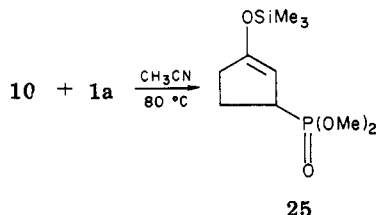Second, as can be noted by comparison of Tables I and II, the reaction times and temperatures required for efficient adduct formation with cyclic enones far exceed those required for the corresponding acyclic systems. In fact, when **1a** is allowed to react with **10** at 80 °C for 12 h, **25** is formed as the only observable product. Therefore the reported inability of cyclic enones to form adducts with **1a** or **1b** is simply the result of the experimental conditions chosen rather than the intrinsic inability of cyclic enones to undergo this type of reactions. This sluggish reactivity is most probably due to the fact that the silicon transfer step must be intermolecular with α,β-unsaturated ketones locked in a transoid geometry.[5]

25

Further applications of this methodology will be the subject of future reports.
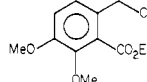
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A Novel Entry into Indole Alkaloids

Summary: By use of α-amino carbanions generated from β-carbolines and the successful blocking of indole nitrogen, the elaboration of these systems to indole alkaloids is described.

Sir: The indole class of alkaloids has been the subject of extensive synthetic efforts over the years.[1] However, modern methodology has added a new dimension to the synthesis of these substances. Among the more conceptual advances in alkaloid syntheses has been the work of Shono[2] using electrochemical techniques and the generation of carbanions adjacent to a modified amino function (A–D)

Table I. Synthetic Yields Leading to 7, 10, and 13 from 4

| electrophile	% yield[a]	% hydrazinolysis[a]	% hydrolysis	mp, °C
MeI	5 (84)	6a (68)	7a (77)[f]	177–180[i]
i-BuI	5 (87)	6b (91)[c]	7b (78)[g]	258–260[j]
PhCHO	5 (89)			
Cl(CH₂)₄Br	8[b]	9 (68)[d]	10 (77)[g]	150–152[k]
	11 (89)	12 (83)[e]	13 (75)[h]	253–255[h]

[a] Following chromatography.   [b] Not purified, carried on to **9**.   [c] Mp 72–73 °C (pentane).   [d] Overall yield from **4**.   [e] Mp 165–166 °C, M⁺ 392.   [f] Stirred for 15 min with 3 N HCl, neutralized to pH 10 with NaOH, stirred for 1 h at 25 °C.   [g] Heated at 60–65 °C for 1 h in 3 N HCl–THF (1:1), neutralized to pH >11, two layers stirred overnight.   [h] Same conditions as in [g] except heating was continued for 5.5 h.   [i] Mp 178–180 °C: Badger, G. M; Beecham, A. F. *Nature (London)* 1951, 168, 517.   [j] Hydrochloride salt, mp 257–259 °C: Slywka, G. W. A.; Locock, R. A. *Tetrahedron Lett.* 1969, 4635.   [k] Mp 147–149 °C: Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* 1981, 46, 4914.   [h] Recrystallized from ethyl acetate–hexane, analytical data satisfactory.

which upon alkylation produces the elaborated heterocycles.[3]
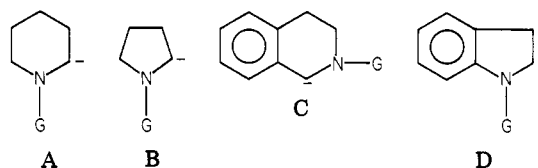
G = NO,[3a] C(=O)CR₃,[3b] PO(NMe₂)₂,[3c] CH=N-*t*-Bu[3d]

We now report that the amino carbanion derived from tetrahydro-β-carboline has been successfully employed as a viable precursor to indole alkaloids, affording three representative systems **7**, **10**, and **13** (Scheme I). To our knowledge there is no precedent for generating the carbanion from the tetrahydrocarbolines and this may have been the result of the inability to generate the dianion E

E
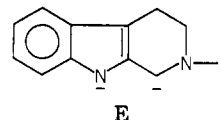
or the difficulty in finding a suitable protecting group for the indole nitrogen.[4] The indole alkaloid approach begins with the conversion of tetrahydro-β-carboline to its formamidine derivative **1** by heating with 3.0 equiv of *N,N*-dimethyl-*N'*-*tert*-butylformamidine[5] in toluene overnight (80%, mp 168–170 °C after chromatography on silica, 10% Et₃N, 20% acetone, 70% hexane). Efforts to generate the dianion E with various bases (LDA, *sec*-BuLi, *t*-BuLi) failed and only the use of 2.0 equiv of *n*-butylpotassium[6]

(1) For an excellent review on indole alkaloids, see Kutney, J. P. In "The Total Synthesis of Natural Products"; Wiley-Interscience: New York, 1977; Vol. 3, pp 273–438.

(2) Shono, T.; Sasaki, M.; Nagami, K.; Hamaguchi, H. *Tetrahedron Lett.* 1982, 23, 97.

(3) (a) Seebach, D.; Wykpiel, W. *Synthesis* 1979, 423. (b) Reitz, D. B.; Beek, P.; Tse, A. *J. Org. Chem.* 1981, 46, 4316. (c) Seebach D.; Yoshifuji, M. *Helv. Chim. Acta* 1981, 64, 643. (d) Meyers, A. I.; Hellring, S.; Ten Hoeve, W. *Tetrahedron Lett.* 1981, 22, 5115 and earlier references cited.
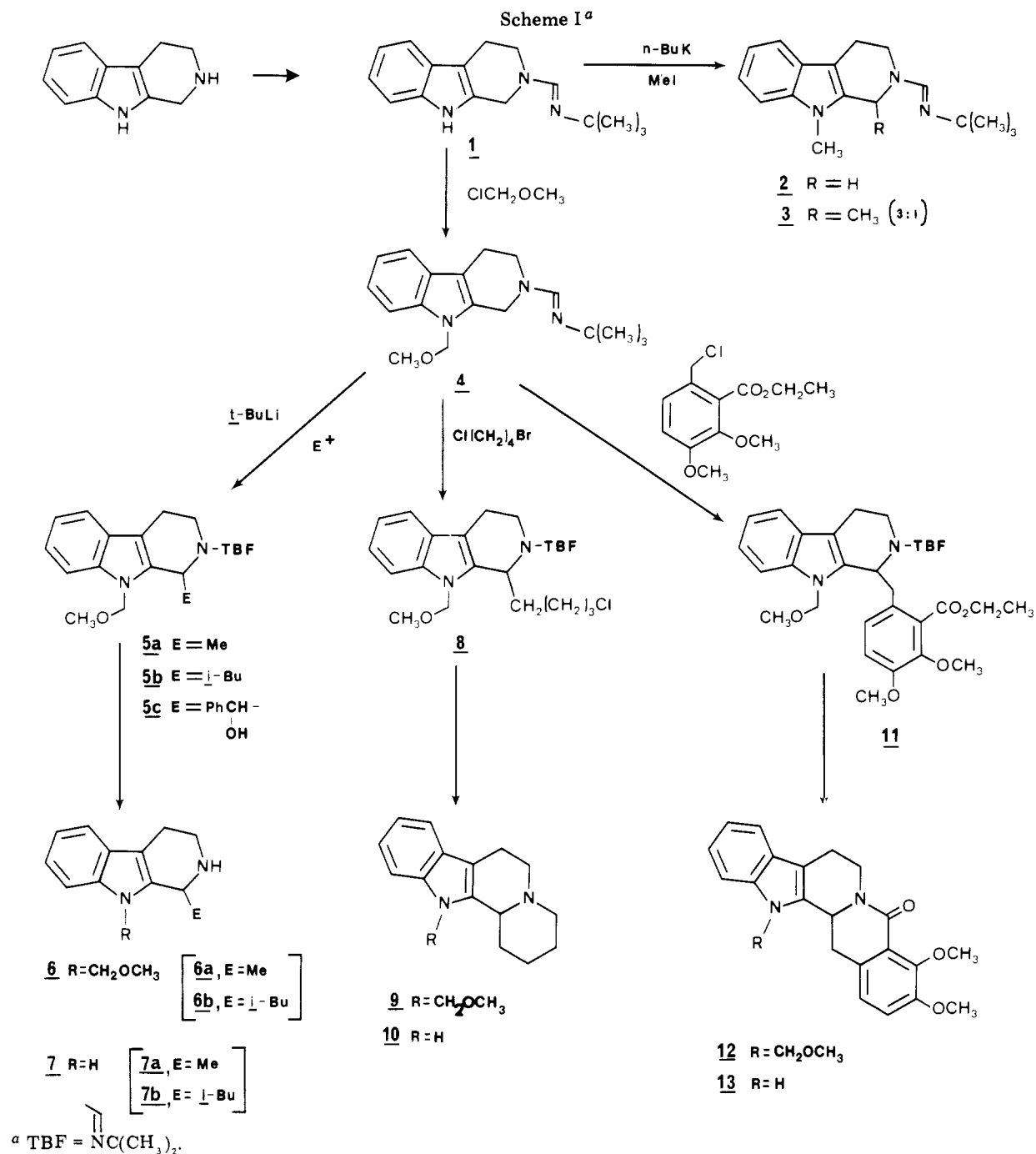
(4) A study on protecting groups for indole nitrogen indicated that the methoxymethyl was inappropriate due to its resistance to hydrolytic cleavage: Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* 1973, 38, 3324.

(5) Meyers, A. I.; Ten Hoeve, W. *J. Am. Chem. Soc.* 1980, 102, 7125.

(6) Renger, B.; Hügel, H.; Wykypiel, W.; Seebach, D. *Chem. Ber.* 1978, 111, 2630.

Scheme I[a]

^{a} TBF = NC(CH$_3$)$_2$.

followed by 2.0 equiv of methyl iodide gave a mixture of 2 and 3 in a 1:3 ratio. The production of 3, however, was found to occur only after the indole nitrogen had been first methylated. The poor results obtained by direct metalation–alkylation on 1 suggested that a suitable protecting group on the indole nitrogen would alleviate this problem. Sundberg[4] had reported that the benzenesulfonyl group was superior as an indole nitrogen protecting group while methoxymethyl was difficult to remove. However, metalation of the carboline containing the N-benzenesulfonyl group failed under a variety of conditions. In spite of the previous report[4] on using the methoxymethyl protecting group, 4 was readily prepared (1.1 equiv of t-BuOK, ether, 0.1 equiv of 18-crown-6, 1.1 equiv of chloromethyl methyl ether, 25 °C, 30 min, 75% yield)[7] and represented a key starting compound for the alkaloidal systems.

Treating a solution of 4 in THF, cooled to –25 °C, with 1.05 equiv of *tert*-butyllithium gave a red anion solution within 45 min. After cooling of the solution to –78 °C, addition of various electrophiles, and then allowing the mixture to warm to –30 °C before quenching, the alkylated derivatives 5a–c were obtained (Table I). A 1:1 mixture of diastereomers was formed for 5c.

Removal of the formamidine moiety by using hydrazine–acetic acid–aqueous ethanol at 50–60 °C[3d] gave 6 and acidic hydrolysis followed by an essential alkaline treatment[8] (Table I, footnotes *f* and *g*)cleanly removed the methoxymethyl group, affording the 3-substituted carbolines 7. The preparation of indolo[b]quinolizidines was

(7) Guida, W. C.; Mathre, D. J. *J. Org. Chem.* **1980**, *45*, 3172.

(8) The crude product after acid hydrolysis showed complete loss of the methoxy singlet (δ 3.1) in the NMR spectrum, while the NCH$_2$O methylene singlet (δ 5.2) was retained; the product is presumed to be the hemiaminal (i.e., 6, 9, 12 R = CH$_2$OH). Cf. Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6493.

demonstrated by metalation of **4** and addition of 1-bromo-4-chlorobutane which led to **8** and the latter was transformed into **9** in a single step upon warming with the hydrazine solution. Removal of the methoxymethyl group (Table I) gave **10**. In a third approach to indole alkaloids, the yohimbane skeleton was efficiently reached by metalation of **4** followed by addition of the ethyl benzoate derivative,[9] furnishing **11**. When **11** was warmed with the hydrazine reagent, the lactam **12** was formed directly (Table I). As before, the methoxymethyl group was removed without event, affording **13**.

In summary, the α-amino carbanions derived from tetrahydro-β-carbolines are now accessible and were found to be suitable precursors to a variety of indole alkaloidal systems. Further studies directed toward specific target molecules are in progress.

(9) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115.

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Reductive Cyclization of Mercurial Enones

Summary: A series of enones containing pendant isolated olefinic linkages was prepared. Solvomercuration could be conducted specifically at the isolated double bond. Treatment of these systems with sodium trimethoxyborohydride results in reductive cyclization.

Sir: Organometallic systems that bear hetero substituents at the β-carbon and that are attacked by a range of electrophiles (E$^+$) are potentially useful implements in synthesis. Equations 1 and 2 implicitly express both the opportunities and stability problems inherent in such structures.[1-3]


(2)

$$Y—C—C—E \quad (1)$$

Y = hetero group   Met = metal
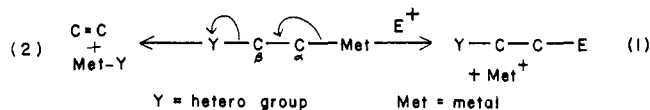
(1) For early attempts to prepare such systems, see: (a) Normant, H. *Bull. Soc. Chim. Fr.* **1972**, 2161. (b) Steinborn, D. *J. Organomet. Chem.* **1979**, *182*, 313. (c) Schlosser, M.; Ladenberger, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 519.

(2) For recent reports on successful generation of such systems, see: Barluenga, J.; Fananas, F. J.; Yus, M. *J. Org. Chem.* **1981**, *46*, 1281 and ref 13 and 14 therein.

(3) For some recent examples of vinyllithium reagents bearing β-hetero substituents, see: (a) Ficini, J.; Falou, S.; Touzin, A. M.; d'Angelo, J. *Tetrahedron Lett.* **1977**, 3589. (b) Wollenberg, R. H.; Ablizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365. (c) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. (d) Skold, C. N. *Synth. Commun.* **1976**, *6* (2), 119. (e) Vlattas, I.; Vecchia, L. D.; Lee, A. O. *J. Am. Chem. Soc.* **1976**, *98*, 2008.

Scheme I
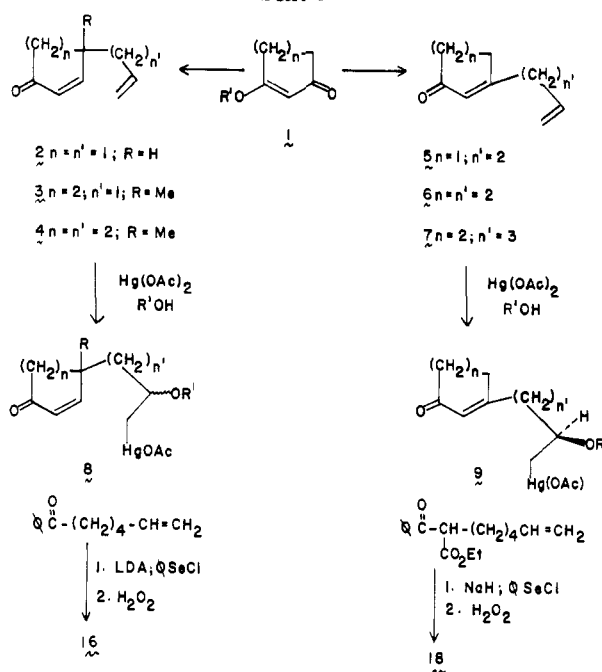
Mercurials bearing β-hetero substitution are readily available through the solvomercuration of olefins.[4-8] Unfortunately, the carbon–mercury bond is insufficiently nucleophilic to participate in many reactions such as are implied in eq 1.[5-8] Indeed, the viability of such compounds is probably not unrelated to the covalent character of the carbon–mercury bond.

We were, therefore, struck by some findings of Giese[9-11] (eq 3) to the effect that several β-methoxy mercurials undergo "reductive" coupling with electrophilic olefins upon treatment with sodium trimethoxyborohydride. Though proceeding presumably through a free-radical pathway,[12-14] the Giese reaction corresponds, in its overall synthetic consequence, to eq 1.

We have begun to study the synthetic potentialities[15,16] implicit in the reductive coupling of mercurials. For instance, it was of interest to learn whether the process would be operative with electrophilic substrates that are more

(4) Butler, R. N. In "Synthetic Reagents"; Pizey, J. S.; Ed.; Ellis Horwood: Chichester, England, 1977; Vol. 3, pp 15–145.

(5) Staul, H.; Zeller, K. P.; Leditsche, H. *Methoden Org. Chem. (Houben-Weyl),* 4th Ed. **1974**, 13/2b, 130–152.

(6) Bloodwoth, A. J. In "The Chemistry of Mercury"; McAuliffe, C. A.; Ed.; Macmillian: London, 1977; pp 235–243.

(7) Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27.

(8) Negishi, E. I. "Organometallics in Organic Synthesis"; Wiley: New York, 1980; pp 455–479.

(9) Giese, B.; Heuck, K. *Chem. Ber.* **1979**, *112*, 3759.

(10) Giese, B.; Heuck, K. *Tetrahedron Lett.* **1980**, *21*, 1829.

(11) (a) Giese, B.; Heuck, K. *Chem. Ber.* **1981**, *114*, 1572. (b) In a paper that appeared since submission of our manuscript, Giese has extended his intermolecular reaction to include α,β-unsaturated ketones. (See: Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* **1982**, 531.)

(12) Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 2588.

(13) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.

(14) Jensen, F. R.; Miller, J. J.; Cristol, S. J.; Beckley, R. S. *J. Org. Chem.* **1972**, *37*, 4341.

(15) Similar objectives have been accomplished by cyclization of a protonated enone to a proximal double bond or aromatic ring with attack by a nucleophile. For example, see: (a) Naegeli, P. *Tetrahedron Lett.* **1978**, 2127 and references therein. (b) Harding, K. E.; Cooper, J. L.; Puckett, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 993. (c) Davis, B. R.; Johnson, S. J. *J. Chem. Soc., Chem. Commun.* **1978**, 614.

(16) Related cyclizations of alkyl tin(iv) compounds have been described by Macdonald. It will be noted that our method proceeds from an olefinic precursor and allows for the introduction of a β-hetero substituent. Macdonald, T. L.; Mahalingam, L. *J. Am. Chem. Soc.* **1980**, *102*, 2113.