like or E1cb-like transition state by means of the paired TFA (Figure 3).[40,41] Another possibility is that the formation of **II** could be from the intramolecular deprotonation of C7–H by the pendant *N*-trifluoroacetyl moiety.[21]

To explore the mechanistic differences between the classic Polonovski reaction and the more active

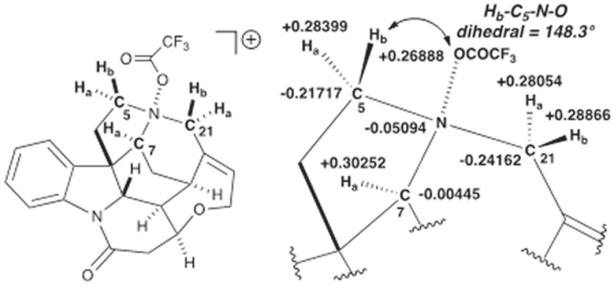


Figure 3. Natural population analysis of **IV**.

Potier variant, we also conducted experimental studies to investigate the effect of both acylating agent and temperature on the regioselective functionalization of strychnine *N*-oxide.[41] As shown in Table 1, the reactions with TFAA (entries 1-3) were less sensitive than the ones with Ac_2O (entries 4-6) in terms of both percent conversion and ratios of **8** to **7**. These results can be attributed to the high nucleofugacity of trifluoacetate.[41] The highest ratio of **8** to **7** was obtained at 35 °C for 4 h when Ac_2O was used as acylating reagent (entry 6). These results are in line with an E2 mechanism, whereby the more basic acetate favors the formation of the desired carbinolamine **8** via the removal of the *anti*-periplanar C5–H_b from an *N*-acyloxyammonium strychnine intermediate.

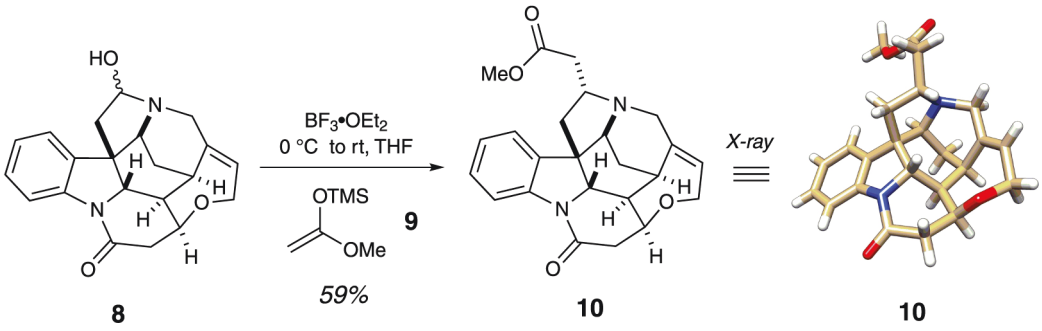
With the desired carbinolamine **8** in hand, we were able to test the feasibility of the Mannich coupling reaction.[42] Treatment of **8** with BF_3•OEt_2[43] followed by addition of silyl ketene acetal **9**[44] produced the ester **10** in 59% yield (Scheme 4). Single crystal X-ray analysis of **10** confirmed the stereochemical course of the Mukaiyama-Mannich reaction and the regioselectivity of the Polonovski-Potier reaction of **5**.

Later, when we tried to get a better chromatographic separation of **8** from **7**, the crude reaction mixture from the sequential Polonovski-Potier reaction and KOH trapping was loaded on a neutral Al_2O_3 column for the column chromatography purification. Carbinolamine **7** was quickly eluted off the column with 50% acetone in ethyl acetate. However, **8** remained on the column even when eluted

Table 1. Effect of acylating agent and temperature on the formation of **7** and **8**

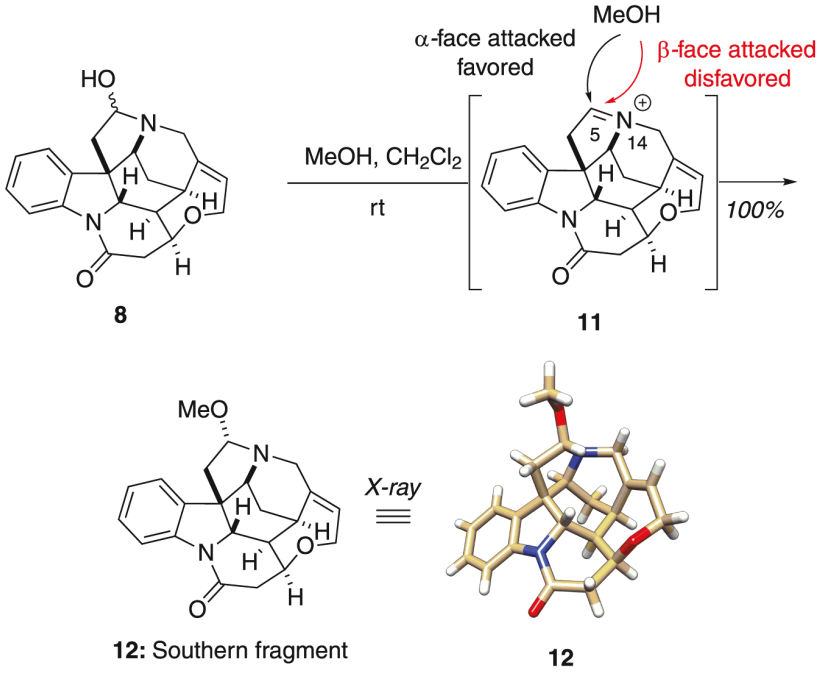
entry	Acylating agent[a]	Temperature / °C	time[b] / h	Conversion[c] / %	**7**/**8**[d]
1	TFAA	0	2	49	1:1.6
2	TFAA	23	2	58	1:1.4
3	TFAA	35	2	52	1:1.9
4	Ac_2O	0	4	21	1:1.3
5	Ac_2O	23	4	41	1:2.7
6	Ac_2O	35	4	62	1:3.1

[a]Two equivalents of the reagent were used with CH_2Cl_2 as a solvent; [b]iminium ion was trapped with aqueous KOH after 2 or 4 h; [c]percent conversion was calculated by ^{1}H NMR spectroscopy; [d]ratio of **7** to **8** was determined by ^{1}H NMR spectroscopy.



Scheme 4. A model Mukaiyama-Mannich reaction of **8** with silyl ketene acetal **9**.

with 100% acetone. Switching acetone to 5% methanol in dichloromethane resulted in the isolation of a new compound, whose ^{1}H nuclear magnetic resonance (NMR) showed the presence of only one single isomer. Similarly, when **8** was treated with 5% methanol in dichloromethane in the presence of silica gel, the same single isomer was also obtained. To rationalize this observation, we hypothesized that the new product might be formed from the addition of methanol to the corresponding iminium ion **11**, which was generated in the presence of Al_2O_3 or silica gel.[45] The quantitative conversion of **8** to *N*,*O*-acetal **12** was achieved when carbinolamine **8** was stirred in 5% methanol in dichloromethane. The stereochemistry of **12** was confirmed by single crystal X-ray analysis (Scheme 5).



Scheme 5. Synthesis of *N*,*O*-acetal **12** from carbinolamine **8**.

The stereoselectivity of this conversion can be attributable to the steric hindrance. Specifically, during the attack of methanol on iminium ion **11**, the presumed intermediate, methanol would experience more steric interactions on the β-face of C5–N4 double bond (concave side) than on the α-face (convex side). The same explanation is also applicable to the selective formation of ester **10** as a single diastereomer from the Mukaiyama-Mannich reaction of **8** with silyl ketene acetal **9**. Considering the acidic proton in carbinolamine **8** may complicate the Mannich coupling reaction with the Northern fragment, we selected *N*,*O*-acetal **12** as the Southern fragment.

2.3. Synthesis of the Northern fragment

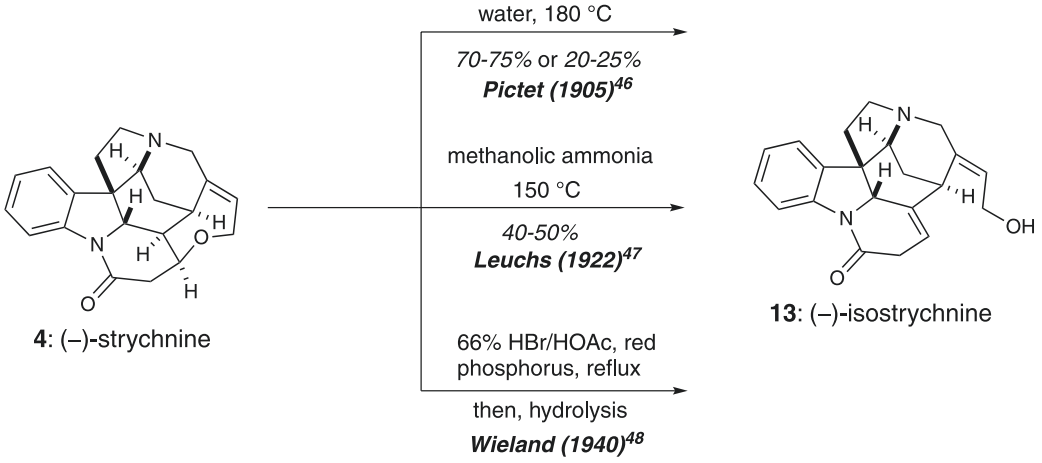
Our retrosynthetic plan of (–)-sungucine (**1**), (–)-isosungucine (**2**) and (–)-strychnogucine B (**3**) included the Northern fragment as an isostrychnine monomer with a suitably protected C18 hydroxyl moiety. A survey of the literature[46-48] showed the synthesis of isostrychnine from strychnine (i.e., degradation studies) had been long known with selected examples shown in Scheme 6. However, each protocol had its drawbacks such that in order to reliably access the Northern fragment on a multigram scale, we needed to develop a new protocol for converting strychnine (**4**) into isostrychnine (**13**).

Generally, the conversion of strychnine to isostrychnine consists of two seemingly simple steps.[49] The first step is an acid- or base-mediated elimination of the ether oxygen at the β-position of the lactam carbonyl group. The second step involves the isomerization of the conjugated double bond in the α,β-position into a trisubstituted, non-conjugated double bond in the β,γ-position.

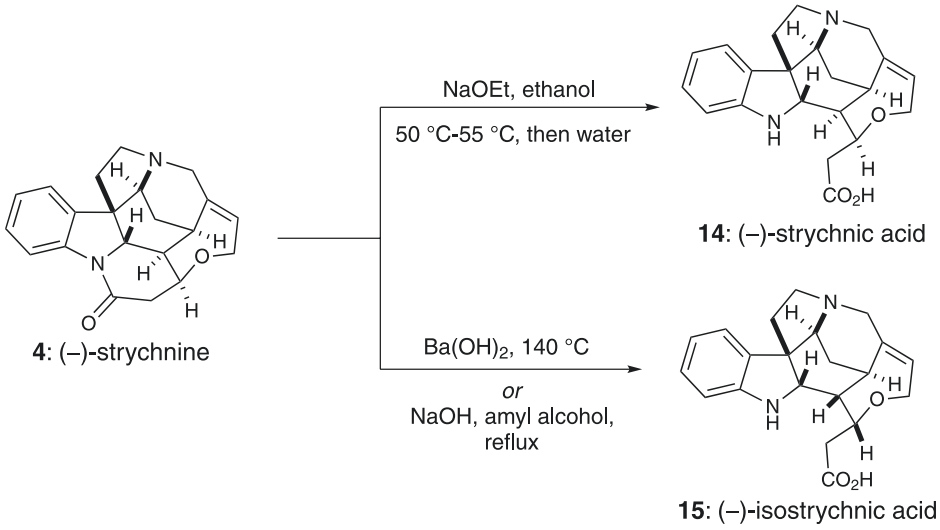
In order to develop a new protocol for the preparation of isostrychnine from strychnine, we realized that a prudent choice of a base was paramount. It was observed that bases used in the previous protocols might not be just promoters of the elimination of the ether oxygen but also perpetrators of the lactam opening. For example, strychnine was found to be easily converted to strychnic acid (**14**) under relatively mild alkaline conditions (e.g., NaOEt at 50 °C).[50-52] However, the use of more vigorous conditions (e.g., aqueous barium hydroxide at 140 °C[53] or NaOH in boiling amyl alcohol)[54] led to the formation of isostrychnic acid (**15**), as shown in Scheme 7.

In light of these experimental facts, we believed that a bulky non-nucleophilic base would minimize the side reactions relating to the lactam ring-opening. The non-nucleophilic amidine base 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) has been utilized in a variety of base-mediated transformations including eliminations and alkene isomerizations.[55] Moreover, since only water was used in Pictet's synthesis of isostrychnine, it would be interesting to know what effect DBU would have on the reaction if it was added to a water suspension of strychnine.[46] Some of the results are presented in Table 2. However, the conversion of strychnine was very low at 110 or 150 °C, even with up to 10 equivalents of DBU (Table 2, entries 1-2). Replacement of water with dimethyl sulfoxide (DMSO) did not improve the conversion. Conversely, another aprotic polar solvent, dimethylformamide (DMF), allowed for the formation of isostrychnine (**13**) in 29% yield after stirring strychnine (**4**) with 10 equivalents of DBU at 160 °C for 24 h (Table 2, entry 5). Further extension of the reaction time or increased temperature did not benefit the reaction.

Owing to the instability of DMF[56] or DMSO[57] at high temperatures, we opted for using a more stable, aprotic polar solvent with a higher boiling point. *N*-Methyl-2-pyrrolidinone (NMP) has been known to have advantages over both DMF and DMSO for nucleophilic displacement reactions due to its greater stability,[58] and its higher boiling point (202 °C) certainly was advantageous. Moreover, the

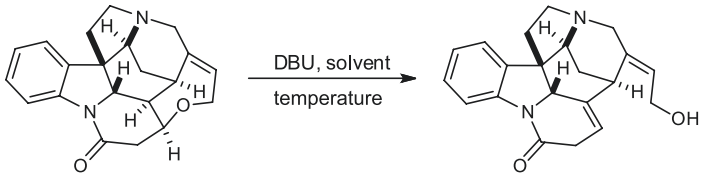


Scheme 6. Prior art regarding the chemical transformations of strychnine (**4**).



Scheme 7. Reported lactam ring-opening of strychnine with different bases.

Table 2. Screening the conditions for the conversion of (–)-**4** to (–)-**13** with DBU



entry	Solvent	Temperature / °C	DBU / equivalent	Reaction time / h	Yield[b] / %
1	H_2O[a]	110	3	44	–[c]
2	H_2O[a]	150	5	36	–[c]
3	DMSO[a]	150	10	16	–[c]
4	DMF[a]	160	10	15	25
5	DMF[a]	160	10	24	29
6	NMP	120	10	24	25
7	NMP	120	10	32	28
8	NMP	120	10	45	13
9	NMP	160	10	24	24

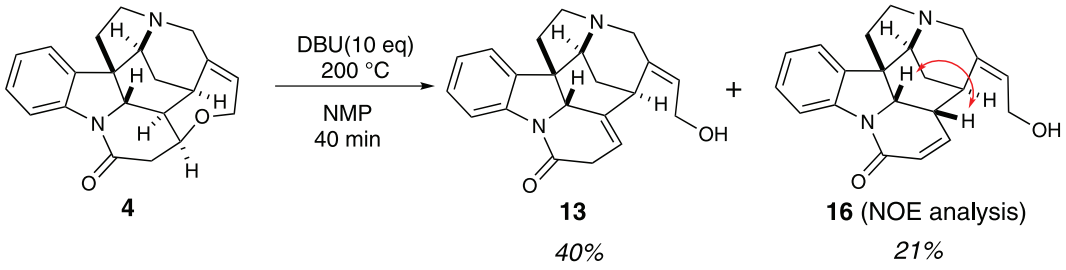
[a]The reaction was carried out in a sealed tube; [b]isolated yields; [c]the product was not isolated due to low conversion.

formation of its conjugate base would be possible due to the acidity of its hydrogens (β to the lactam group), which then could serve as a potential source of base.[59,60] Our preliminary experiments showed the best yield was 28% when NMP was used as solvent (Table 2, entry 7). We also found longer reaction times and high temperatures were detrimental to the reaction (Table 2, entry 8).

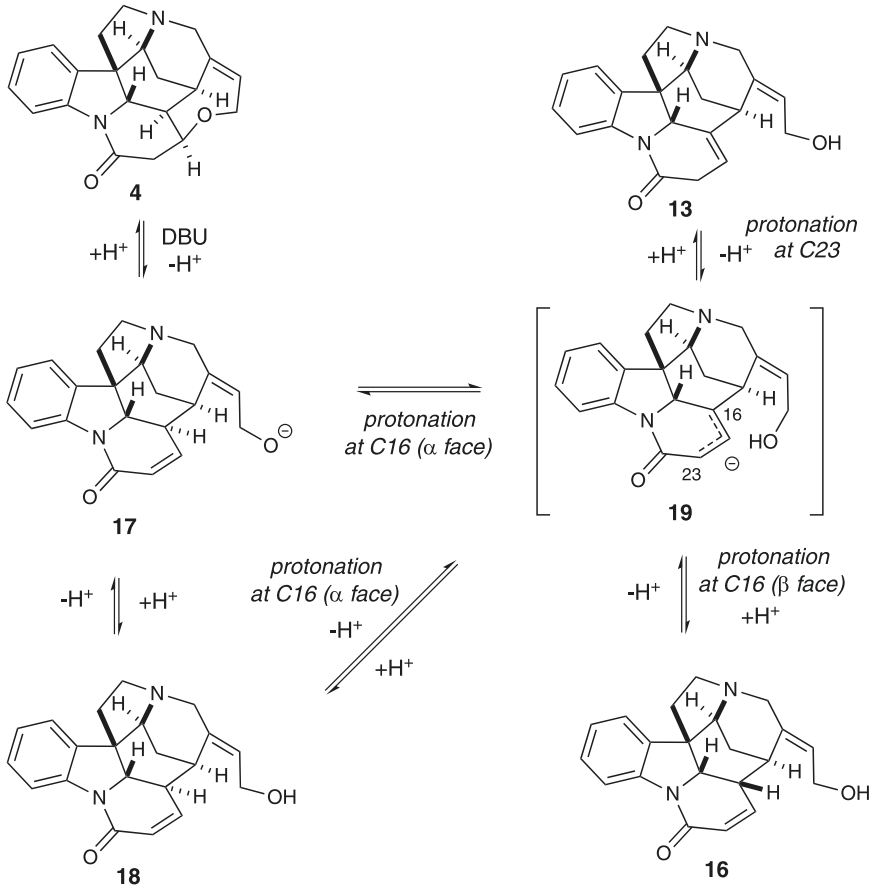
Finally, upon treatment of a deaerated NMP solution of **4** with DBU at 200 °C for 40 min, a mixture of the expected isostrychnine (**13**) and 13-*epi*-isostrychnine (**16**) was obtained in a 2:1 ratio in 61% yield (Scheme 8). It should be noted that the formation of **16** was also observed in the previous screening, but its characterization was not complete due to the difficulties with its purification (e.g., its high polarity and the presence of other polar byproducts).

The plausible reaction pathways of strychnine upon treatment with DBU are presented in Scheme 9. Anion **17** was assumed to be the product from the deprotonation step, whether or not the mechanism for the first step is E2 or E1cb. If **17** is stable enough during the reaction, it would give rise to the formation of **18**. On the other hand, proton transfer of **17** would produce anion **19**, from which all three alcohols (**13**, **16** and **18**) could be formed.

To explain why only **13** and 13-*epi*-isostrychnine (**16**) were isolated from the three possible products, we turned to computational analysis using DFT. Calculations were



Scheme 8. The synthesis of isostrychnine (–)-**13** and 13-*epi*-isostrychnine (–)-**16** from (–)-strychnine (**4**) with DBU in NMP.



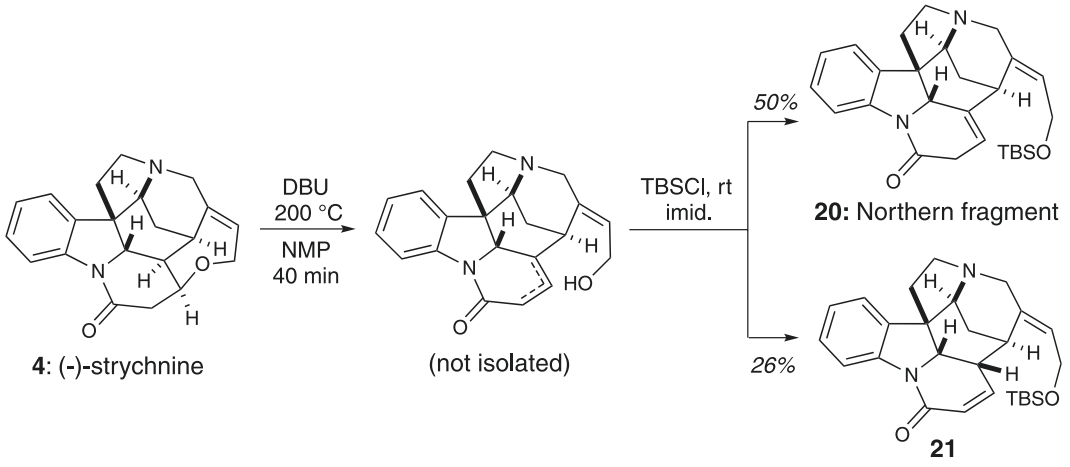
Scheme 9. Plausible reaction pathways for the DBU-mediated conversion of strychnine into regioisomeric alkenes **13** and **16**.

performed at the mpw1pw91/cc-pvdz level of theory. Computational data were consistent with experimental findings wherein **18** is 7 kcal mol^{-1} higher in free energy than **16** and 6.5 kcal mol^{-1} higher in free energy than **13**.

To facilitate the purification of **13** and **16**, we treated the reaction mixture from the DBU-mediated reaction of strychnine with TBSCl (*tert*-butyldimethylsilyl chloride) and imidazole. The resulting products, TBS-protected isostrychnine (**20**) and TBS-protected 13-*epi*-isostrychnine (**21**), were isolated in 50 and 26% yields, respectively (Scheme 10). Thus, we developed a one-pot synthesis of the Northern fragment **20** from (–)-strychnine **4**. With the synthetic routes to Northern and Southern fragments established, we turned to the task of joining the two via a biomimetic Mannich reaction.

2.4. The Mannich coupling reaction of the Northern and Southern fragments

The Mannich reaction is the preeminent method for making C–C bonds between nucleophilic C_α–H acidic (i.e., carbonyl) compounds and electrophilic imines or iminium salts.[42,61-63] To forge the characteristic C23–C5' bond in bis-*Strychnos* alkaloids **1**-**3**, the reaction of the amide enolate derived from **20** with iminium ion **11** would be desirable. However, a survey of the literature regarding the reaction



Scheme 10. One-pot synthesis of Northern fragment **20** from (–)-strychnine **4**.

of amide enolates with iminium salts is surprisingly limited.[42] Presumably, the challenges stem not only from the difficulties with the generation of amide enolates, but also from the higher basicity of the amide enolates. In particular, the use of strong bases to generate the amide enolates might not be compatible with the conditions for the generation of the iminium ions. Furthermore, the strong basic conditions could cause other side reactions with the iminium ions such as isomerization to the corresponding enamines in the presence of strong bases.[31]

One way to circumvent such problems would be to employ the silyl enol derivative of **20**, which would then be used in a separate Mukaiyama-Mannich reaction using *in situ* generated iminium ion **11**. However, the conversion of **20** to its silyl enol derivative turned out to be unsuccessful in our hands (e.g., LHMDS/LiCl followed by trapping with TMSCl).[64,65] Thus, this approach was abandoned.

At this stage, our attention returned to the generation of the amide enolate of **20**. We were encouraged by a literature[66] example wherein ketone lithium enolates were reacted with trimethylorthoformate in the presence of BF_3•OEt_2 to give the dimethoxymethylated ketone, suggesting this Lewis acid was compatible with lithium enolates. In addition, it was found that Grignard reagents were employed for nucleophilic addition reactions with iminium ions, which indicated the isomerization of iminium ions to enamines in the presence of Grignard reagents could be avoided.[67,68]

Based on this information, we planned to employ the magnesium amide enolate of **20** for the Mannich coupling owing to its weaker basicity compared to that of a Li variant. Moreover, the Lewis acidity of Mg has been leveraged for the generation of iminium ions from *N*,*O*-acetals.[69] The Mg amide enolate in turn could be obtained from the Li amide enolate via transmetallation with $MgBr_2$•OEt_2.[70,71] For the generation of iminium ion **11** from the Southern fragment **12**, BF_3•OEt_2 was employed because of its successful reaction with carbinolamine **8** in our model Mukaiyama-Mannich studies (Scheme 4). Since both **20** and **12** contain several Lewis basic sites, an excess of BF_3•OEt_2 was employed to ensure the productive generation of **11**.

The reaction results are summarized in Table 3. Lithiation of **20** with lithium di(isopropyl)amide (LDA) and subsequent transmetallation with $MgBr_2$•OEt_2 afforded the Mg amide enolate, which was added dropwise to a solution of **12** followed by treatment with BF_3•OEt_2 to afford Mannich base **22** as a mixture of epimers at C5'. For each entry in Table 3, the ratio of the epimers was not determined due to the instability of one epimer, which was slowly converted to the other isomer during isolation by silica gel chromatography.

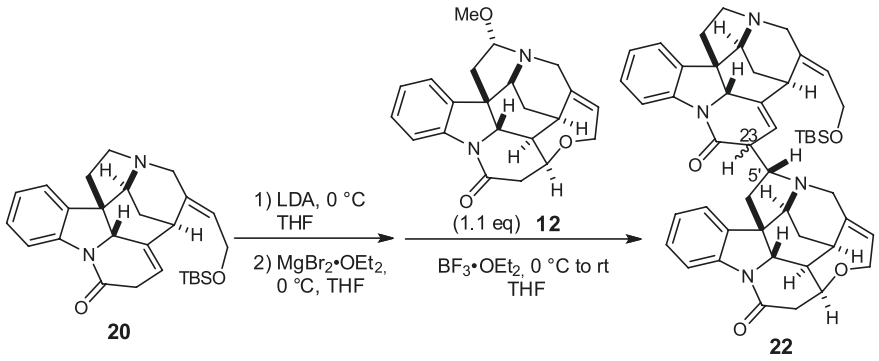
As shown in Table 3, it was interesting to observe that increasing the equivalents of $MgBr_2$•OEt_2 had a negative effect on the reaction yields (Table 3, entries 1-4). Finally, the highest yield (67%) of **22** was obtained with 1.1 equivalents of LDA with no addition of $MgBr_2$•OEt_2 (Table 3, entry 6)! We attribute the increase in yield of **22** to the increased nucleophilicity of the Li enolate *vis-à-vis* the Mg enolate.

Nevertheless, the first Mannich reaction was accomplished between a Li amide enolate and *N*,*O*-acetal in the presence of BF_3•OEt_2, and the successful formation of the key C23–C5' bond enabled the synthesis of bis-*Strychnos* alkaloids **1**-**3**. Next, attention was turned to the synthesis of (–)-strychnogucine B (**3**).

2.5. Synthesis of (–)-strychnogucine B (**3**)

The synthesis of (–)-strychnogucine B (**3**) from **22** required two steps. The first step was the removal of the primary TBS ether. To our delight, treatment of **22** with HF•pyridine in tetrahydrofuran (THF) buffered with

Table 3. The Mannich reaction to couple Northern fragment **20** with Southern fragment **12** to afford bis-*Strychnos* intermediate **22**[a]



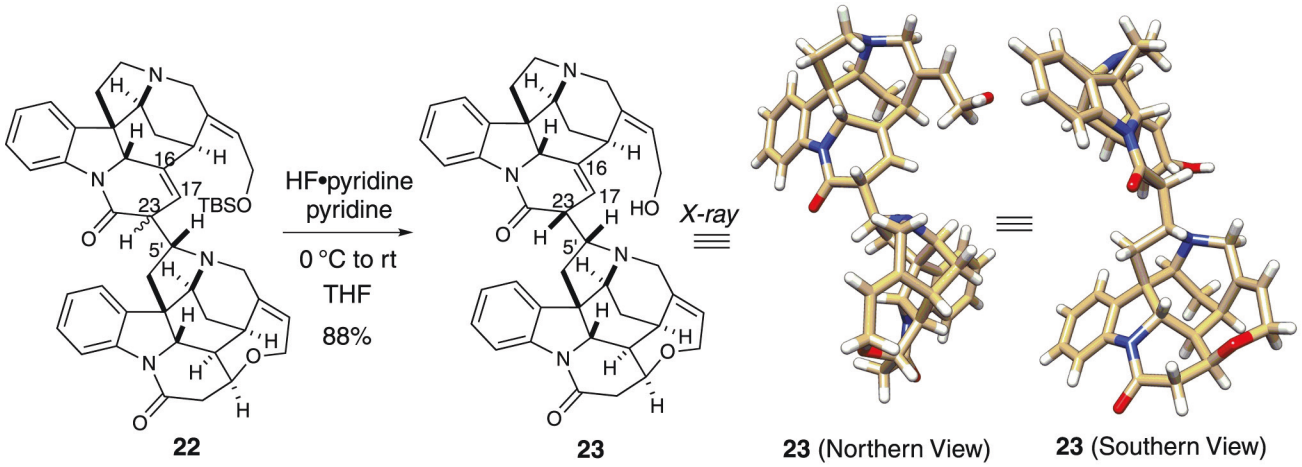
entry	LDA / equiv.	$MgBr_2$•OEt_2 / equiv.	BF_3•OEt_2 / equiv.	Temperature / °C	Yield[b] / %
1	2.2	3	5	0 to rt	24
2	2.2	2	5	0 to rt	36
3	2.2	1	5	0 to rt	36
4	2.2	0.5	5	0 to rt	52
5	2.2	0	9	0 to rt	–[c]
6	1.1	0	9	0 to rt	67

[a]The typical reaction conditions are as follows: **19** (1 equiv., 0.2 mmol) in tetrahydrofuran (THF, 2 mL) with *in situ* generated lithium di(isopropyl)amide (LDA, 1.2 equiv.) in THF (2 mL), 0 °C, 1 h; then, $MgBr_2$•OEt_2, THF (2 mL), 0 °C, 1 h; then, **12** (1.5 equiv.) in THF (2 mL) and BF_3•OEt_2, 0 °C to room temperature (rt), 16 h; [b]isolated yields; [c]not determined due to low conversion.

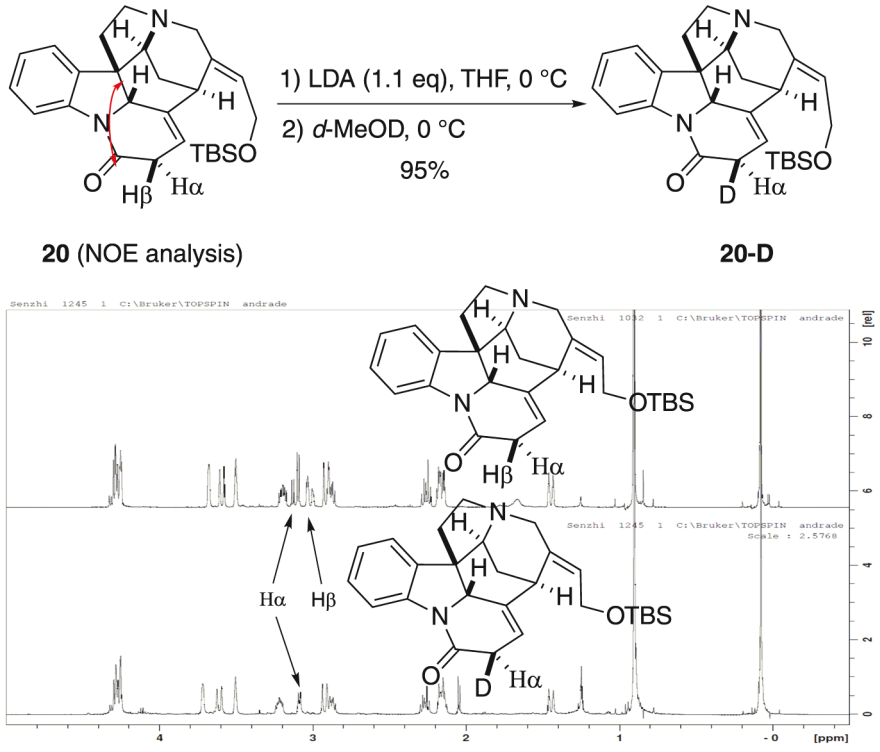
pyridine[72-74] not only removed the TBS group but also effected epimerization at C23 to furnish **23** as a single isomer, the structure of which was further confirmed by X-ray analysis (Scheme 11).

The confirmation of the structure of **23** made us believe that the Mannich reaction of **20** with **12** might be under kinetic control and the more stable isomer of **22** should have the same stereochemistry at C23, although it is not the major isomer. To lend support to this assumption, a deuterium quench experiment was performed, in which treatment of **20** with LDA at 0 °C was followed by quenching with *d*-MeOD to give a crude product that was directly used for NMR analysis. The ^{1}H NMR of the crude product showed only one isomer **20-D**, with the deuterium on the β side of C23, which was considered to be the kinetic product (Scheme 12).

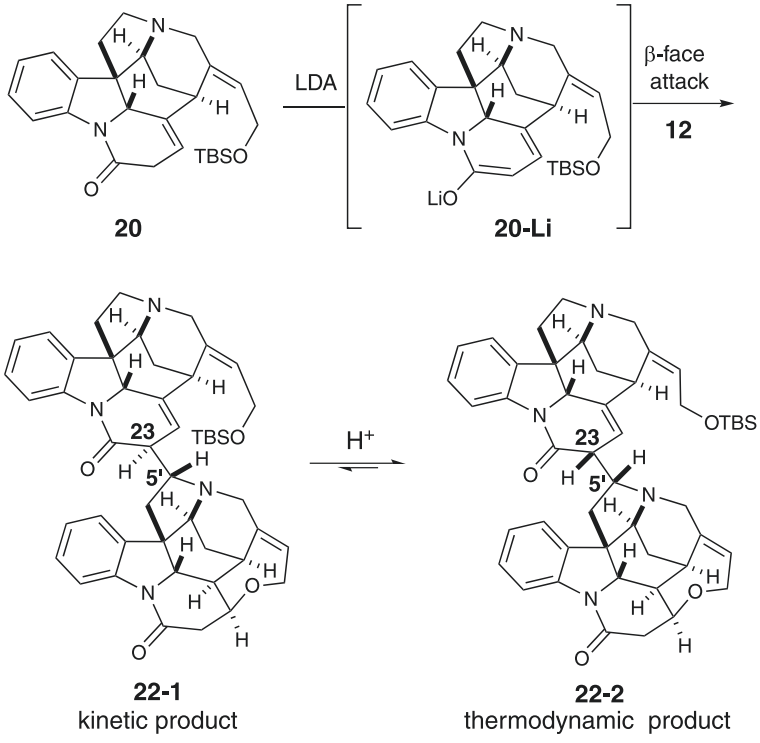
Regarding the Mannich reaction of **20**, it was assumed that iminium ion **11**, generated from *N*,*O*-acetal **12**, would attack Li amide enolate **20-Li** from the β face to give the kinetic product **22-1**. Since the latter is not the more stable epimer, it would undergo epimerization at C23 to give the thermodynamic epimer **22-2** (Scheme 13). As previously



Scheme 11. Deprotection and epimerization of Mannich product **22**.



Scheme 12. Deuterium quenching of the lithium enolate derived from **20**.



Scheme 13. Proposed pathway for the Mannich reaction of **20** with **12**.

mentioned, the conversion of **22-1** to **22-2** was observed during the chromatographic purification.

The last step for the synthesis of (–)-strychnogucine B (**3**) required the isomerization of the C16–C17 double bond in **23** to conjugation with the lactam carbonyl (i.e., C23–C17). To realize this transformation, we drew on a crucial discovery made by Magnus *et al.*[75] when attempting to improve the conversion of isostrychnine to strychnine.

Specifically, they found that treating isostrychnine (**13**) with cesium carbonate in refluxing *tert*-butyl alcohol isomerized the olefin into conjugation with the lactam carbonyl, affording 13-*epi*-isostrychnine (**16**) (Scheme 14).[75]

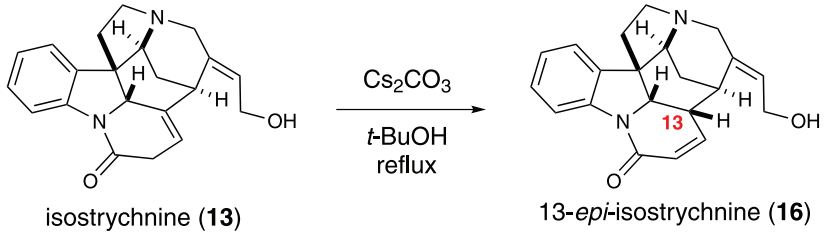
After inspecting the structure of **23**, we were confident that the isomerization of **23** to strychnogucine B would take place, because the isomerized double bond not only is in conjugation with the lactam carbonyl group but is also trisubstituted one and therefore thermodynamically more favorable. To our delight, treatment of **23** with Cs_2CO_3 in deaerated *tert*-butanol at 85 °C for 3 h furnished (–)-strychnogucine B (**3**) in 70% yield. Spectral data for **3** (e.g., ^{1}H NMR, ^{13}C NMR and infrared (IR)) were in complete agreement with those reported in the literature.[5] The structure of **3** was further confirmed by X-ray analysis (Scheme 15).

2.6. Syntheses of (–)-sungucine (**1**) and (–)-isosungucine (**2**)

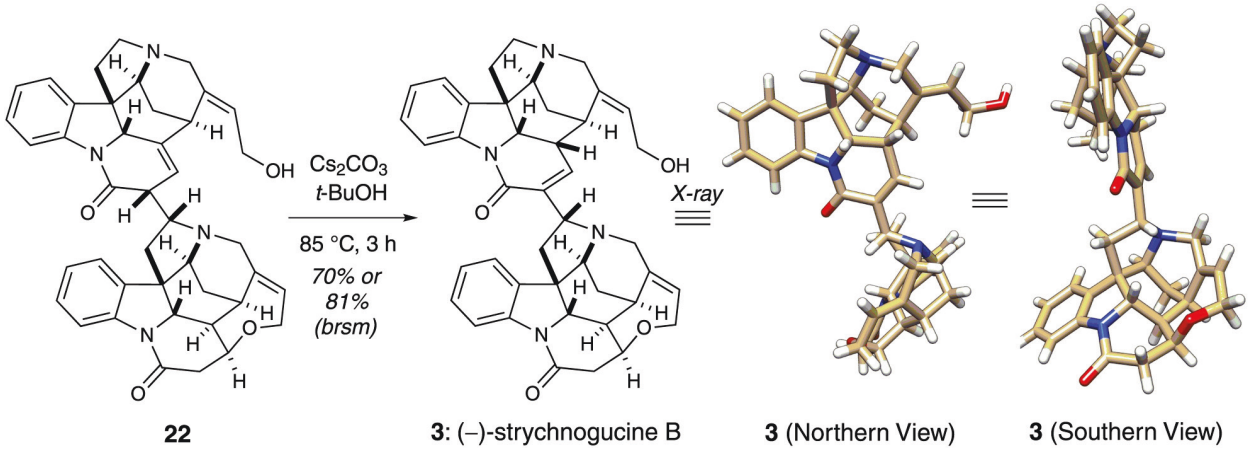
With (–)-strychnogucine B (**3**) in hand, a critical stage was reached for testing the projected conversion of **3** to (–)-sungucine (**1**) and (–)-isosungucine (**2**). We envisaged the conversion would be performed in two steps. The first step required the elimination of the allylic ether oxygen with concomitant ring-opening of the Southern oxepane F-ring, which could be accomplished by applying tactics used in the synthesis of Northern fragment **20**. The successful application of this strategy would deliver two alkene regioisomers with the newly formed C=C double bond at different positions (i.e., conjugated and non-conjugated). Both regioisomers were important as bis-deoxygenation thereof would furnish (–)-sungucine (**1**) and (–)-isosungucine (**2**), respectively. The second step required deoxygenation site-specifically at C18 (Northern monomer) and C18' (Southern monomer).

Given that numerous deoxygenation methods can be found in the literature,[76-89] we were confident this task could be accomplished. Unfortunately, most modern deoxygenation conditions (e.g., Pd-catalyzed reduction with various hydride sources,[84] MsCl/$LiBEt_3H$,[89] thiocarbonyl diimidazole/Bu_3SnH)[81] did not work in our hands. Finally, promising results were obtained when we conducted model studies of deoxygenation on *O*-acetyl isostrychnine (**24**), which was readily prepared from **13** with standard conditions (Scheme 16).

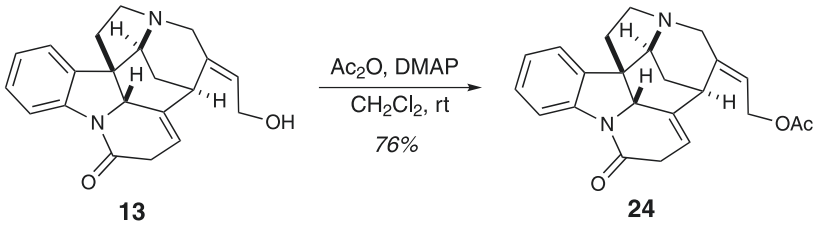
When **24** was subjected to 33% HBr in HOAc, the corresponding allylic bromide HBr salt **25** was obtained (Table 4), which was subsequently treated with various hydride source to afford deoxygenated isostrychnine (**26**). Among the hydride sources screened [e.g., $LiAlH_4$, $LiBEt_3H$ (Super-Hydride®),[89] $NaB(OMe)_3H$, and $NaBH_3CN$],[90] Super-Hydride was found to give the best result (Table 4, entry 2). The success of this protocol was attributed to the protection of the tertiary amine in **26** as HBr salt, since



Scheme 14. Magnus's Cs_2CO_3-mediated isomerization of isostrychnine (**13**).

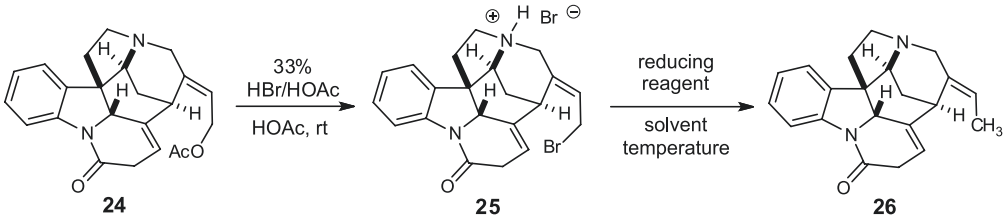


Scheme 15. Synthesis of (–)-strychnogucine B (**3**) using Magnus's conditions.



Scheme 16. Synthesis of *O*-acetyl isostrychnine (**24**) from isostrychnine (**13**) as a model substrate for deoxygenation reactions.

Table 4. Deoxygenation of model substrate **24**[a]



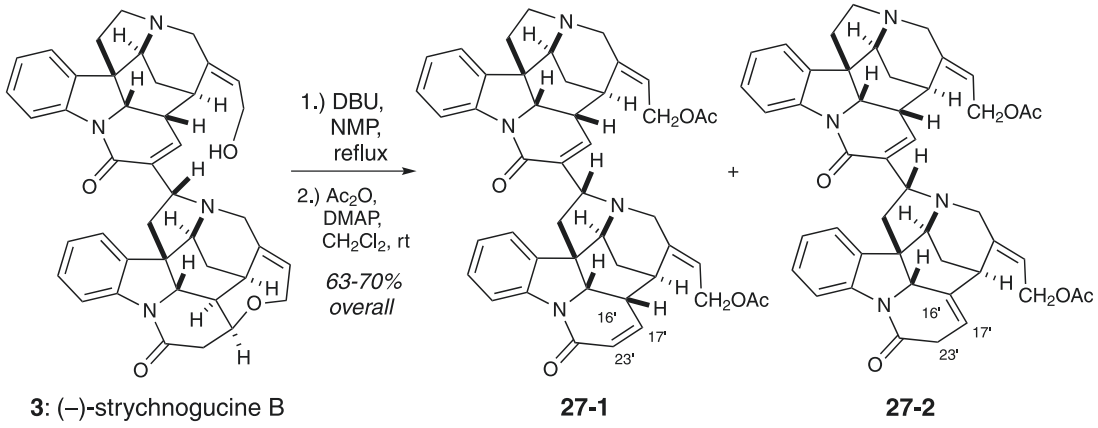
entry	Reducing reagent	Solvent	Temperature / °C	Yield[b] (overall) / %
1	LAH	THF	–78	57
2	$LiBEt_3H$ (Super-Hydride)	THF	–78	84
3	$NaBH(OMe)_3$	HMPA	70	36
4	$NaBH_3CN$	HMPA	70	47

[a]Typical reaction conditions: **24** (1 equiv., 0.01 mmol) in HOAc (2 mL) with HBr (33% in HOAc, 0.1 mL), 10 °C to room temperature (rt), 24 h; the reaction mixture was concentrated *in vacuo*; then, reducing reagent (3 to 8 equiv.) in solvent, 1-2 h; [b]isolated yields.

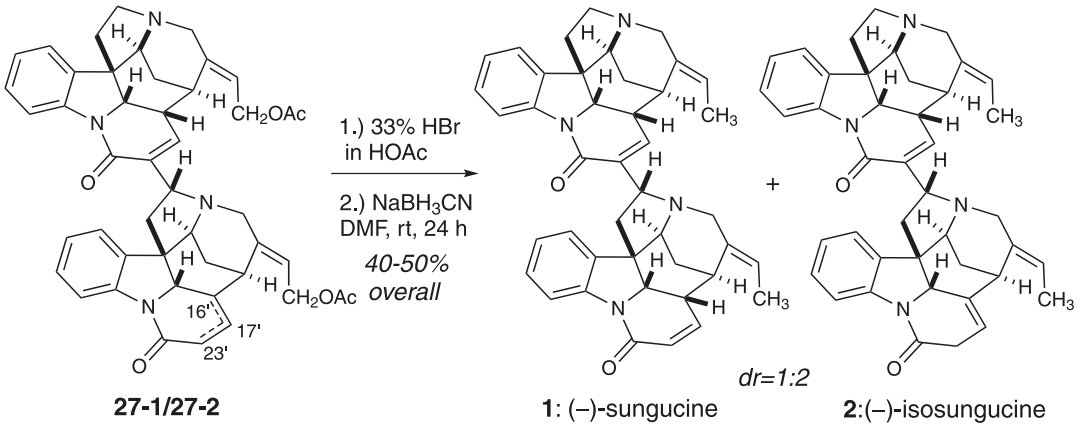
other attempts to directly activate the hydroxyl group in isostrychnine (**13**) for deoxygenation were not successful.

Having established a reliable deoxygenation method on a closely related model system, we proceed to apply those conditions on (–)-strychnogucine B (**3**) to access (–)-sungucine (**1**) and (–)-isosungucine (**2**). First, subjection of **3** to the conditions employed for the synthesis of Northern fragment **20** (i.e., DBU, NMP, reflux) afforded two diols as a mixture of regioisomeric alkenes. Subsequent acetylation thereof with Ac_2O yielded a mixture of bis-acetates **27-1** and **27-2** in a 1:2 ratio in 63-70% overall yield (Scheme 17). Significantly, we required the bis-acetates as substrates for our two-step deoxygenation protocol (*vide supra*).

With bis-acetates **27-1** and **27-2** in hand, we subjected the mixture to 33% HBr in HOAc to generate the corresponding allylic bromides (as HBr salts). After considerable optimization, we discovered that $NaBH_3CN$ as hydride source in DMF at room temperature (rt) for 24 h delivered (–)-sungucine (**1**) and (–)-isosungucine (**2**) as a separable 1:2 mixture, respectively, in 40-50% overall yield (Scheme 18). Curiously, Super-Hydride was inferior to $NaBH_3CN$ in the deoxygenation of bis-acetates **27-1**



Scheme 17. Synthesis of bis-acetates from (–)-strychnogucine B (**3**).



Scheme 18. Syntheses of (–)-sungucine (**1**) and (–)-isosungucine (**2**).

and **27-2**, further illustrating the limitations associated with model studies in natural product total synthesis. Spectral data for **1** and **2** (e.g., ^{1}H NMR, ^{13}C NMR and IR) were in complete agreement with those reported in the literature.[4,5,91]

3. Conclusions

In summary, the first syntheses of bis-*Strychnos* alkaloids (–)-strychnogucine B, (–)-sungucine and (–)-isosungucine have been successfully accomplished from inexpensive and commercially available (–)-strychnine. Key steps in the syntheses include the following: (*i*) a DBU-mediated conversion of strychnine into isostrychnine; (*ii*) a Polonovski-Potier reaction of strychnine *N*-oxide for regioselective Southern fragment activation; (*iii*) a stereoselective $BF_3 \bullet OEt_2$-mediated Mannich reaction for the coupling of Northern and Southern fragments; (*iv*) a Cs_2CO_3-mediated olefin isomerization reaction; and (*v*) a $NaBH_3CN$-mediated reduction of allylic bromide intermediates to install the requisite ethylidene moieties in the bis-*Strychnos* targets.

4. Experimental

All reactions containing moisture- or air-sensitive reagents were performed in oven-dried glassware under nitrogen or argon. Tetrahydrofuran, diethyl ether and dichloromethane were passed through two columns of neutral alumina prior to use. All other reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used as received. Flash column chromatography was performed according to the procedure of Still *et al.*[92] using 60 Å silica gel with the indicated solvents. For all ring-closing metathesis reactions, CH_2Cl_2 was deaerated by bubbling argon (1 min mL^{-1}). Thin layer chromatography was performed on 60 F_{254} silica gel plates. Detection was performed using UV light, $KMnO_4$ stain, phosphomolybdic acid (PMA) stain and subsequent heating. Infrared spectra were measured on a Fourier transform infrared spectrometer (FTIR). ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz instrument in $CDCl_3$ at 298 K. Chemical shifts are indicated in parts *per* million (ppm) and internally referenced to residual solvent signals. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), bs (broad singlet), bd (broad doublet), t (triplet), q (quartet) and m (multiplet). High-resolution mass spectra (HRMS) were obtained on a time-of-flight (TOF) mass spectrometer using an electrospray ionization (ESI) source.

(–)-(4a*R*,4a1*R*,5a*S*,8a*S*,8a1*S*,15a*S*)-8-(2,2,2-Trifluoroacetyl)-2,4a,4a1,5,5a,8a1,15,15a-octahydro-14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinolin-14-one (**6**)

To a stirred clear solution of strychnine *N*-oxide **5** (50 mg, 0.143 mmol), KCN (47 mg, 0.72 mmol) and Et_3N (0.12 mL, 0.86 mmol) in CH_2Cl_2 (2 mL) was added TFAA (0.1 mL, 0.71 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with addition of saturated aqueous $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 30% EtOAc in CH_2Cl_2 to afford 32 mg (52%) of vinylogous trifluoromethyl amide **6** as a pale yellow foam. $[\alpha]_D^{20}$ –691.8 (*c* 2.1, $CHCl_3$); IR (neat) ν / cm^{-1} 2980, 2883, 1645, 1545, 1480, 1393, 1286, 1160, 1136, 969, 918, 754, 720; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* 7.9 Hz, 1H), 7.31-7.22 (m, 2H), 7.22 (s, 1H), 5.95 (m, 1H), 4.53 (s, 1H), 4.25 (dt, *J* 8.5, 3.2 Hz, 1H), 4.18 (dd, *J* 13.9, 7.1 Hz, 1H), 4.09 (dd, *J* 14.1, 1.2 Hz, 1H), 4.05-4.00 (m, 2H), 3.58 (d, *J* 14.1 Hz,

1H), 3.23 (s, 1H), 3.10 (dd, *J* 17.3, 8.5 Hz, 1H), 2.61 (dd, *J* 17.2, 3.2 Hz, 1H), 2.52 (dt, *J* 14.8, 4.3 Hz, 1H), 1.66 (d, *J* 14.7 Hz, 1H), 1.38 (dt, *J* 10.3, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0 (q, *J* 34.4 Hz), 167.3, 155.7 (q, *J* 4.5 Hz), 144.3, 140.8, 129.3, 128.6, 126.9, 123.7, 123.6, 122.4, 116.7 (q, *J* 290 Hz), 116.3, 77.4, 64.6, 63.9, 62.3, 58.6, 51.0, 50.9, 42.6, 31.5, 26.1; HRMS (ESI) calcd. for $C_{23}H_{19}F_3N_2O_3$ + H = 429.1426, found 429.1416.

(–)-Methyl 2-((4a*R*,4a1*R*,5a*S*,7*R*,8a*R*,8a1*S*,15a*S*)-14-oxo-2,4a,4a1,5,5a,7,8,8a1,15,15a-decahydro-14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinolin-7-yl)acetate (**10**)

To a stirred clear solution of secondary amino alcohols **8** (44 mg, 0.126 mmol), and ketene silyl acetal (55 mg, 0.378 mmol) in THF (4 mL) was added BF_3•OEt_2 (62 µL, 0.5 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with addition of MeOH (1 mL) and saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (1 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 50% acetone in EtOAc to afford 30 mg (59%) of ester **10** as a white foam. $[\alpha]_D^{20}$ –50.2 (*c* 1.3, $CHCl_3$); IR (neat) ν / cm^{-1} 2981, 2883, 1733, 1596, 1479, 1458, 1389, 1169, 1049, 958, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* 7.9 Hz, 1H), 7.26-7.22 (m, 1H), 7.16 (d, *J* 6.8 Hz, 1H), 7.08 (td, *J* 7.4, 0.9 Hz, 1H), 5.92 (m, 1H), 4.28 (dt, *J* 8.4, 3.3 Hz, 1H), 4.14 (dd, *J* 13.8, 6.9 Hz, 1H), 4.07-4.01 (m, 2H), 3.93 (d, *J* 10.5 Hz, 1H), 3.67 (s, 3H), 3.64 (d, *J* 15.0 Hz, 1H), 3.43-3.35 (m, 1H), 3.17-3.07 (m, 2H), 2.77 (d, *J* 15.0 Hz, 1H), 2.67 (dd, *J* 17.4, 3.3 Hz, 1H), 2.64-2.60 (m, 1H), 2.46 (dd, *J* 14.9, 7.6 Hz, 1H), 2.33 (dt, *J* 14.4, 4.3 Hz, 1H), 2.16 (dd, *J* 12.7, 5.7 Hz, 1H), 1.67 (dd, *J* 12.7, 11.5 Hz, 1H), 1.43 (d, *J* 14.4 Hz, 1H), 1.27-1.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.3, 142.1, 140.5, 132.2, 128.6, 127.3, 124.2, 122.2, 116.2, 77.4, 64.5, 60.6, 60.3, 58.3, 52.2, 51.6, 51.1, 49.3, 47.8, 42.4, 40.5, 31.4, 26.9; HRMS (ESI) calcd. for $C_{24}H_{26}N_2O_4$ + H = 407.1971, found 407.1973.

(–)-(3a*S*,5*S*,5a1*S*,13b*R*,*E*)-14-(2-Hydroxyethylidene)-1,2,3a,4,5a1,7-hexahydro-5*H*,8*H*-3,5-ethanopyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-8-one (**13**)

A stirred suspension of (–)-strychnine **4** (2.0 g, 5.98 mmol) and DBU (8.9 mL, 60 mmol) in *N*-methyl-2-pyrrolidone (40 mL) was deaerated by bubbling argon (1 min mL^{-1}) for 1 h. The reaction mixture was stirred at 200 °C for 40 min under inert atmosphere. The resultant reaction mixture was cooled to rt and purified by flash column chromatography eluting with MeOH/DCM (1:100 to 20:100) to afford 0.8 g (40%) of **13** as a white foam. $[\alpha]_D^{20}$ –22.2 (*c* 0.98, $CHCl_3$); IR (neat) ν / cm^{-1} 3383, 2931, 1653, 1595, 1483, 1397, 1150, 1076, 1013, 919, 757, 731; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 7.21-7.18 (m, 1H), 7.09 (td, *J* 7.5, 1.0 Hz, 1H), 5.87-5.84 (m, 1H), 5.59 (t, *J* 6.5 Hz, 1H), 4.31-4.24 (m, 3H), 3.68-3.66 (m, 1H), 3.61-3.58 (m, 2H), 3.21 (ddd, *J* 11.1, 7.8, 5.3 Hz, 1H), 3.12 (dd, *J* 17.4, 6.7 Hz, 1H), 3.05-2.98 (m, 1H), 2.94 (d, *J* 14.4 Hz, 1H), 2.89 (dt, *J* 11.1, 7.1 Hz, 1H), 2.28 (dt, *J* 13.1, 7.7 Hz, 1H), 2.21 (dd, *J* 13.1, 6.1 Hz, 1H), 2.18-2.12 (m, 1H), 1.47 (dt, *J* 14.0, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 142.1, 141.3, 137.5, 134.5, 128.4, 126.7, 124.2, 122.5, 120.5, 114.6, 67.2, 63.3, 58.1, 53.9, 52.8, 52.2, 46.1, 36.8, 34.6, 25.7; HRMS (ESI) calcd. for $C_{21}H_{22}N_2O_2$ + H = 335.176, found 335.1768.

(–)-(3a*S*,5*R*,5a*S*,5a1*S*,13b*R*,*E*)-14-(2-Hydroxyethylidene)-1,2,3a,4,5a,5a1-hexahydro-5*H*,8*H*-3,5-ethanopyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-8-one (**16**)

The same procedure was followed as the one for the synthesis of isostrychnine (**13**). The residue was purified by flash column chromatography eluting with MeOH/DCM (1:100 to 20:100) to afford 0.42 g (21%) of **16** as a white foam. $[\alpha]_D^{20}$ –317.8 (*c* 0.9, $CHCl_3$); IR (neat) ν / cm^{-1} 3383, 2981, 2884, 1664, 1591, 1481, 1424, 1146, 1075, 1010, 812, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* 8.0 Hz, 1H), 7.29-7.22 (m, 2H), 7.12 (td, *J* 7.5, 1.0 Hz, 1H), 6.79 (dd, *J* 9.8, 6.5 Hz, 1H), 6.01 (dd, *J* 9.8, 1.0 Hz, 1H), 5.52 (t, *J* 6.5 Hz, 1H), 4.26 (d, *J* 6.5 Hz, 1H), 4.20 (dd, *J* 6.5, 2.5 Hz, 2H), 3.63 (d, *J* 15.3 Hz, 1H), 3.30 (d, *J* 15.3 Hz, 1H), 3.27-3.20 (m, 2H), 3.06 (ddd, *J* 10.5, 8.1, 6.4 Hz, 1H), 2.74 (m, 1H), 2.63-2.59 (m, 1H), 2.58-2.52 (m, 1H), 2.15 (dt, *J* 13.3, 5.9 Hz, 1H), 1.87-1.83 (m, 1H), 1.75 (ddd, *J* 14.3, 4.7, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 144.3, 142.4, 141.3, 135.4, 128.4, 124.5, 123.7, 123.3, 122.3, 116.4, 65.2, 64.4, 57.9, 53.9, 52.5, 51.9, 38.1, 37.0, 31.4, 23.2; HRMS (ESI) calcd. for $C_{21}H_{22}N_2O_2$ + Na = 357.1579, found 357.1571.

(–)-(3a*S*,5*S*,5a1*S*,7*R*,13b*R*,*E*)-14-(2-((*tert*-Butyldimethylsilyl)oxy)ethylidene)-1,2,3a,4,5a1,7-hexahydro-5*H*,8*H*-3,5-ethanopyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-8-one-7-d (**20-D**)

To a stirred solution of (*i*-Pr)$_2$NH (7.5 µL, 0.054 mmol) in THF(1 mL) was added *n*-BuLi (2.35 M solution in hexanes, 20.9 µL, 0.049 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, followed by addition of a

solution of Northern fragment **20** (20 mg, 0.045 mmol) in THF (1 mL). The mixture was stirred at 0 °C for 1 h and the reaction was quenched by addition of MeOD (0.5 mL). The resulting mixture was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 19 mg (95%) of **20-D** as a gray foam. $[\alpha]_D^{20}$ –21.4 (*c* 1.0, $CHCl_3$); IR (neat) ν / cm^{-1} 2954, 2924, 2885, 2855, 1671, 1483, 1461, 1393, 1254, 1105, 1063, 836, 777, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* 7.9 Hz, 1H), 7.25-7.18 (m, 2H), 7.08 (td, *J* 7.5, 0.8 Hz, 1H), 5.80-5.78 (m, 1H), 5.50 (t, *J* 5.5 Hz, 1H), 4.30-4.23 (m, 3H), 3.71 (s, 1H), 3.61 (d, *J* 14.4 Hz, 1H), 3.50 (s, 1H), 3.24-3.18 (m, 1H), 3.10-3.07 (m, 1H), 2.92 (d, *J* 14.4 Hz, 1H), 2.89-2.85 (m, 1H), 2.29-2.23 (m, 1H), 2.18-2.11 (m, 2H), 1.44 (d, *J* 14.1 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 142.0, 141.4, 135.5, 134.5, 128.3, 127.9, 124.1, 122.5, 120.2, 114.6, 66.9, 63.0, 59.1, 53.7, 52.6, 52.3, 45.9, 36.5 (t, *J* 18 Hz), 34.8, 25.9, 25.4, 18.3, –5.1, –5.2; HRMS (ESI) calcd. for $C_{27}H_{35}DN_2O_2Si$ + Na = 472.2507, found 472.2516.

(–)-(*E*)-2-((3a*S*,5*S*,5a1*S*,13b*R*)-8-Oxo-1,2,3a,4,5a1,7-hexahydro-5*H*,8*H*-3,5-ethanopyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-14-ylidene)ethyl acetate (**24**)

To a stirred suspension of (–)-isostrychnine (**13**) (100 mg, 0.3 mmol) and 4-dimethylaminopyridine (18.3 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was added Ac_2O (66 µL, 0.66 mmol) at rt. The resulting mixture was stirred at rt overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with acetone/EtOAc (50 to 70%) to afford 86 mg (76%) of **24** as a white foam. $[\alpha]_D^{20}$ –10.0 (*c* 1.15, $CHCl_3$); IR (neat) ν / cm^{-1} 2937, 1733, 1667, 1596, 1483, 1461, 1394, 1232, 1150, 1023, 757; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* 7.8 Hz, 1H), 7.25-7.21 (m, 1H), 7.20-7.17 (m, 1H), 7.08 (td, *J* 7.5, 1.0 Hz, 1H), 5.89-5.87 (m, 1H), 5.50 (t, *J* 6.4 Hz, 1H), 4.74-4.62 (m, 2H), 4.29-4.24 (m, 1H), 3.66 (m, 1H), 3.58 (d, *J* 14.6 Hz, 2H), 3.19 (ddd, *J* 11.1, 7.8, 5.3 Hz, 1H), 3.12 (dd, *J* 17.4, 6.7 Hz, 1H), 3.05-2.97 (m, 1H), 2.93 (d, *J* 14.6 Hz, 1H), 2.87 (dt, *J* 11.1, 7.1 Hz, 1H), 2.29-2.23 (m, 1H), 2.22-2.12 (m, 2H), 2.06 (s, 3H), 1.47 (dt, *J* 14.0, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 168.4, 141.9, 141.4, 140.7, 134.6, 128.3, 124.1, 122.4, 120.9, 120.8, 114.6, 67.2, 63.3, 59.8, 53.9, 52.9, 52.3, 46.2, 36.9, 34.8, 25.7, 20.9; HRMS (ESI) calcd. for $C_{23}H_{24}N_2O_3$ + H = 377.1865, found 377.1863.

(–)-(3a*S*,5*S*,5a1*S*,13b*R*,*E*)-14-Ethylidene-1,2,3a,4,5a1,7-hexahydro-5*H*,8*H*-3,5-ethanopyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-8-one (**26**)

To a stirred solution of **24** (35 mg, 0.093 mmol) in HOAc (2 mL) was added HBr (33% in HOAc, 0.1 mL) at 10 °C. The cooling bath was removed and the reaction mixture was stirred at rt for 24 h. The solvent was then removed under reduced pressure. The crude residue was dissolved in THF (3 mL) and cooled to –78 °C. A solution of lithium triethylborohydride (1 M in THF, 0.744 mL, 0.744 mmol) was added dropwise, and the reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched by addition of water (2 mL) at –78 °C. The resulting mixture was diluted with EtOAc (10 mL) and washed with brine (5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was first purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (5:100 to 10:100) to afford 25 mg (84%) of **26** as a white foam. $[\alpha]_D^{20}$ –41.0 (*c* 1.1, $CHCl_3$); IR (neat) ν / cm^{-1} 2924, 2851, 1666, 1595, 1482, 1392, 1313, 1284, 1149, 1106, 1080, 932, 754, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* 8.0 Hz, 1H), 7.25-7.22 (m, 1H), 7.21-7.18 (m, 1H), 7.09 (td, *J* 7.5, 1.0 Hz, 1H), 5.85-5.82 (m, 1H), 5.47-5.42 (m, 1H), 4.29-4.25 (m, 1H), 3.67 (m, 1H), 3.57-3.54 (m, 2H), 3.18 (ddd, *J* 11.1, 7.8, 5.3 Hz, 1H), 3.11 (dd, *J* 17.3, 6.6 Hz, 1H), 3.06-2.99 (m, 1H), 2.90-2.84 (m, 2H), 2.26 (dt, *J* 13.4, 7.7 Hz, 1H), 2.21-2.17 (m, 1H), 2.16-2.11 (m, 1H), 1.68 (d, *J* 6.9 Hz, 3H), 1.46 (dt, *J* 13.9, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 142.1, 141.4, 135.5, 135.0, 128.2, 124.0, 122.5, 121.2, 120.0, 114.5, 67.4, 63.6, 54.2, 52.8, 52.3, 46.3, 36.8, 34.3, 25.8, 12.8; HRMS (ESI) calcd. for $C_{21}H_{22}N_2O$ + H = 319.181, found 319.1821.

Supplementary Information

Supplementary information (^{1}H and ^{13}C NMR spectra for **6**, **10**, **13**, **16**, **20-D**, **24** and **26**) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Crystallographic data, including instructions file, atomic coordinates, and intensity data of **6** and **10** are available for download in CIF format at http://jbcs.sbq.org.br.

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