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A New Approach to the Synthesis of the Strychnos Alkaloids Core Structure

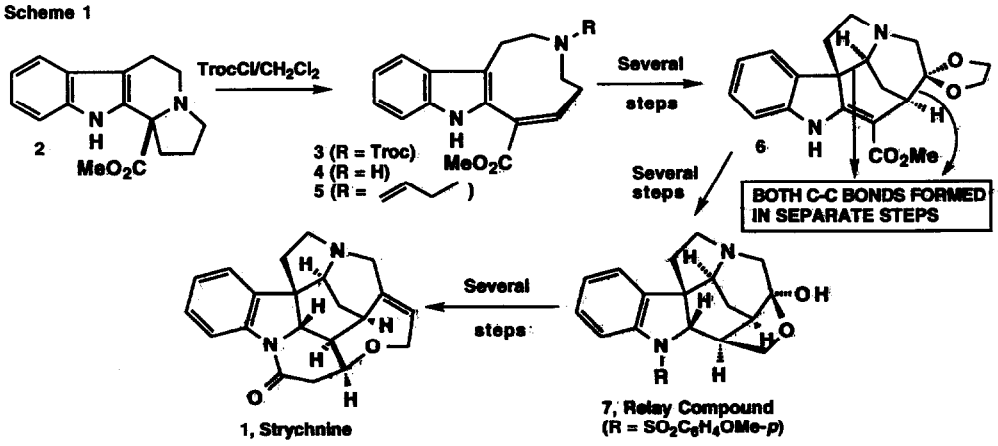
Philip Magnus* and Melvyn Giles

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

Abstract: The nine-membered ring sec-amine **4** reacts with methyl propiolate/sodium hydride in toluene at reflux to give the strychnos core structure **12** in a single step.

We recently reported the synthesis of strychnine **1** *via* the relay compound **7**.[1] The overall strategy, outlined in **Scheme 1**, involved the chloroformate induced cleavage of the tetracyclic amine **2** to give the nine-membered ring carbamate **3**, and deprotection to give **4** followed by several steps to give the core skeleton **6**. The indicated C-C bonds in compound **6** are made in separate steps. The synthesis was completed by conversion of **6** into **7**, which was also available by degradation of strychnine. Finally, **7** was converted into strychnine *via* the Wieland-Gumlich aldehyde.[2] While this work was in progress Kuehne reported that the same nine-membered *sec*-amine **4** on treatment with *n*-butanal formed the enamine **5** which at room temperature underwent intramolecular [2+4] cycloaddition to the indole 2-acrylate to give the strychnos alkaloid tubotaiwine.[3]

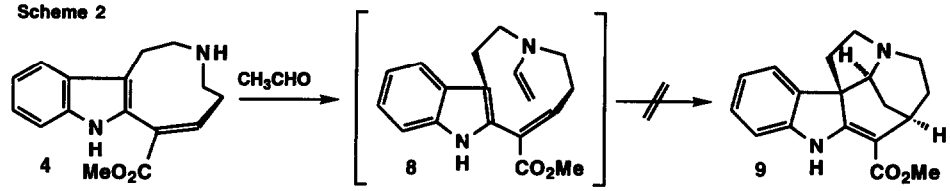
Scheme 1



This offers an extremely rapid and elegant entry into the strychnos skeleton and we were interested to try the Kuehne strategy to simplify the synthesis of

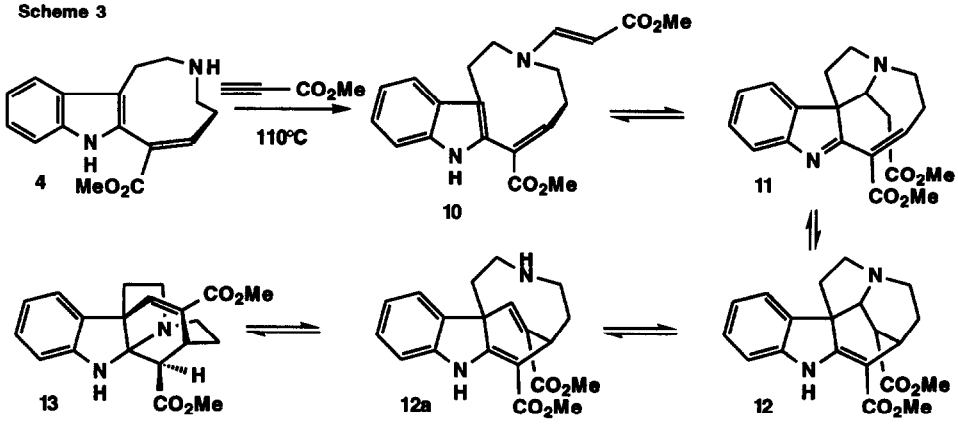
strychnine. Treatment of the *sec*-amine **4** with acetaldehyde gave a complex mixture of products that did not contain any of the required β-amino acrylate adduct **9** [characteristic UV (MeOH) [$\lambda_{max}(\varepsilon)$] 323.3 (12,900)]. The use of acetaldehyde equivalents such as ethyl vinyl ether, vinyl acetate, vinyl imidazole and N-vinyl pyrrolidine did not improve the situation. Consequently, it was decided to examine the reaction of **4** with electron-deficient acetylenes.

Scheme 2



Treatment of **4** with methyl propiolate in dichloromethane at room temperature gave the conjugate addition adduct **10** (90%). Heating the adduct **10** in toluene at reflux in the presence of trimethylsilyl triflate gave the rearranged compound **13** in low yield (structure by X-ray). The same reaction at room temperature gave the intermediate **11** (92%). Presumably **13** is formed by further reaction of **11** to give **12**, which can β-eliminate to the 1,4-cyclohexadiene **12a** and add the liberated *sec*-amine functionality to the β-aminoacrylate, resulting in **13**.

Scheme 3

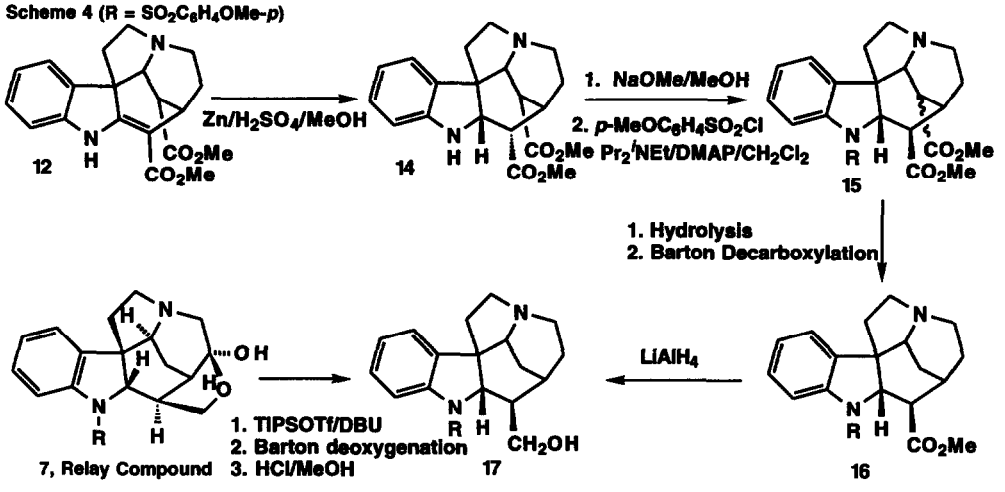


Fortunately, we discovered that treatment of **10** with sodium hydride in toluene heated at reflux gave the required adduct **12** (61%). The success of these reaction conditions may be attributed to the formation of **12** as its sodium salt, effectively prohibiting further transformation into **13**. A similar sequence of reactions was attempted using phenylethnylsulfone but the initial conjugate addition

adduct (cf. **10**) did not react further, consequently we had to distinquish between the two ester groups in **12**.

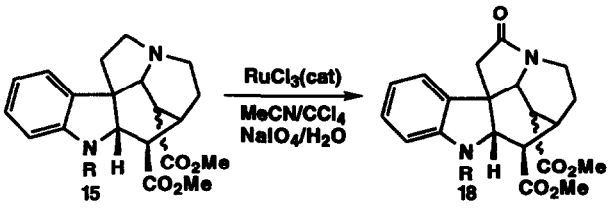
Reduction of the β-aminoacrylate double bond with Zn/H_2SO_4/MeOH gave **14**, which was epimerized and the indoline nitrogen protected as its *p*-$MeOC_6H_4SO_2$- derivative **15** (85%, from **12**). Treatment of **15** with LiOH/MeOH/THF (56%) followed by Barton decarboxylation[4] ((DBU/Pr^{i}COCl/N-hydroxypyridine-2-thione, hv/Bu^{t}SH) gave **16** (76%). Its structure was confirmed by reduction to the alcohol **17** and comparison with an authentic sample made from the relay compound **7** by silylation, deoxygenation[5] and hydrolysis (16% overall).

Scheme 4 (R = $SO_2C_6H_4OMe$-*p*)



We were interested to see if either **15** and/or **16** could be selectively oxidized adjacent to the *t*-amine and provide a possible handle to attach the hydroxyethylidene group. A number of reagents are available that can oxidize amines to amides *via* the iminium ion.[6] Treatment of **15** with $RuCl_3$ (cat)/$NaIO_4$ gave the five-membered ring amide **18** (50%).[7] Under the same oxidation conditions **16** gave a very complex mixture of products. Attempts to use the alcohol **17** to direct intramolecular functionalization [$Pb(OAc)_4/I_2$ etc] resulted in complex mixtures with no evidence for any functionalization either α- or β- to the *t*-amine.

Scheme 5 (R = $SO_2C_6H_4OMe$-*p*)



In summary, this strategy offers a very direct route into the strychnos alkaloid skeleton, and may be modified by introducing more functionality into the starting amine **2**. The tetracyclic amine **2** is available from a Pictet-Spengler cyclization of tryptamine and dimethyl-2-ketoglutarate followed by reduction of the amide group.[8]

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References and Footnotes.

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