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

Senzhi Zhao, Christiana N. Teijaro, Heng Chen, Gopal Sirasani, Shivaiah Vaddypally, Michael J. Zdilla, Graham E. Dobereiner, and Rodrigo B. Andrade*

Abstract: We report the first chemical syntheses of complex, bis-*Strychnos* alkaloids (–)-sungucine (**1**), (–)-isosungucine (**2**), and (–)-strychnogucine B (**3**) from (–)-strychnine (**4**). Key steps included (1) the Polonovski–Potier activation of strychnine *N*-oxide; (2) a biomimetic Mannich coupling to forge the signature C23–C5' bond that joins two monoterpene indole monomers; and, (3) a sequential HBr/$NaBH_3CN$-mediated reduction to fashion the ethylidene moieties in **1**–**3**. DFT calculations were employed to rationalize the regiochemical course of reactions involving strychnine congeners.

Scheme 2. Syntheses of Northern fragment **5** and Southern fragment **9** from (–)-st

The chemical synthesis of complex natural products remains a vibrant and dynamic enterprise within the rich field of organic chemistry. Many natural products are represented in our current pharmacopeia, including those in the bis-indole alkaloid class.[1] (–)-Sungucine (**1**) was isolated by Angenot and co-workers in 1979 from the roots of *Strychnos icaja*, a liana native only to central Africa (Scheme 1).[2] The structure of **1** was rigorously established by single-crystal X-ray analysis.[3] Reinvestigation of *Strychnos icaja* by Frédérich and co-workers in the 1990s resulted in the discovery of novel sungucine congeners (–)-isosungucine (**2**) and (–)-strychnogucine B (**3**).[4]

The structurally unique bis-*Strychnos* alkaloids **1**–**3** feature a common C23–C5' bond yet differ in oxidation states at C18 and C18' (Scheme 1). (–)-Sungucine (**1**) possesses anticancer activity in the low μM range, as confirmed through NCI's *in vitro* 60 human tumor cell line screen.[5] Pharmacological evaluation of **1** revealed it induced apoptosis in both leukemia and colon cancer cells via a p53-independent mechanism.[6] In addition, **2** and **3** were found to possess potent and selective anti-plasmodial activities against *Plasmodium falciparum* strains.[4,7] Herein, we report the first enantiospecific chemical syntheses of bioactive, bis-*Strychnos* alkaloids (–)-sungucine (**1**), (–)-isosungucine (**2**), and (–)-strychnogucine B (**3**) from commercially available and inexpensive (–)-strychnine (**4**).

In our retrosynthetic analysis (Scheme 1), we envisioned (–)-sungucine (**1**) and (–)-isosungucine (**2**) could be synthesized from (–)-strychnogucine B (**3**) by base-mediated ring-opening and deoxygenation of the ethylidene moieties. To make (–)-**3** in a convergent manner, one can logically disconnect the C23–C5' bond, which could arise from the biomimetic Mannich coupling of a northern C23-synthon with a southern C5'-synthon. As both synthons are structurally homologous to strychnine (**4**), we reasoned the most step-efficient syntheses of **1**–**3** must start with inexpensive, commercially available (–)-strychnine (**4**).

1: (–)-sungucine **2:** (–)-isosungucine **3:** (–)-strychnogucine B

Northern synthon *Southern synthon* **4:** (–)-strychnine

Scheme 1. Structures of (–)-sungucine (**1**), (–)-isosungucine (**2**), (–)-strychnogucine B (**3**) and retrosynthetic analysis leading to northern and southern synthons derived from (–)-strychnine (**4**).

As outlined in Scheme 2, our syntheses of bis-*Strychnos* alkaloids **1**–**3** began with the construction of northern fragment **5** (i.e., TBS-protected isostrychnine). In order to readily access **5** on a multi-gram scale, we needed a reliable and effective method for converting strychnine into isostrychine. While literature reports of this transformation are known,[8] we were not satisfied with the results. Ultimately, we found that when (–)-strychnine (**4**) was first treated with 1,8-diazabicyclo[5.4.0]undecene (DBU) at 200 °C in *N*-methyl-2-pyrrolidone (NMP) then TBSCl and imidazole at rt, we routinely isolated **5** in 50% overall yield, in addition to minor regioisomer **6** (26% yield) on gram scale. Experimental results were consistent with DFT calculations inasmuch as only **5** and 13-*epi*-isostrychnine (**6**) were isolated out of the three possible products (see Table S1).

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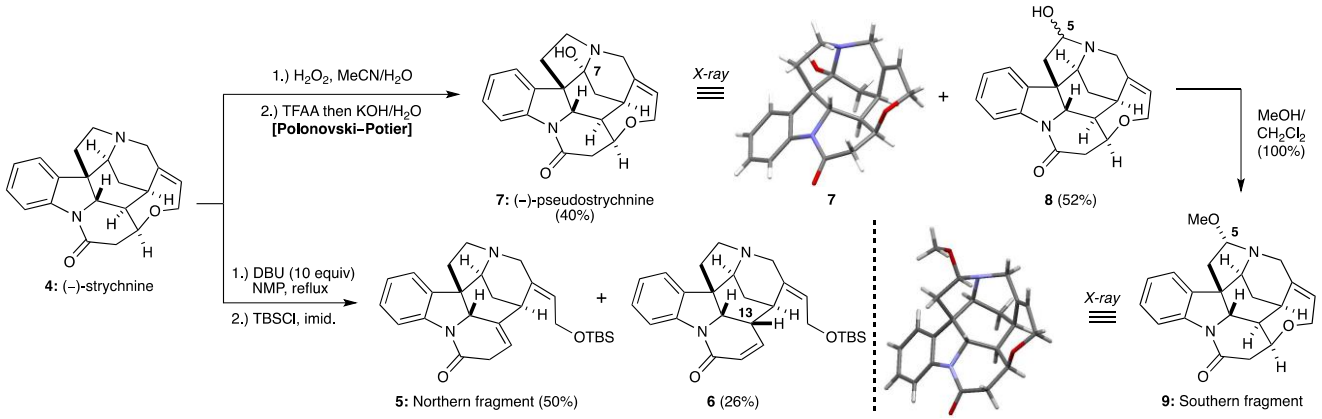
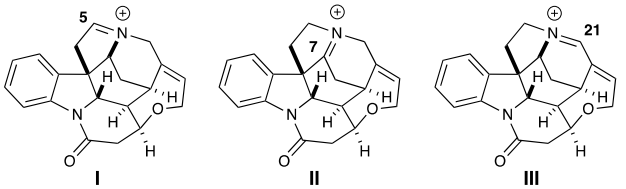


Scheme 2. Syntheses of Northern fragment **5** and Southern fragment **9** from (–)-strychnine (**4**).

The next stage of the synthesis enlisted the venerable Polonovski–Potier reaction[9] to regioselectively generate and trap C5–N4 iminium ion **I** (Figure 1) to access southern fragment **9** (Scheme 2). Thus, (–)-**4** was oxidized with H_2O_2 to afford strychnine *N*-oxide in 98% yield. Reaction with trifluoroacetic anhydride (TFAA) then KCN gave an intractable mixture of regioisomers. Replacing KCN with $NaHCO_3$ (aq.) furnished pseudostrychnine (**7**) and regioisomeric carbinolamine **8** in a 2.2:1 ratio, respectively, and 71% yield. The structure of **7** was confirmed by single-crystal X-ray analysis. The use of more basic and nucleophilic KOH was able to invert the ratio of products and delivered the desired regioisomer **8** in 52% yield, along with 40% of **7**. Spectral (i.e., ^{1}H NMR) analysis of major carbinolamine **8** revealed it was a mixture of epimers at C5. Treatment of this mixture with 10% MeOH/CH_2Cl_2 effected *N*,*O*-aminal ether equilibration to afford the requisite southern fragment **9** in quantitative yield. The structure of **9** was rigorously established by single-crystal X-ray analysis (Scheme 2).

To rationalize the regiochemical course of the Polonovski–Potier reaction, we employed DFT analysis (mPW1PW91/cc-pvdz) to determine relative free energies of three iminium cations that may form upon trifluoroacetate elimination (Figure 1). The carbinolamine derived from the lowest-energy iminium considered **III** was not observed in experiment; meanwhile, isolated regioisomer **7** was derived from the highest-energy iminium **II**. Besides the error inherent in the chosen DFT method, the effects of ion pairing[10] may dictate the stability of **I**–**III**. Nonetheless, at this stage the experimental results cannot be understood solely by comparing the relative computed energies of **I**–**III**.



	I	II	III
ΔE	0 kcal/mol	+3.3 kcal/mol	–2.3 kcal/mol
ΔG	0 kcal/mol	+3.0 kcal/mol	–1.8 kcal/mol

Figure 1. Relative DFT energies for iminium ions **I**–**III**.

Further DFT analysis afforded the minimized structure of parent *N*-acyloxyammonium ion **IV** (Table S2). **IV** lacks a hydrogen *anti*-periplanar to the N–O_{acyl} bond (Figure S1A–C), a strict prerequisite for the E2 pathway expected in the Polonovski–Potier mechanism. The stereochemistry between C5–H_b and N4–O_{acyl} bonds (i.e., H_b–C5–N4–O dihedral=148.3°, Figures S1A and 2) are closest to being *anti*-periplanar. The formation of **8** may follow an E2-like mechanism via elimination from **IV** to **I**.

A natural population analysis (NPA)[11] of **IV** (Figure 2) indicates that C7 is the least negative carbon bound to N4 (C7, –0.00445; C5, –□.21717; C21, –0.24162), and the charge on C7–H (+0.30252) is more positive than those on C5 and C21 protons. To the extent that pKa and natural charge (Q_A, Q_H) are correlated,[12] NPA suggests that C7–H, which is *syn*-coplanar to the N–O_{acyl} bond (11.5°), has the lowest pKa of the C–H bonds adjacent to N4 (Figures 2 and S1B). Thus, reaction at C7 of **IV** to form iminium **II** could occur through an E1-like or E1cb-like transition state by means of the paired TFA.[13] An alternative to the bimolecular pathway would be the entropically favored *syn* elimination arising from the intramolecular deprotonation of C7–H by the pendant *N*-trifluoroacetyl moiety.

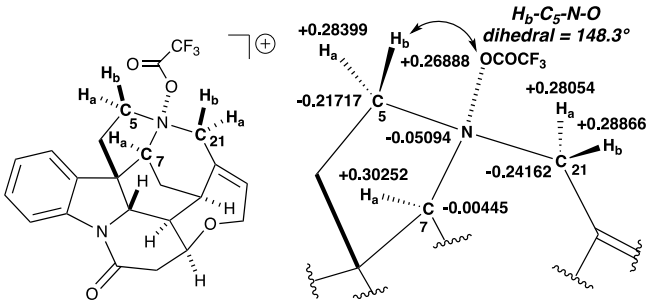
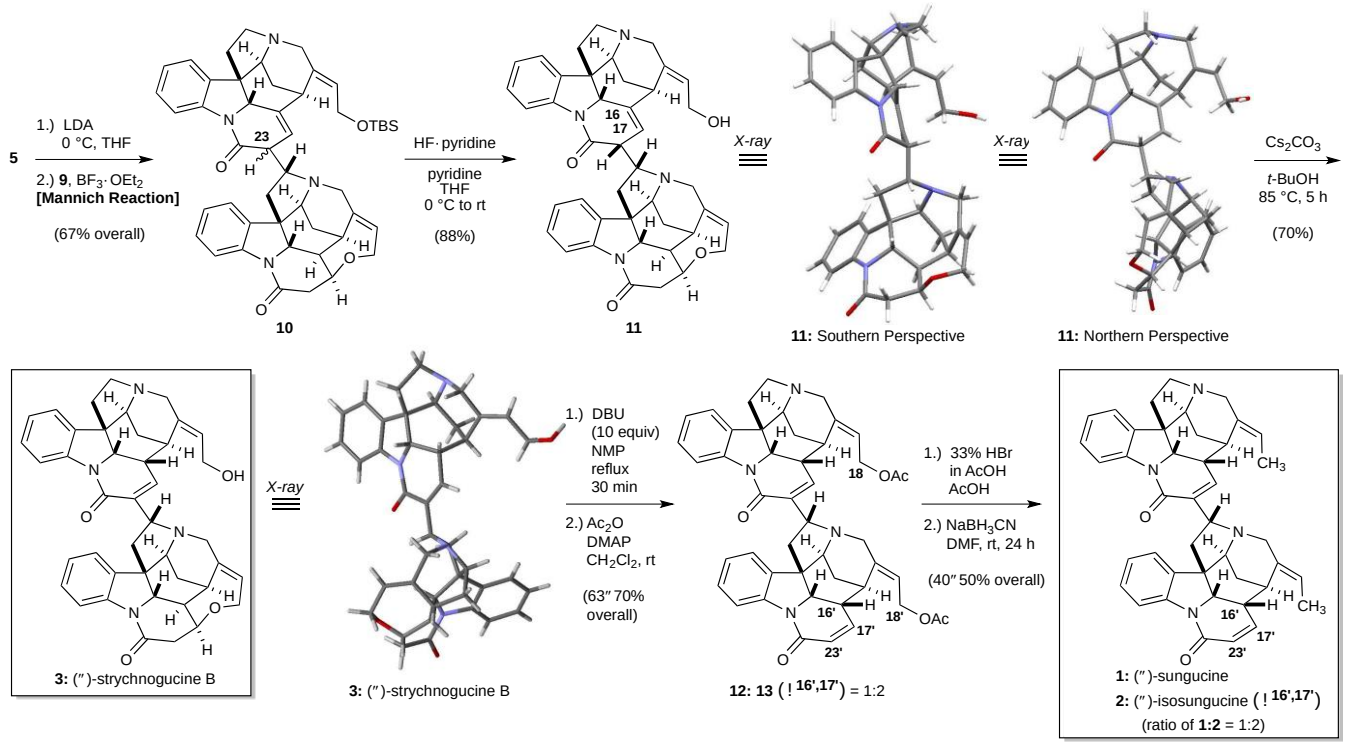


Figure 2. Charges on C and H from the natural population analysis of *N*-acyloxyammonium ion **IV**.

The mechanistic nuances between the classical Polonovski reaction (acetic anhydride, Ac_2O) and the more reactive Potier variant (TFAA) prompted us to to investigate the effect of both acylating agent and temperature on the regioselective functionalization of strychnine *N*-oxide.[13] The results of those experiments are summarized in Table 1.

Reactions with TFAA (entries 1–3) were less sensitive to temperature such that both percent conversion and ratios of **8** to



Scheme 3. Syntheses of (–)-sungucine (**1**), (–)-isosungucine (**2**), and (–)-strychnogucine B (**3**).

7 remained fairly constant. This can be rationalized by considering the nucleofugacity of trifluoroacetate, which greatly favors iminium ion formation.[13]

On the other hand, reactions with Ac_2O (entries 4–6) gave higher ratios of desired carbinolamine **8** to **7**. Moreover, they proceeded at a slower rate and required higher temperature for the conversion of starting material to products. The highest ratio of **8** to **7** (3.1:1) was obtained at 35 °C for 4 h (entry 6). These results are consistent with an E2 mechanism whereby the more basic acetate can remove the *anti*-periplanar C5□H_b from an *N*-acyloxyammonium strychnine intermediate (Figure 1) to afford the desired carbinolamine **8**.

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

Entry	Acylating Agent[a]	Temperature (°C)	Time (hours)[b]	Percent Conversion[c]	Ratio of **7** to **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 using CH_2Cl_2 as solvent.
[b] Iminium ion was trapped with aqueous KOH after 2 or 4 hours.
[c] Percent conversion calculated by ^{1}H NMR.
[d] Ratio of **7** to **8** determined by ^{1}H NMR.

With both northern and southern fragments in hand, we focused on forging the characteristic C23–C5' bond in **1**–**3** using a biomimetic Mannich reaction.[14] After considerable experimentation with various metalation conditions of **5** and screening Lewis acids, we were pleased to find favorable conditions for the Mannich-mediated fragment coupling of **5** and **9**. In the event, **5** was first treated with LDA to generate the lithium enolate (Scheme 3). Addition thereof to the iminium derived from BF_3•Et_2O-treatment of **9** smoothly delivered **10** as a mixture of diastereomers at C23.[15] Subsequent treatment of **10** with HF•Pyridine served to remove the TBS group and effect equilibration at C23 to afford **11** as a single diastereomer; moreover, X-ray analysis of **11** confirmed the stereo- and regiochemical course of the transformations.

The synthesis of (–)-strychnogucine B (**3**) required olefin isomerization from the trisubstituted C16–C17 position into conjugation with the carbonyl. Fortuitously, Magnus had reported a similar reaction during early synthetic studies toward strychnine.[16] Thus, treatment of **11** with Cs_2CO_3 in deaerated *tert*-butanol at 85 °C furnished (–)-strychnogucine B (**3**) in 70% yield. Spectral data for **3** (e.g., ^{1}H and ^{13}C NMR, IR) were in complete agreement with those reported in the literature.[4b]

The syntheses of (–)-sungucine (**1**) and (–)-isosungucine (**2**) from (–)-**3** required two tasks: (1) rupture of the oxepene ring in the southern portion of (–)-strychnogucine B and (2) global deoxygenation of the attendant hydroxyethylidene moieties. The first task was addressed by employing tactics used for northern fragment **5**. Successful execution thereof would deliver two alkene regioisomers (i.e., conjugated and nonconjugated) that map onto **1** and **2**, respectively. In the event, (–)-strychnogucine B (**3**) was first treated with DBU in NMP at 200 °C to afford two bis-diols as a mixture of alkene regioisomers. Subsequent acetylation of this mixture with acetic anhydride to facilitate purification yielded **12** and **13** in a ratio of 1:2 (63–70% overall yield).

Endgame for the syntheses of **1**–**2** called for adjusting the oxidation states at C18 and C18' in **12**–**13**. We screened a battery of deoxygenation protocols (e.g., Pd-catalyzed deoxygenation,[17] MsCl/$LiEt_3BH$,[18] thiocarbonyl di-imidazole/Bu_3SnH),[19] but none yielded satisfactory results. Success was ultimately realized by first converting the allylic acetates into their corresponding bromides under acidic conditions and subsequent reduction with $NaBH_3CN$ in DMF.[20] Thus, a mixture of **12** and **13** was treated sequentially with 33%

HBr followed by $NaBH_3CN$ to furnish (–)-sungucine (**1**) and (–)-isosungucine (**2**) in 40–50% overall yield following chromatographic separation. Spectra data for **1** and **2** (e.g., ^1H and ^{13}C NMR, IR) were in complete agreement with the reported values.[1,4]

In summary, we have completed the first syntheses of (–)-sungucine (**1**), (–)-isosungucine (**2**), and (–)-strychnogucine B (**3**) from commercially available (–)-strychnine (**4**). Key steps included (1) a DBU-mediated synthesis of isostrychnine from **4**; (2) the Polonovski–Potier reaction of strychnine *N*-oxide; (3) a BF_3•Et_2O-mediated, biomimetic Mannich coupling; (4) a Cs_2CO_3-mediated alkene isomerization; and, (5) a $NaBH_3CN$-mediated reduction of allylic bromides intermediates to install the requisite ethylidene moieties found in targets **1**–**3**.

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Keywords: sungucine • bis-*Strychnos* alkaloids • Polonovski–Potier • biomimetic synthesis • strychnine

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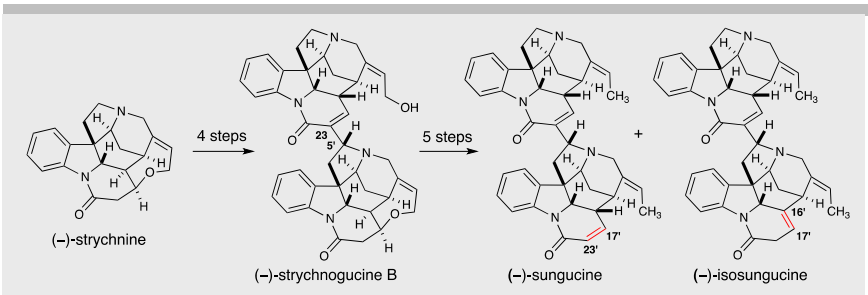

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Page No. – Page No.

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