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ALKALOID SYNTHESIS VIA THE INTRAMOLECULAR IMIDATE METHYLIDE 1,3-DIPOLAR CYCLOADDITION REACTION

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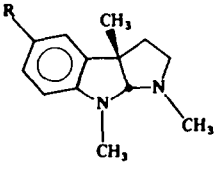
Abstract—A concise synthesis for the neurotoxic physostigmine alkaloid *d,l*-eserethole is described which relys upon an intramolecular cycloaddition reaction involving a "non-stabilized" imidate methylide and an unactivated alkene. The facility of this cyclization is enhanced by the rigid alignment inforced upon the dipole and dipolarophile by their *ortho*-disposition on an aryl nucleus. The synthetic limitations of this annulation method were revealed in an attempted synthesis of the erythrina skeleton. In this instance, prototropic rearrangement of the imidate methylide to the isomeric enamine occurred to the exclusion of the desired cyclization reaction.

An expedient synthesis of the physostigmine skeleton

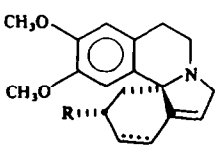
The general utility of intramolecular 1,3-dipolar cycloaddition reactions for the synthesis of naturally occurring heterocycles has become well established over the last several years. Recently we embarked upon an investigation which had, as its goal, the development of methods for the generation of *non-stabilized* imidate methylides and the subsequent utilization of these species in the above context. In principle, 1,3-dipolar cycloaddition reactions between an imidate methylide moiety and a strategically situated dipolarophile should facilitate the elaboration of numerous naturally occurring ring systems (e.g. **1** → **2**). The alkaloids belonging to the physostigmine and erythrina subgroups were envisaged as appropriate initial targets to probe the synthetic practicality associated with this process.[1]

1 **2**

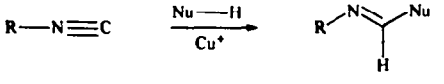
Physostigmine **3a**, one of the major alkaloid components of the calabar bean (*Physostigma venenosum* Balf) has been shown to inhibit acetylcholinesterase at low concentrations.[2] In addition to exhibiting a powerful myotic action, this substance has recently been shown to reverse the toxic effects resulting from diazepam overdose.[3] The potent curariform activity of Erythramine **4a** has stimulated a renewed interest in the pharmacology of this alkaloid. This activity has been attributed to the inhibition of cholinergic transmission in the brain and spinal cord.[4]



3a: R = O NCH$_3$
3b: R = OC$_2$H$_5$
3c: R = H



4a: R = OCH$_3$
4b: R = H, $\Delta^{1,2}$ = H$_2$

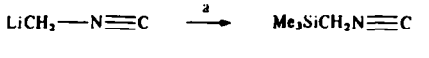


5 **6**

Scheme 1.

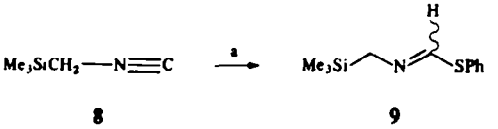
Our initial investigations directed toward the synthesis of these alkaloids focused on the development of practical methods for the generation of transient imidate methylides. The intriguing propensity of organic isonitriles to undergo terminal insertion with protic nucleophiles[5,6] (Scheme 1) bears particular relevance to the above objective.

The requisite isocyanide **8** was readily prepared on a multigram scale by quenching lithiomethyl isocyanide (**7**) with 2 equiv of chlorotrimethylsilane.[7]



7 **8**

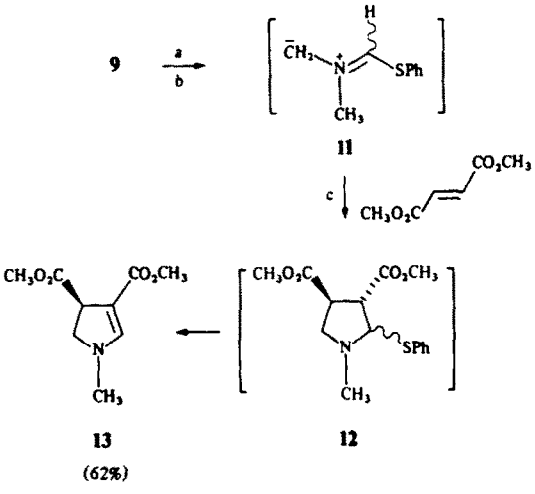
(a) Me_3SiCl (2 equiv), $CH_3OCH_2OCH_3$.



8 **9** (96%)

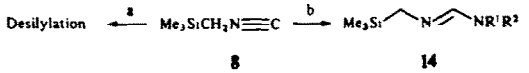
(a) PhSH, Cu(acac)$_2$.

The ability of the isonitrile **8** to serve as a progenitor for non-stabilized imidate methylides was demonstrated in the following manner. Exposure of the isonitrile **8** to thiophenol (1 equiv, 50°, 3 hr) in the presence of a catalytic quantity of Cu(acac)$_2$ furnished the thioformimidate **9** in 96% yield. The conversion of thioformimidates such as **9** into the corresponding dipolar methylides proved experimentally straightforward as evidenced by the following example.[8a,b] Treatment of **9** with 1 equiv of iodomethane (CH_3CN, 25°, 16 hr) followed by the addition of dimethyl fumarate (1.1 equiv) and cesium fluoride (2.5 equiv) afforded the pyrroline **13** in 62% yield. Presumably **13** arose via elimination of thiophenol from the initially formed pyrrolidine **12**.[9]



(a) CH_3I, CH_3CN. (b) CsF.

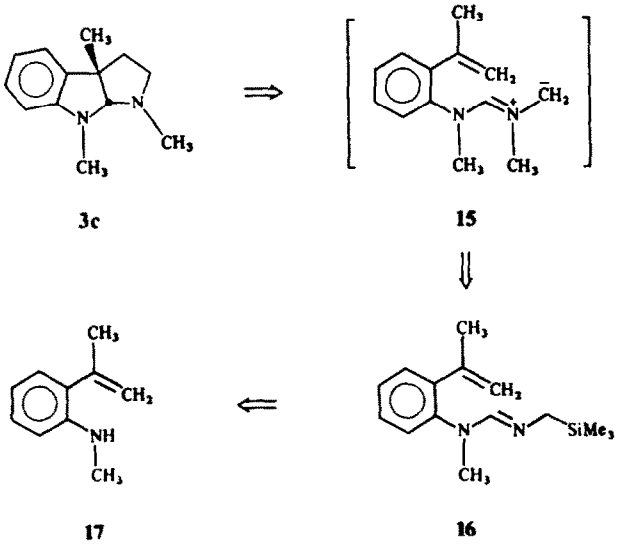
In contrast to the observed facile conversion of the isonitrile **8** into thioformimidates by thiol treatment, the corresponding terminal insertion reactions between **8** and other protic nucleophiles proved somewhat problematic. Accordingly, efforts to effect the conversion of **8** to imidates via exposure to alcohols under a variety of experimental conditions led only to the formation of products resulting from desilylation. Indeed, several initial attempts to utilize **8** for the synthesis of trimethylsilylmethylformamidines by terminal amine insertion also gave rise to partial desilylation. Fortunately it was found that the reactions of the isocyanide **8** with numerous simple amines cleanly afforded the corresponding formamidines in high yield (e.g. **8** → **14**) when mediated by *cuprous chloride.*



(a) ROH, Cu^+. (b) R_1R_2NH, CuCl (cat.).

Having established the experimental feasibility of converting trimethylsilylmethyl isocyanide (**8**) into simple heteroatom substituted imidate methylides of type **11**[10] we directed our efforts to the utilization of this methodology for the synthesis of the physostigmine ring system present in deoxyeseroline (**3c**). Conceivably, this objective could be realized as depicted retrosynthetically in Scheme 2.

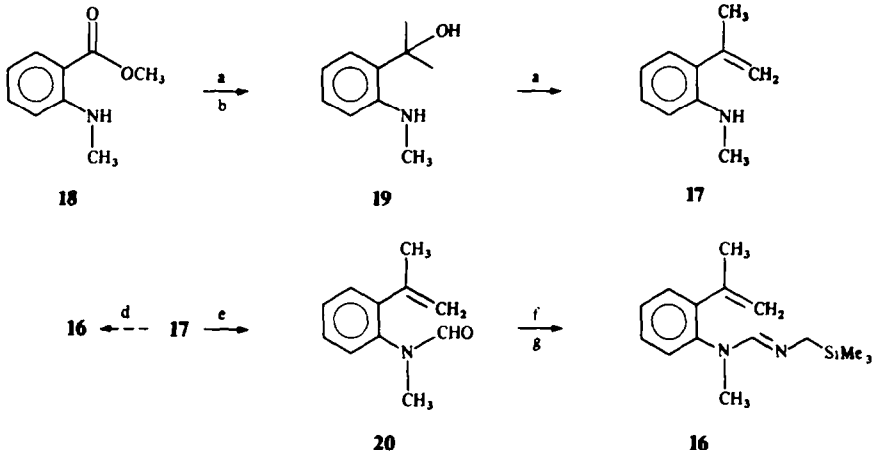
The requisite aminostyrene **17** for the preparation of deoxyeseroline (**3c**) by way of the foregoing plan was prepared in two steps (73% overall yield) from methyl N-methylanthranilate (**18**).[11] Treatment of the ester **18** with excess methyllithium (3.5 equiv, 0–25°, 30 min) afforded the aminoalcohol **19** in 93% yield. Dehydration of **19** was conveniently accomplished by thermolysis at 250° in the absence of catalyst to provide the aminostyrene **17** in 78% yield. Unfortunately, numerous efforts intended to effect the conversion of **17** directly into the desired formamidine **16** by reaction with trimethylsilylmethyl isocyanide (**8**) in the presence of cuprous chloride or under a variety of alternative experimental conditions met with little success. The sterically congested nature of the amine moiety present in **17** was deemed responsible for the observed lethargy of this compound in the isocyanide insertion reaction. An alternative pathway was sought for the conversion of **17** to the formamidine **16**. The amination procedure described by Meyers and Ten Hoeve[12] for the conversion of formamides to formamidines was envisaged as a viable option. Initial attempts to convert **17** to the corresponding formamide via the agency of either formic acetic anhydride or refluxing ethyl formate furnished only recovered starting material. These failures were again attributed to the low reactivity of the sterically hindered amine moiety in **17**. In accordance with this assertion, complete formylation of **17** could be achieved only after prolonged heating in the presence of excess n-butyl formate (108°, 96 hr). With the unsaturated formamide **20** in hand, the preparation of the requisite formamidine **16** proved experimentally straightforward. Sequential O-methylation of **20** (1 equiv $CH_3O_3SCF_3$, 25°) followed



Scheme 2.

by the addition of trimethylsilylmethylamine provided **16** in 71% overall yield after column chromatography.

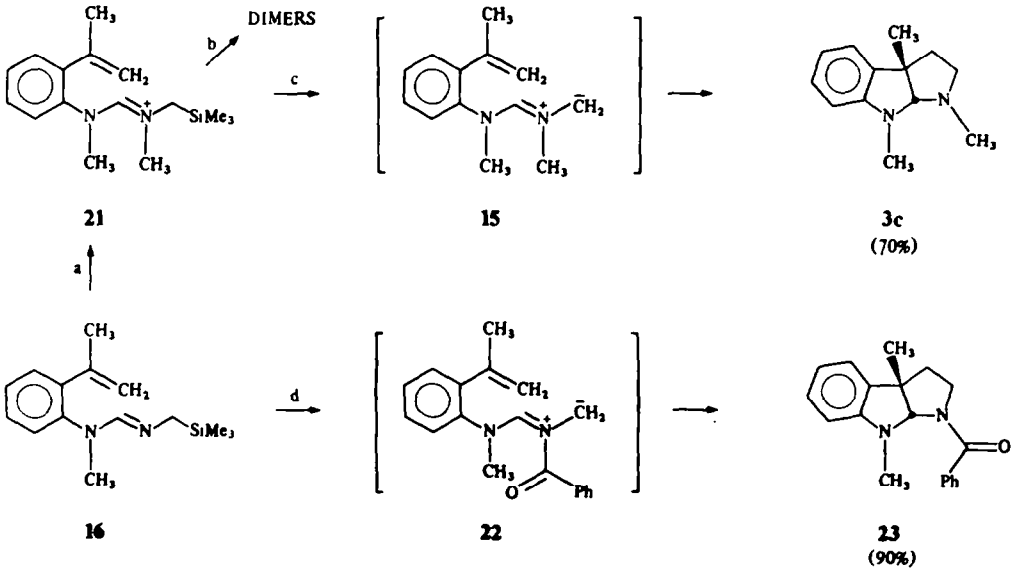
A previous report from this laboratory has disclosed a direct method for the generation of N-acylimidate



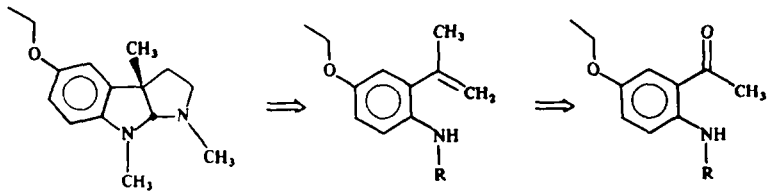
(a) $2CH_3Li$. (b) NH_4Cl. (c) 250°. (d) Me_3SiCH_2NC, CuCl. (e) n-BuOCHO, 108°. (f) $CH_3O_3SCF_3$. (g) $Me_3SiCH_2NH_2$.

The final assault on deoxyeseroline (**3c**) was implemented in the following manner. Methylation of the formamidine nitrogen was most readily accomplished with methyl trifluoromethanesulfonate (1.0 equiv, CH_2Cl_2, 25°). To our dismay, preliminary attempts to cleanly generate the transient methylide **15** and effect its intramolecular cyclization onto the pendent styrene moiety via the agency of cesium fluoride led only to the formation of dimers and other undesired products. It was subsequently discovered that slow addition of a solution of the methylformamidinium trifluoromethanesulfonate **21** via a mechanical syringe to a suspension of cesium fluoride in 1,2-DME maintained at 50° cleanly afforded deoxyeseroline (**3c**) in 70% yield. Interestingly, none of the corresponding *trans* isomer could be isolated from the reaction mixture.[13]

methylides and the subsequent utilization of these species *in situ* for the synthesis of pyrrolidine derivatives.[10] We felt that the examination of this methodology in an intramolecular context deserved exploration. To this end, it was revealed that the slow addition of a solution of the formamidine **16** via a mechanical syringe to benzoyl fluoride (1.1 equiv) in acetonitrile maintained at 45° furnished the anticipated tricyclic amide **23** in 90% yield after recrystallization. The physostigmine alkaloids bearing a 5-O substituent have attracted considerable attention largely as a result of the diverse spectrum of biological activities these compounds exhibit.[14] In principle, these alkaloids should be subject to efficient chemical synthesis via the foregoing methodology if convenient preparations for the requisite alkoxyaminostyrene derivatives (e.g. **24a,b**) were available. Unfortunately, previous litera-



(a) $CH_3O_3SCF_3$. (b) CsF, 1,2-DME. (c) CsF, 1,2-DME (inverse addition). (d) PhCOF, CH_3CN (inverse addition).

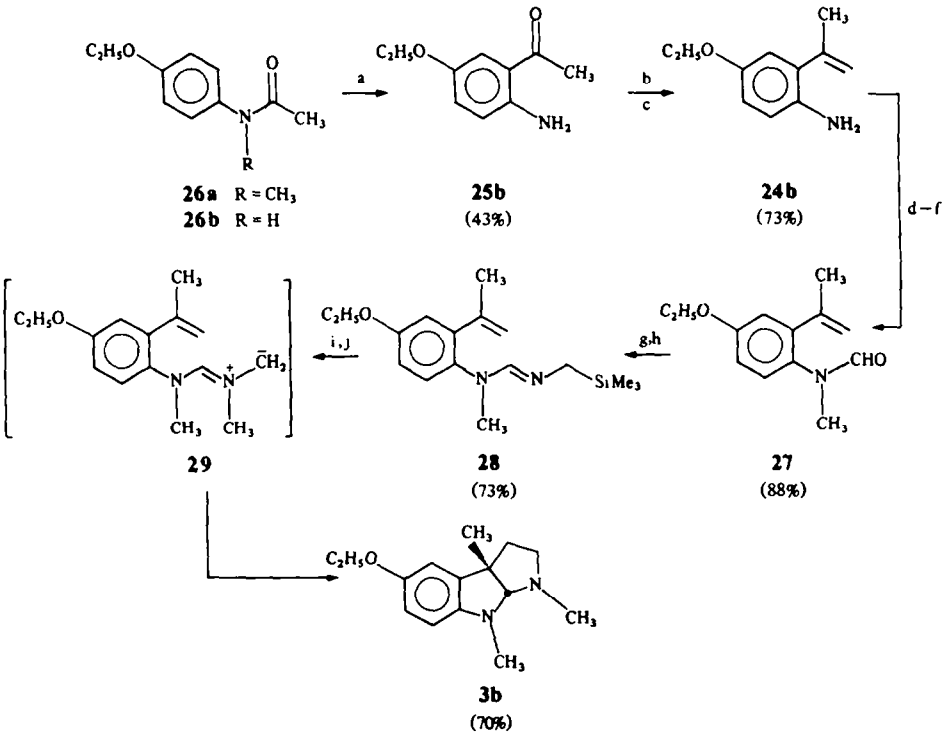


3b **24a**: R = CH_3 **25a**: R = CH_3
24b: R = H **25b**: R = H

ture preparations for the anticipated aminoacetophenone precursors **25a,b** for eserethole (**3b**) were discovered to be highly inefficient in terms of both length and overall yield. It was expected that the photochemical Fries type rearrangement[15] of the appropriate *p*-ethoxyacetanilide derivatives **26a,b** would provide direct access to these compounds. After considerable experimentation it was determined that the desired rearrangement could optimally be achieved when a 0.089 molar solution of *p*-ethoxyacetanilide **26b** in acetonitrile was irradiated at 254 nm at 25°. In this way 40–50% yields of the aminoacetophenone **25b** could reproducibly be obtained on a multigram scale. Curiously, all efforts intended to effect the analogous rearrangement of the corresponding N-methyl derivative **26a** under these or other photochemical conditions led to the quantitative recovery of unchanged starting material.

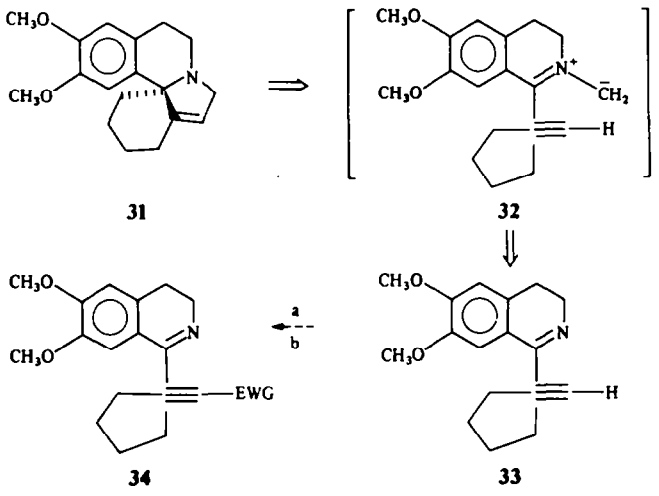
The synthesis of *d,l*-eserethole (**3b**) from the aminoacetophenone **25b** was subsequently accomplished in an exceedingly straightforward manner. Treatment of **25b** with 2 equiv of methyllithium (0–25°, 30 min) followed by thermal dehydration at 250° furnished the aminostyrene **24b** in 73% overall yield. Sequential formylation of **24b** with n-butyl formate (108°, 72 hr) followed by N-methylation [NaH (1 equiv), then CH_3I (1 equiv)] in refluxing xylene afforded the crucial formamide **27** in 88% yield.

Treatment of **27** with methyl trifluoromethanesulfonate (1.0 equiv) and subsequent amination via the agency of trimethylsilylmethylamine (1.15 equiv, 0°) provided the penultimate formamidine **28** in 77% yield after chromatography. Surprisingly, the formamidine **28** proved remarkably resilient towards alkylation. Methylation of **28** was ultimately accomplished employing 10 equiv of methyl trifluoromethanesulfonate at 25° for 12 hr. Final cyclization of the resultant formamiolinium derivative via the transient imidate methylide **29** was readily accomplished by exposure to tetra-n-butyl ammonium fluoride (45°, THF) under high dilution conditions to provide *d,l*-eserethole (**3b**) as the exclusive product in 70% overall yield. The synthetic *d,l*-eserethole prepared in this manner was determined identical in all respects (^{13}C resonance spectrum, 300 MHz proton resonance spectrum, IR spectrum, and TLC) with an authentic sample of *l*-(−)-eserethole.[16]



26a R = CH_3
26b R = H
25b (43%)
24b (73%)
29
28 (73%)
27 (88%)
3b (70%)

(a) 254 nm, CH_3CN. (b) CH_3Li. (c) 250°, $-H_2O$.
(d) *n*-BuOCHO. (e) NaH. (f) CH_3I. (g) $CH_3O_3SCF_3$.
(h) $Me_3SiCH_2NH_2$. (i) $CH_3O_3SCF_3$. (j) $Bu_4N^+F^-$.

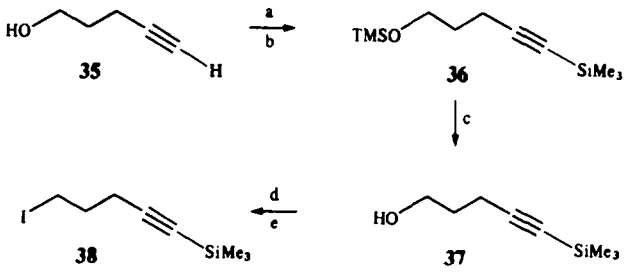


(a) LDA. (b) EWG–X

Scheme 3.

The scope and apparent limitations of intramolecular imidate methylide 1,3-dipolar cycloaddition reactions. An approach to the synthesis of the erythrina alkaloid skeleton.

The initial successes with the utilization of the intramolecular imidate methylide cycloaddition reaction for the construction of the physostigmine skeleton stimulated our efforts to extend this methodology to the synthesis of other naturally occurring ring systems. The polycondensed heterocyclic skeleton possessed by the erythrina alkaloids **31**[17] appeared an attractive challenge to probe the generality associated with this process. Conceivably, this synthetic objective could be attained as depicted retrosynthetically in Scheme 3. The entropy of activation for this intramolecular cycloaddition was predicted to be much greater than that associated with the corresponding annulation in the physostigmine series. In light of this, a terminal acetylene moiety was initially designated as the prospective dipolarophilic component. This strategy appeared compelling in that the electronic character of the acetylenic LUMO could be conveniently adjusted, if required, by the attachment of a terminal electron withdrawing auxiliary (e.g. **33** → **34**) to enhance the efficiency of the desired electrocyclic event.[18]



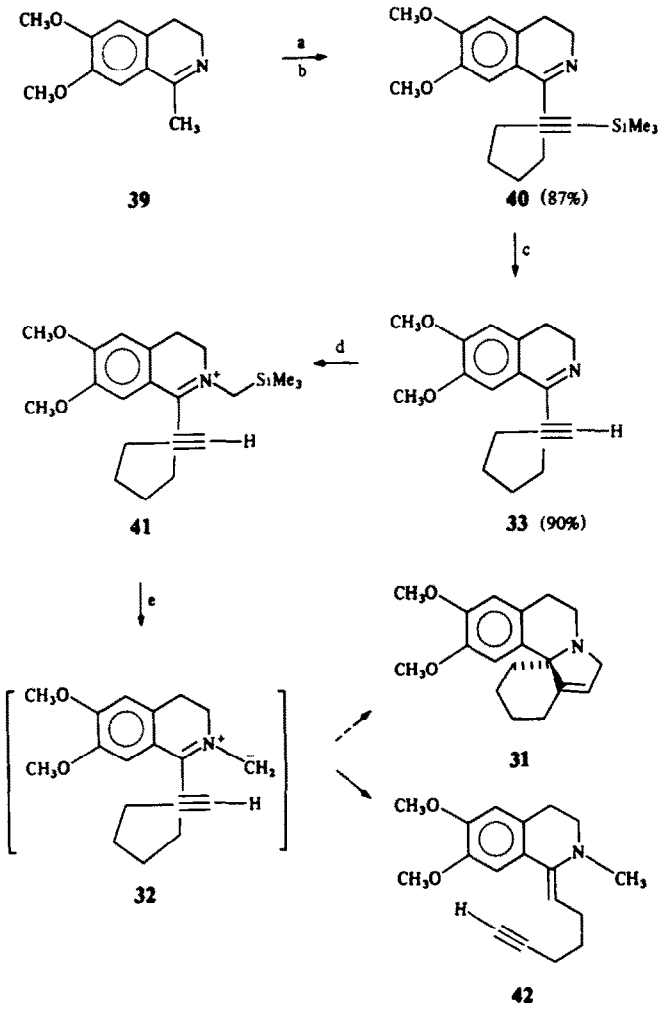
(a) BuLi. (b) Me_3SiCl. (c) K_2CO_3, CH_3OH.
(d) CH_3SO_2Cl, Et_3N. (e) NaI, acetone.

A potentially efficient synthesis of the requisite acetylenic dihydroisoquinoline precursor **33** was reduced to practice by way of the following procedure. Sequential treatment of 4-pentyn-1-ol (**35**)[19] with 2 equiv of n-butyllithium (−78° to −35°) followed by 3 equiv of chlorotrimethylsilane (−78° to 25°) afforded the silyl ether **36** in 95% yield. Exposure of **36** to potassium carbonate in methanol (0°, 45 min) and subsequent mesylation of the resultant alcohol **37** followed by displacement with iodide ion furnished the acetylene **38** in 70% overall yield. The final assembly of the intended heterocyclic precursors for the erythrina skeleton was accomplished in the following manner. Lithiation of 1 - methyl - 6,7 - dimethoxydihydroisoquinoline (**39**)[20] with lithium diisopropyl amide in the presence of HMPA (−78°, 2 hr 15 min) followed by the addition of the iodide **38** [−78° (2 hr), −20° (12 hr)] provided the acetylenic dihydroisoquinoline **40** in 87% yield.[21] Desilylation of **40** was readily effected via the agency of potassium hydroxide in aqueous methanol[22] (25°, 1.5 hr) to afford the corresponding terminal acetylane **33** in 90% yield. With the requisite dihydroisoquinoline **33** in hand, we were now in a position to test the crucial intramolecular imidate methylide cycloaddition. Alkylation of **33** was efficiently accomplished by treatment with trimethylsilylmethyl trifluoromethanesulfonate[23] to afford the crystalline dihydroisoquinolinium salt **41** (CH_2Cl_2, 25°) in quantitative yield.

Unfortunately, repeated efforts to effect the cyclization of the imidate methylide **32** generated via the fluoride ion mediated desilylation of **41** under a variety of experimental conditions furnished only the enamine **42**.

The structure of **42** was confirmed by comparison to an authentic sample prepared by the methylation of **33** ($CH_3O_3SCF_3$ 1 equiv, CH_2Cl_2, 0°) followed by triethylamine treatment. An effort to "activate" the acetylenic moiety present in **33** was made in the following manner. Lithiation of **33** with lithium diisopropylamide [−35° (1 hr), 0° (1 hr)] followed by the addition of methyl thiocyanate[24] provided the corresponding sulfide **43** in 88% yield. Regretfully, all attempts to oxidize **43** to the desired sulfone **44** led either to incomplete oxidation or competing oxidation of the imine nitrogen present in **43**. As anticipated, numerous attempts to effect the intramolecular cyclization of the imidate methylide **45** corresponding to **43** led only to the production of the exocyclic enamine **46**.[25,26]

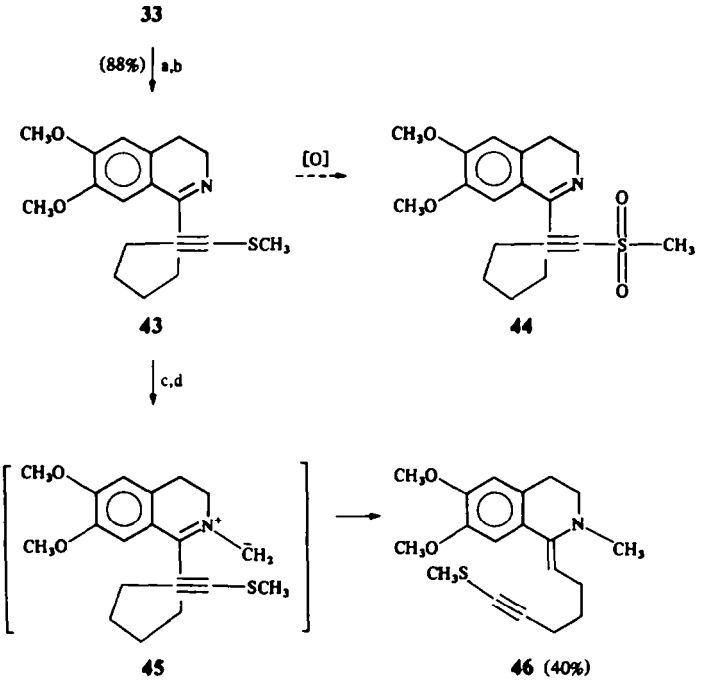
contain the pyrrolidine ring. The synthetic practicality of this methodology has been demonstrated by its successful application to the elaboration of the tricyclic physostigmine skeleton. Recently, however, several synthetic limitations inherent to imidate methylide cyclizations have become apparent. The most prominent of these involves the propensity of these species and/or their precursors to undergo enamine formation when this reaction manifold is an option. This competing and totally undesired pathway may be expected to gain particular significance in substrate molecules which require a large entropy of activation for the preliminary alignment of the pendent dipolarophile. The above tendency will assume increased importance when an electronically non-activated dipolarophile is implicated in the prospective



(a) LDA. (b) 38. (c) KOH, CH_3OH–H_2O.
(d) $Me_3SiCH_2O_3SCF_3$, CH_2Cl_2. (e) CsF, 1,2-DME (inverse addition).

CONCLUSION

Heterocycle annulations reliant upon intramolecular 1,3-dipolar cycloaddition reactions involving *non-stabilized* imidate methylides should, *in principle*, facilitate the synthesis of numerous alkaloids which synthetic approach. The development of a synthetic protocol to circumvent the foregoing difficulties via the electronic modification of the imidate methylide dipole is currently under way. Progress toward this objective will be the topic of future reports from these laboratories.



(a) LDA. (b) CH_3SCN. (c) $Me_3SiCH_2O_3SCF_3$.
(d) CsF, 1,2-DME (inverse addition).

EXPERIMENTAL

Pyrroline **13**

A 5 ml one-necked flask equipped with a magnetic stirring bar and serum cap was charged with trimethylsilylmethyl isocyanide **8**, 226 mg (2 mmol), thiophenol, 220 mg (2 mmol), and copper acetylacetonate, 10 mg, and then flushed with N_2. The mixture was then warmed to 65° and stirred at this temp for 3 hr. The mixture was subsequently cooled to 25° and diluted with dry acetonitrile, 1.5 ml. MeI, 284 mg (2 mmol) was added and the resultant soln stirred for 18 hr. Dimethyl fumarate, 317 mg (2.2 mmol) was then added and the mixture subsequently cooled to 0°. The mixture was then treated with anhyd cesium fluoride, 760 mg (5 mmol) and stirred at 25° for 13 hr. The suspension was diluted with ether–CH_2Cl_2 (1 : 1) and filtered through a bed of silica-gel, 7 g. Chromatography of the residue obtained upon evaporation of the solvent (silica gel–CH_2Cl_2–EtOAc (95 : 5) for elution) afforded 123 mg (62%) of **13** as a colorless oil. NMR ($CDCl_3$, TMS) δ 2.41 (1H, m, CH), 282 (3H, s, CH_3), 3.25 (2H, m, CH_2) 3.60 (3H, s, CH_3), 3.69 (3H, s, CH_3), 7.03 (1H, s, vinyl CH); IR (film) 2985–2760 (C—H), 1745 (C=O), 1709 cm^{-1} (C=O); high resolution mass spectrum, calc for $C_9H_{13}NO_4$, M^+ = 199.084; found M^+ = 199.084.

Alcohol **19**

A flame dried 250-ml three-necked flask equipped with a thermometer, a reflux condenser and a magnetic stirring bar was charged with methyl N-methylanthranilate **18**, 6.244 g (37.8 mmol) and dry ether, 20 ml. The resulting soln was treated with MeLi (1.45 M in ether) 78 ml (132.2 mmol) keeping the mixture below 0° with ice cooling. The mixture was refluxed for 0.5 hr, cooled to 0°, quenched with 1.3 ml of MeOH and subsequently treated with sat NH_4Cl aq, 200 ml. The mixture was then extracted with ether (250 ml) and washed successively with water, brine and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to afford the crude product. Light yellow crystals of **19**, 5.79 g (92.7% yield) were obtained upon bulb to bulb distillation of the residue (75°, 0.1 Torr). NMR δ 1.60 (6H, s, CH_3), 2.82 (3H, s, CH_3), 6.63 (2H, m, aromatic CH), 7.15 (2H, m, aromatic CH); IR (CCl_4) 3650–3250 (OH), 3080–2740 cm^{-1} (CH).

Aminostyrene **17**

An oven dried 25-ml three-necked flask equipped with an air-cooled condenser, addition funnel, and a magnetic stirring bar was heated to 250°. The alcohol **19**, 7.3 g (44.2 mmol) was added to the heated flask at a rate of 1 drop s^{-1}. After completion of addition the mixture was heated until dehydration was completed (evidenced by TLC). The amino **17** 5.072 g (78.1% yield) was used without further purification. NMR δ 2.01 (3H, s, CH_3), 2.65 (3H, s, CH_3), 5.03 (1H, dd, J = 0.5 Hz, vinyl CH), 5.27 (1H, dd, J = 0.5 Hz, vinyl CH), 6.71 (2H, m, aromatic CH), 7.12 (2H, m, aromatic CH); IR (film) 3420–3250 (NH), 3080–2700 cm^{-1} (CH). (Found: C, 81.57; H, 8.86. Calc for $C_{10}H_{13}N$: C, 81.59; H, 8.90%.)

Formamide **20**

An oven dried 100-ml round-bottom flask equipped with a reflux condenser and a magnetic stirring bar was charged with the amine **17**, 5.072 g (34.5 mmol) and n-butyl formate 50 ml. The mixture was stirred under reflux for 96 hr. The n-butyl formate was removed *in vacuo* and the residue purified by bulb to bulb distillation (110°, 0.1 Torr) to give **20** as a light yellow oil 5.83 g (96.1% yield). NMR δ 1.98 (3H, s, CH_3), 3.19 (3H, s, CH_3), 5.02 (1H, dd, J = 0.5 Hz, vinyl CH), 5.21 (1H, dd, J = 0.5 Hz, vinyl CH), 7.22 (4H, m, aromatic CH), 8.18 (1H, s, formamide CH); IR (film) 3080–2740 (CH), 1670 cm^{-1} (C=O).

Formamidine **16**

An oven dried 10-ml round-bottom flask equipped with a magnetic stirring bar was charged with **20**, 1.63 g (9.3 mmol), CH_2Cl_2, 5 ml, and methyl trifluoromethanesulfonate, 1.33 ml (11.2 mmol). The mixture was then stirred for 4 hr at 25°. The soln was cooled to −20°, treated with a Et_3N, 0.28 ml (2.0 mmol) and trimethylsilylmethylamine 1.18 g (11.2 mmol). The mixture was stirred for 0.5 hr at −20° and subsequently treated with 10% KOH aq, 15 ml and extracted with benzene, 30 ml. The organic layer was washed successively with water, brine and then dried over $NaSO_4$. After filtration, the solvents were removed *in vacuo* and the residue submitted to reverse phase column chromatography (10% MeOH: 90% ac-

etonitrile for elution). The formamidine **16**, 1.74 g (72% yield) was obtained after concentration of the fractions and evaporative distillation. NMR δ 0.09 (9H, s, CH_3), 1.83 (3H, s, CH_3), 2.80 (2H, s, CH_2), 3.00 (3H, s, CH_3), 4.86 (1H, dd, J = 0.5 Hz, vinyl CH), 4.98 (1H, dd, J = 0.5 Hz, vinyl), 6.75 (2H, m, aromatic CH), 7.22 (2H, m, aromatic), 7.98 (1H, s, CH); IR (film) 3080–2740 (CH), 1640 cm^{-1} (C=N). (Found: C, 69.27; H, 9.40. Calc for $C_{15}H_{24}N_2Si$: C, 69.18; H, 9.29%.)

Deoxyeseroline **3c**

An oven dried 5-ml round-bottom flask equipped with a magnetic stirring bar was charged with tetra-n-butylammonium fluoride, 0.5 g (1.9 mmol), dry tetrahydrofuran 3 ml and 4 Å molecular sieves, 1.0 g. The flask was flushed with N_2, stoppered with a serum cap and heated to 50°. The formamidine **16**, 148 mg (0.57 mmol) was methylated by treatment with methyl trifluoromethanesulfonate, 93.5 mg in CH_2Cl_2, 1 ml for 12 hr at −20°. After removal of the CH_2Cl_2 the residue was dissolved in 1,2-DME, 0.75 ml. The resulting soln was added via a mechanical syringe to the tetra-n-butylammonium fluoride soln over 3.5 hr. The mixture was stirred for 12 hr at 50°, treated with sat K_2CO_3 aq, 20 ml and extracted with ether, 30 ml. The organic layer was sequentially washed with water, brine and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the residue submitted to column chromatography on silica gel (EtOAc–hexene 1:1 for elution). Deoxyeseroline **3c**, 81 mg (70% yield) was obtained on concentration of the fractions followed by evaporative distillation. 300 MHz NMR δ 1.35 (3H, s, CH_3), 1.90 (2H, m, J = 5.4, 7.3, 9.1, CH_2), 2.48 (3H, s, CH_3), 2.63 (2H, m, J = 5.4, 7.3, 9.1, CH_2), 2.90 (3H, s, CH_3), 4.08 (1H, s, CH), 6.40 (1H, m, aromatic CH), 6.8 (1H, m, aromatic CH), 7.00 (1H, m, aromatic CH), 7.10 (1H, m, aromatic CH), 300 MHz ^{13}C 27.22, 36.29, 38.77, 40.67, 52.56, 53.14, 97.44, 106.43, 117.42, 122.01, 127.54, 136.47, 151.70; mass spectrum, *m/e* 202, M^+ = 158; IR (film) 3080–2840 (CH), 1620 cm^{-1} (C=C).

Tricyclic amide **23**

An oven dried 5-ml round-bottom flask equipped with a magnetic stirring bar was charged with benzoyl fluoride, 58.1 mg (0.46 mmol) and dry acetonitrile, 1.0 ml. The flask was flushed with N_2, stoppered with a serum cap, and heated to 45°. A soln of **16**, 124 mg (0.46 mmol) in dry acetonitrile 0.5 ml was added via a mechanical syringe to the benzoyl fluoride solution over 2 hr. The mixture was stirred at 45° for an additional 12 hr and subsequently diluted with water, 10 ml and extracted with ether, 20 ml. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the residue submitted to column chromatography (35% EtOAc–65% hexane for elution). The amide **23**, 121 mg (90% yield) was obtained upon concentration of the fractions. 300 MHz NMR δ 1.43 (3H, s, CH_3), 300 (3H, s, CH_3), 3.22 (2H, m, J = 5.6, 7.0, 8.9, CH_2), 5.65 (1H, s, CH), 6.40 (1H, m, aromatic CH), 6.80 (1H, m, aromatic CH), 7.3 (7H, m, aromatic CH); IR ($CDCl_3$) 1670 cm^{-1} (C=C); mass spectrum, *m/e* (292), M^+ (105).

Aminoacetophenone **25b**

A 2-l photowell was charged with **26b**, 18.6 g (104 mmol) and dry acetonitrile, 1.2 l and N_2 was bubbled through the soln for 0.5 hr. The mixture was irradiated at 254 nm for 25 hr. The acetonitrile was then removed *in vacuo* leaving a black viscous residue. The residue was washed with hot hexane, 3 × 200 ml. The hexane was removed *in vacuo* and the crystalline residue was submitted to column chromatography on activity III alumina (hexane–EtOAc, 3:1 for elution). Aminoacetophenone **25b**, 8.6 g (43% yield) was obtained as yellow crystals (m.p. 89–91°) upon concentration of the fractions. NMR δ 1.32 (3H, t, J = 7.6 Hz, CH_3), 2.42 (3H, s, CH_3), 3.88 (2H, t, J = 7.6 Hz, CH_2), 6.54 (2H, m, aromatic CH), 6.79 (1H, m, aromatic CH), 7.04 (1H, m, aromatic CH); IR (CCl_4) 3450–3250 (NH), 3070–2820 (CH), 1705 cm^{-1} (C=O).

Aminostyrene **24b**

A flame dried 100-ml round-bottom flask equipped with a magnetic stirring bar was charged with **25b**, 1.635 g (8.52 mmol) and dry THF, 40 ml. The resulting soln was cooled to −78° and MeLi (1.50 M in ether) 1.75 ml (26.3 mmol) was slowly added by syringe. The resulting mixture was heated at reflux for 0.5 hr. After cooling to 0°, MeOH, 2.0 ml was added followed by sat NH_4Cl aq, 50 ml and the mixture was extracted with ether, 75 ml. The organic layer was washed successively with water, brine, and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to afford the crude product as a dark yellow oil. The tertiary alcohol, 1.55 g (93.0% yield) was obtained upon bulb to bulb distillation of the residue (85°, 0.1 Torr). NMR δ 1.32 (3H, t, J = 7.6, CH_3), 1.60 (6H, s, CH_3), 3.88 (2H, q, J = 7.6 Hz, CH_2), 3.70 (2H, broad s, NH_2), 6.73 (2H, m, aromatic CH), 6.98 (1H, s, aromatic CH); IR (CCl_4) 3650–3250 (OH), 3080–2800 cm^{-1} (CH). The material obtained in this way was used directly for the next step. (Found: C, 67.58; H, 8.52. Calc for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78%.)

An oven dried 25-ml three-necked flask equipped with an air-cooled condenser, addition funnel, and a magnetic stirring bar was heated to 250°. The tertiary alcohol, 1.55 g (7.95 mmol) was added to the heated flask at a rate of 1 drop s^{-1}. After completion of the addition the mixture was heated until dehydration was completed (evidenced by TLC). The aminostyrene **24b**, 1.03 g (73% yield) was used without further purification. NMR δ 1.32 (3H, t, J = 7.6 Hz, CH_3), 1.98 (3H, s, CH_3), 3.49 (2H, broad s, NH), 3.88 (2H, q, J = 7.6 Hz, CH_2), 4.91 (1H, m, J = 0.5 Hz, vinyl CH_2), 5.13 (1H, m, J = 0.5 Hz, vinyl CH_2), 6.60 (3H, s, aromatic CH); IR (film) 3450–3250 (NH), 3080–2780 cm^{-1} (CH); high resolution mass spectrum, calc for $C_{11}H_{15}NO$ M^+ = 177.1154; found M^+ = 177.1160.

N-*Methylformamide* **27**

An oven dried 50-ml round-bottom flask equipped with a reflux condenser and magnetic stirring bar was charged with **24b**, 1.03 g (5.82 mmol), n-butyl formate 25 ml, and the mixture stirred under reflux for 72 hr. The excess n-butyl formate was removed *in vacuo* and the crude formamide precipitated by addition of hexane. The secondary formamide was collected by filtration and used without further purification. A purified sample was submitted for chemical analysis. (Found: C, 70.30; H, 7.35. Calc for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37%.)

A flame dried 25-ml three-neck flask equipped with a reflux condenser, addition funnel and magnetic stirring bar was charged with NaH, 31.5 mg (60% oil dispersion, 0.79 mmol) and toluene, 5 ml. The crude formamide obtained as above, 0.136 mg (0.66 mmol) dissolved in toluene, 3 ml was added dropwise and the mixture was then stirred until H_2 evolution ceased. MeI, 937 mg (6.6 mmol) was added and the mixture stirred under reflux for 2 hr. The hot soln was filtered and the toluene removed *in vacuo*. The residue was submitted to flash chromatography on silica gel (hexane–EtOAc 3:2 for elution) to provide **37**, 127 mg (88% yield). NMR δ 1.32 (3H, t, J = 7.6 Hz, CH_3), 1.98 (3H, s, CH_3), 3.02 (3H, s, CH_3), 3.88 (2H, t, J = 7.6 Hz, CH_2), 4.91 (1H, m, J = 0.5 Hz, vinyl CH_2), 5.13 (1H, m, J = 0.5 Hz, vinyl CH_2), 6.73 (2H, m, aromatic CH), 7.98 (1H, m, aromatic CH), 7.99 (1H, s, CH); IR (film) 3080–2740 (CH), 1670 cm^{-1} (C=O). (Found: C, 70.96; H, 7.60. Calc for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81%.)

Formamidine **28**

An oven dried 5-ml round-bottom flask equipped with a magnetic stirring bar was charged with **27**, 127 mg (0.58 mmol), methyl trifluoromethenesulfonate, 0.6 ml (5.0 mmol) and the mixture was stirred for 3 hr. The excess methyl trifluoromethenesulfonate was removed *in vacuo* at 100 μm. The residue was diluted with 1 ml of CH_2Cl_2 and treated with trimethylsilylmethylamine, 0.075 ml (0.70 mmol). The mixture was then stirred at −20° for 0.5 hr and subsequently treated with KOH aq, 5 ml and extracted with ether, 10 ml. The organic layer was washed with water, brine, and dried over Na_2SO_4. The residue was submitted to column chromatography on silica gel (EtOAc for elution) to give **28**, 122 mg (73% yield) as a

yellow oil. NMR δ 0.09 (9H, s, CH_3), 1.32 (3H, t, J = 7.6, CH_3), 1.83 (3H, s, CH_3), 2.80 (2H, s, CH_2), 3.0 (3H, s, CH_3), 3.88 (2H, q, J = 7.6 Hz, CH_2), 4.86 (1H, m, J = 0.5 Hz, vinyl CH_2), 6.75 (2H, m, aromatic CH), 7.22 (1H, m, aromatic CH), 7.98 (1H, s, CH); IR (film) 3080–2740 (CH), 1640 cm^{-1} (C=N). High resolution mass spectrum, calc for $C_{17}H_{28}N_2OSi$ M^+ = 304.1971; found M^+ = 304.1974. (Found: C, 66.76; H, 9.06. Calc for $C_{17}H_{28}N_2OSi$: C, 67.06; H, 9.27%.)

d,l-Eserethole **3b**

An oven dried 5-ml round-bottom flask equipped with a magnetic stirring bar was charged with tetra-n-butylammonium fluoride, 0.275 g (1.0 mmol), dry tetrahydrofuran, 2 ml, and 4 Å molecular sieves, 0.5 g. The flask was flushed with N_2, stoppered with a serum cap and heated to 50°. The formamidine **28**, 83 mg (0.273 mmol) was then methylated with methyl trifluoromethanesulfonate, 0.50 ml for 12 hr at −20°. The excess methyl trifluoromethanesulfonate was removed *in vacuo* at 100 μm and the residue dissolved in glyme, 0.5 ml. The resulting soln was added via a mechanical syringe to the forementioned tetra-n-butylammonium fluoride soln over 2 hr. The mixture was stirred at 50° for an additional 12 hr, treated with sat K_2CO_3 aq, 10 ml and extracted with ether, 15 ml. The organic layer was sequentially washed with water, brine, and dried over Na_2SO_4. After filtration the solvents were removed *in vacuo* and the residue submitted to column chromatography on silica gel (5% MeOH–95% $CHCl_3$ for elution) *d,l*-**3b**, 47 mg (70% yield) was obtained on concentration of the fractions. 300 MHz NMR δ 1.32 (3H, t, J = 7.6 Hz, CH_3), 1.35 (3H, s, CH_3), 1.90 (2H, m, J = 5.4, 7.3 and 9.1 Hz, CH_2), 2.48 (3H, s, CH_3), 2.63 (2H, m, J = 5.4, 7.3 and 9.1 Hz, CH_2), 2.90 (3H, s, CH_3), 3.88 (2H, q, J = 7.6 Hz, CH_2), 4.08 (1H, s, CH), 6.32 (1H, s, aromatic CH), 6.63 (2H, m, aromatic CH); 300 MHz ^{13}C 15.16, 27.41, 37.83, 38.12, 40.66, 52.97, 53.20, 64.37, 98.12, 107.67, 110.63, 113.25, 137.99, 146.34, 152.43; mass spectrum, *m/e* (246). The synthetic *d,l*-eserethole prepared in this was spectroscopically identical in all respects to an authentic sample of *l*-(−)-eserethole.[16]

Acetylenic dihydroisoquinoline **40**

An oven dried 100-ml round-bottom flask equipped with a magnetic stirring bar was charged with diisopropylamine, 2.58 ml (18.0 mmol), BuLi 7.47 ml (18.0 mmol) 2.46 M in hexane and dry THF, 60 ml. The lithium diisopropylamine soln was cooled to −78° and treated with **39**, 3.124 g (15.7 mmol) dissolved in dry THF 10 ml. The mixture was stirred at −78° for 2 hr and then hexamethylphosphoramide, 5.9 ml was added. After 15 min of additional stirring at −78° the mixture was treated with **38**, 4.06 g (15.2 mmol) dissolved in hexane, 4 ml. The mixture was stirred for 2 hr at 78° and then for an additional 12 hr at −20°.

The mixture was treated with sat NH_4Cl aq, 100 ml and extracted with hexane, 50 ml. The organic layer was washed with water, brine, and dried over Na_2SO_4. After filtration the solvents were removed *in vacuo*. The crude residue was submitted to column chromatography on activity III alumina (EtOAc–hexane, 2:3 for elution). The acetylenic **40**, 4.85 g (87.2% yield) was obtained as a yellow oil upon concentration of the fractions. NMR δ 0.09 (9H, s, CH_3), 1.62 (4H, m, CH_2CH_2, 2.18 (2H, t, J = 7.0 Hz, CH_2), 2.49 (4H, m, overlapping CH_2), 3.41 (2H, t, J = 5.1 Hz, CH_2), 3.92 (6H, s, CH_3), 6.52 (1H, s, aromatic CH), 6.91 (1H, s, aromatic CH); IR (film) 3060–2860 (CH), 2220 (C=C), 1670 cm^{-1} (C=N). (Found: C, 70.25; H, 8.66. Calc for $C_{20}H_{29}NO_2Si$: C, 69.92; H, 8.51%.)

Dihydroisoquinoline **33**

An oven dried 100-ml round-bottom flask equipped with a magnetic stirring bar was charged with **40**, 2.32 g (6.71 mmol), degassed MeOH, 30 ml and KOH, 0.88 g (15.7 mmol) dissolved in water, 4.5 ml. The mixture was stirred for 1.5 hr at 25°, treated with water, 50 ml, extracted with ether, 100 ml, and dried over Na_2SO_4. After filtration the solvents are removed *in vacuo*. The crude residue is submitted to column chromatography on activity III alumina (EtOAc–hexane, 2:3 for elution). The dihydroisoquinoline **33**, 1.64 g (90% yield) was obtained as white crystals (m.p. 93–94°) upon concentration of the fractions NMR δ1.70 (4H, m, CH_2CH_2), 1.89 (1H, t, J = 2.5, acetylenic CH), 2.21 (2H, dt, J = 7.0, 2.5, CH_2), 2.62 (4H, m, overlapping CH_2), 3.56 (2H, t, J = 5.1 Hz, CH_2), 3.88 (6H, s, CH_3), 6.66 (1H, s, aromatic CH), 6.97 (1H, s, aromatic CH); IR ($CHCl_3$) 3340 (CH), 3050–2840 (CH), 2220 (C≡C), 1670 cm^{-1} (C≡N). (Found: C, 75.42; H, 7.91. Calc for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80%.)

Sulfide **43**

An oven dried 50-ml round-bottom flask equipped with a magnetic stirring bar was charged with diisopropylamine, 0.506 ml (4.0 mmol), and THF, 25 ml. BuLi, 1.47 ml (2.46 M in hexane, 4.0 mmol) was then added and the mixture stirred at 0° for 30 min. The lithium diisopropylamine soln was cooled to −35° and treated with **33**, 1.08 g (3.62 mmol) in dry THF, 4 ml, stirred for a further hour at −35° and then treated with hexamethylphosphoramide, 0.50 ml. The mixture was stirred for an additional hour at 0° and subsequently treated with methylthiocyanate, 0.246 ml (4.0 mmol). The mixture was allowed to warm to room temp and stirred for an additional 0.5 hr. The mixture was treated with sat NH_4Cl aq, 50 ml and extracted with ether, 100 ml. The organic layer was dried over Na_2SO_4, filtered, and the solvents removed *in vacuo*. The crude residue was submitted to column chromatography on activity III alumina (EtOAc–hexene, 2:3 for elution). The sulfide **43**, 1.11 g (88% yield) was obtained as a yellow oil which crystalized upon standing for 24 hr (m.p. 68–70°). NMR δ 1.70 (4H, m, CH_2CH_2), 2.27 (3H, s, CH_3), 2.30 (2H, t, J = 7.0 Hz, CH_2), 2.65 (4H, m, overlapping CH_2), 3.56 (2H, t, J = 5.1 Hz, CH_2), 3.88 (6H, s, CH_3), 6.66 (1H, s, aromatic CH), 6.97 (1H, s, aromatic CH); IR (film) 3050–2840 (CH), 2220 (C≡C), 1670 cm^{-1} (C=N). (Found: C, 68.31; H, 7.44. Calc for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.30%.)

Enamine **46**

An oven dried 10-ml round-bottom flask equipped with a magnetic stirring bar was charged with anhyd cesium fluoride, 400 mg (2.6 mmol) and 1,2-dimethoxyethane, 4.0 ml. The sulfide **43**, 251 mg (0.79 mmol) was alkylated with trimethylsilylmethyl triflate, 187 mg (0.79 mmol) in CH_2Cl_2, 3 ml for 0.5 hr at 25°. After removal of the CH_2Cl_2, the residue was dissolved in 1,2-dimethoxyethane, 1.5 ml and the resulting soln was added via a mechanical syringe to the cesium fluoride suspension over 3 hr. The mixture was stirred at 25° for an additional 12 hr, treated with water, 15 ml, and subsequently extracted with $CHCl_3$, 30 ml. The organic layer was washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue submitted to column chromatography on activity III alumina (MeOH–$CHCl_3$, 1:19 for elution). The unstable **46**, 105 mg (40%) was obtained as a brown oil upon concentration of the fractions. NMR δ 1.70 (4H, m, —CH_2CH_2—), 2.27 (3H, s, CH_3), 2.38 (2H, t, J = 6.2 Hz, CH_2), 3.17 (4H, m, overlapping CH_2), 3.79 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.92 (3H, s, CH_3), 4.05 (1H, t, J = 8.3 Hz, enamine CH), 6.82 (1H, s, aromatic CH), 7.17 (1H, s, aromatic CH); IR (film) 3050–2840 (CH), 2220 (C≡C), 1625 cm^{-1} (C=C—N).

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