A Concise Formal Synthesis of Alkaloid Cryptotackiene and Substituted 6*H*-Indolo[2,3-*b*]quinolines

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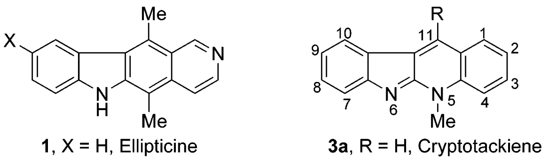
Abstract: A five-step formal synthesis of alkaloid cryptotackiene and its 2-formyl, 11-methyl/phenyl derivatives involving conjugate addition of enolate anion from cyclohexanone (or 4-methylcyclohexanone) to bis[(methylsulfanyl)-methylene]-2-oxindole followed by heterocyclization in the presence of ammonium acetate as the key step has been developed. The 11-methylsulfanyl group in the initial precursor can be either desulfurized (Raney Ni) or replaced by methyl/phenyl groups via nickel-catalyzed cross-coupling reaction with appropriate Grignard reagents.

The discovery of antitumor activity[1] of ellipticine **1** and 9-methoxyellipticine **2** (Chart 1), two naturally occurring 6*H*-pyrido[4,3-*b*]carbazole alkaloids,[2] has led to an explosion of activities toward synthesis and biological evaluation of these polyheteroaromatic alkaloids and their derivatives.[3] More recently, cryptotackiene **3a**, a linear 5-*N*-methyl-5*H*-indolo[2,3-*b*]quinoline alkaloid isolated from the West African shrub *Cryptolepis sanguinolenta*,[4] has been reported to exhibit strong antiplasmodial activity.[5] Also, a few of the methyl-substituted derivatives of cryptotackiene such as **3b** are found to display strong antimicrobial and cytotoxic activities in vitro and significant antitumor properties in vivo.[6] The interesting biological activities of ellipticine and indoloquinolines has stimulated a surge of interest in developing new synthetic pathways to polyheteroaromatic ring systems such as 6*H*-indolo[2,3-*b*]quinolines[7−9] (precursor to cryptotackiene) and 6*H*-indolo[2,3-*b*][1,6]naphthyridines.[10] A few syntheses of cryptotackiene have been recently reported.[6a,11,12] Thus, Molina and co-workers have described two syntheses of cryptotackiene involving eight steps, based on sequential construction of both pyridine and indole rings via aza-Wittig electrocyclic process as the key step for the formation of the appropriate 3-arylquinoline precursors.[11] Timari and co-workers have developed an alternative synthesis of cryptotackiene in which the key 3-(2-aminophenyl)-*N*-methyl-2-quinolone intermediate is obtained by a palladium-catalyzed cross-coupling reaction of the 3-bromo-2-quinolone derivative with (2-*N*-pivaloylaminophenyl)boronic acid.[12] Recently, Wang et al. have reported biradical-mediated thermolysis of *N*-[2-(1-alkynyl)phenyl]-*N′*-phenylcarbodiimides leading to the corresponding 6*H*-indolo[2,3-*b*]quinoline[8] and its 11-alkyl/aryl derivatives which on methylation with dimethyl sulfate are known to yield cryptotackiene and its 11-methyl derivative.

CHART 1



1, X = H, Ellipticine
2, X = OMe, 9-Methoxyellipticine
3a, R = H, Cryptotackiene
3b, R = Me, 11-Methylcryptotackiene

During the course of our studies directed toward synthesis of novel polycyclic aromatic and heteroaromatic compounds based on α-oxoketene dithioacetals mediated aromatic and heteroaromatic annulation,[13,14] we have recently reported an efficient two-step method for the synthesis of a wide range of substituted and annulated pyrido[2,3-*b*]indoles (α-carbolines).[15] The overall transformation involves base-induced conjugate displacement on α-oxoketene dithioacetals by 1-substituted-2-oxindole

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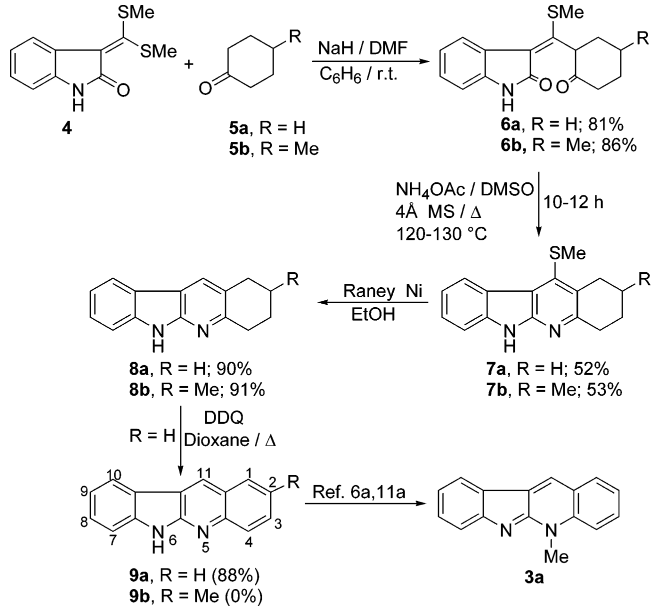
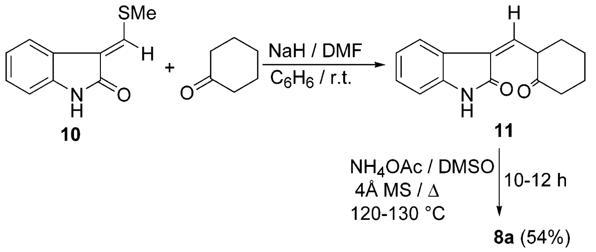
SCHEME 1



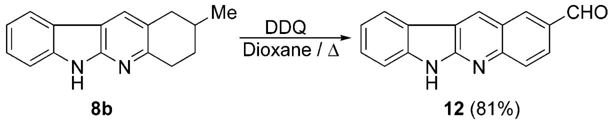
SCHEME 2



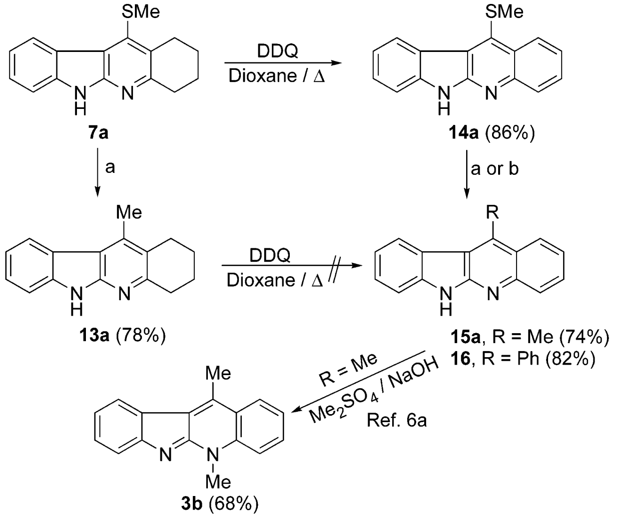
enolate anion and subsequent heterocyclization of the conjugate adduct in the presence of ammonium acetate. In conjunction with these studies, we have now elaborated this strategy for the construction of the 6*H*-indolo[2,3-*b*]quinoline ring system which constitutes a short concise approach to cryptotackiene and its 11-methyl derivative.

The 3-bis[(methylsulfanyl)methylene]-2-oxindole **4**[14e] was subjected to conjugate addition with cyclohexanone **5a** in the presence of sodium hydride to give the requisite adduct **6a** in 81% yield. However, heterocyclization of the adduct **6a** with ammonium acetate in refluxing acetic acid yielded the tetrahydro-6*H*-indolo[2,3-*b*]quinoline **7a** in poor yield (15%). Optimization of the reaction conditions by heating the adduct **6a** with ammonium acetate in dry DMSO in the presence of 4 Å molecular sieves under nitrogen atmosphere yielded the indoloquinoline **7a** in a maximum yield of 52% (Scheme 1). Subsequent dethiomethylation of **7a** with Raney Ni in refluxing ethanol proceeded smoothly to give tetrahydro-6*H*-indolo[2,3-*b*]quinoline **8a** in 90% yield. Alternatively, the synthesis of indoloquinoline **8a** was achieved by heterocyclization of the adduct **11** obtained by base induced conjugate addition of cyclohexanone with 3-[methylsulfanyl(methylene)]-2-oxindole **10** (Scheme 2). It was considered that the absence of the bulkier methylsulfanyl group in the adduct **11** may facilitate its cyclization to **8a** in improved yield. However, treatment of **11** with ammonium acetate under previously described conditions afforded the tetrahydroindolo[2,3-*b*]quinolone **8a** in only a comparable yield of 54% (Scheme 2). Dehydrogenation of tetrahydroindoloquinoline **8a** with DDQ in refluxing 1,4-dioxane afforded the desired 6*H*-indolo[2,3-*b*]quinoline **9a** in 88% yield (Scheme 1). *N*-Methylation of indoloquinoline **9a** with dimethyl sulfate has been reported to give cryptotackiene **3** in good yields.[6a,11a]

SCHEME 3



SCHEME 4



a, $(Ph_3P)_2NiCl_2$ / MeMgI / *n*-BuLi / C6H6 / 80-90 °C
b, $(Ph_3P)_2NiCl_2$ / PhMgBr / *n*-BuLi / C6H6 / 80-90 °C

The methodology was also extended for the synthesis of 2-methyl-6*H*-indolo[2,3-*b*]quinoline **9b** following a similar sequence by subjecting 4-methylcyclohexanone **5b** to conjugate addition–elimination with **4** and subsequent cyclization of the adduct **6b** under identical conditions to give 2-methyl-6*H*-11-(methylsulfanyl)tetrahydroindolo[2,3-*b*]quinoline **7b** in 53% yield (Scheme 1). Dethiomethylation of **7b** with Raney Ni afforded the corresponding 11-unsubstituted compound **8b** in high yield. However, subsequent dehydrogenation of **8b** with DDQ yielded the corresponding 2-formyl-6*H*-indolo[2,3-*b*]quinoline **12** instead of **9b** by concomitant oxidation of the 2-methyl group (Scheme 3).

The synthesis of the corresponding 11-methyl-6*H*-indolo[2,3-*b*]quinoline **15a** was next investigated via nickel-catalyzed displacement of the 11-methylsulfanyl group in **7a** by a methyl Grignard reagent (Scheme 4).[16] It should be noted that the corresponding 11-methyl derivative **3b** of cryptotackiene has been reported to induce significant topoisomerase II-DNA mediated cleavable complexes in in vitro studies, thus making this compound a potential antitumor agent.[6a] Thus, treatment of 11-(methylsulfanyl)tetrahydroindoloquinoline **7a** with

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methylmagnesium iodide in the presence of bis(triphenylphosphino)nickel dichloride and *n*-butyllithium yielded the corresponding 11-methyl-6*H*-tetrahydroindolo[2,3-*b*]quinoline **13a** in 78% yield. However, attempted dehydrogenation of **13a** to **15a** in the presence of DDQ in refluxing 1,4-dioxane yielded only complex product mixture. On the other hand, the corresponding 11-(methylsulfanyl)indoloquinoline **14a** obtained by dehydrogenation of **7a** with DDQ underwent facile displacement of the 11-methylsulfanyl group under the described conditions yielding the desired 11-methyl-6*H*-indolo[2,3-*b*]quinoline **15a** in 74% yield (Scheme 4). Similarly, the corresponding 11-phenylindolo[2,3-*b*]quinoline **16** was also obtained in good yield by displacement of the 11-methylsulfanyl group in **14a** by the phenylmagnesium bromide in the presence of bis(triphenylphosphino)nickel dichloride complex. The 5-*N*-methylation of **15a** in the presence of Me_2SO_4/NaOH is known to furnish the corresponding 11-methylcryptotackiene **3b** in 65% yield.[6a]

In conclusion, we have developed a new formal synthesis of alkaloid cryptotackiene involving only five steps from readily accessible starting materials in overall good yield. Although the yield of the cyclization step (**6** → **7**) is moderate, the overall sequence seems to provide an efficient and short pathway for 6*H*-indolo[2,3-*b*]quinolines with a possibility of placing a number of substituents around the periphery of the heterocyclic ring system by choice of appropriately substituted suitable precursors. In addition, the 11-methylsulfanyl group can be either dethiomethylated (Raney Ni) or displaced by an alkyl/aryl groups through nickel chloride induced cross-coupling with Grignard reagents.

Experimental Section

General Methods. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$, DMSO-d_6, and TMS was used as an internal reference. Melting points are uncorrected. Chromatographic purification was conducted by column chromatography using 60−120 mesh silica gel and neutral alumina obtained from Acme Synthetic Chemicals. DMF and DMSO were distilled over CaH_2 and stored over 4 Å molecular sieves. THF and 1,4-dioxane were distilled over sodium/benzophenone prior to use. NaH (as 60% suspension in oil), cyclohexanone, 4-methylcyclohexanone, *n*-BuLi (1.6 M in hexane), DDQ, and anhydrous NH_4OAc (AR grade) were purchased from the standard firms and used as such, whereas 2-oxindole[17] and 2-bis[(methylsulfanyl)methylene]oxindole[18] were prepared according to the earlier reported procedure. The 3-[(methylsulfanyl)methylene]-2-oxindole[19] was prepared by reduction of **4a** with $NaBH_4$ in AcOH according to a previously reported procedure.

General Procedure for the Preparation of Conjugate Adducts 6a,b and 11. A solution of cyclohexanone (or 4-methylcyclohexanone) (5.0 mmol) in benzene (30 mL) was added to a suspension of sodium hydride (5.0 mmol, 0.12 g) in dry DMF (10 mL) under nitrogen atmosphere at 0 °C over a period of 30 min. The reaction mixture was stirred for 45 min, and a solution of **4** or **10** (5.0 mmol) in dry DMF (30 mL) was added at the same temperature. The reaction mixture was further stirred at room temperature for 12 h (monitored by TLC). The reaction mixture was then poured into saturated ammonium chloride solution (100 mL) and extracted with benzene (2 × 100 mL). The combined benzene layer was washed with water (2 × 100 mL) and dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to give the 1,4-addition−elimination adducts (**6a**, **6b**, or **11**). The adducts **6a** and **6b** were purified by column chromatography over silica gel using hexane/EtOAC (10:1) as eluent for spectral and analytical data, whereas the adduct **11** was used as such for heterocyclization.

General Procedure for Heterocyclization of the Adducts 6a,b and 11 with Ammonium Acetate: Synthesis of Tetrahydroindolo[2,3-*b*]quinolines 7a,b and 8a. To a solution of adducts **6a**,**b** or **11** (1.0 mmol) in dry DMSO (50 mL) were added 4 Å molecular sieves (3.0 g), anhydrous ammonium acetate (15 g), and a drop of acetic acid. The reaction mixture was heated at 120 °C for 12 h. It was then cooled and poured into ice-cold water (100 mL), and the molecular sieves were removed by filtration through G-3 sintered funnel. The filtrate was extracted with chloroform (3 × 100 mL), washed with water (2 × 50 mL), dried (anhydrous Na_2SO_4), and evaporated under reduced pressure to give crude tetrahydroindoloquinolines **7a**,**b** and **8a** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

General Procedure for Raney-Ni Dethiomethylation of Tetrahydroindoloquinolines 7a,b. To a solution of tetrahydroindoloquinolines **7a**,**b** (1.0 mmol) in ethanol (10 mL) was added Raney Ni (W2) (~4 g), and the reaction mixture was refluxed with stirring for 6−7 h. It was then filtered, washed with hot ethanol, and concentrated under reduced pressure to give crude products **8a**,**b** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

6*H*-1,2,3,4-Tetrahydroindolo[2,3-*b*]quinoline (8a): yield 90% (0.20 g); colorless solid (hexanes−EtOAc); mp 220−221 °C (spectral data as in the Supporting Information).

General Procedure for Dehydrogenation of Tetrahydroindoloquinolines 7a and 8a,b with DDQ. To a solution of tetrahydroindoloquinolines **7a**, **8a,** or **8b** (1.0 mmol) in dry 1,4-dioxane (10 mL) was added DDQ (0.34 g, 1.5 mmol), and the reaction mixture was refluxed with stirring under nitrogen atmosphere for 6−8 h (monitored by TLC). It was then cooled, filtered (G-3 sintered funnel), and extracted with chloroform (3 × 50 mL), washed with water (3 × 50 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give crude products **14a**, **9a**,[20] or **12**, which were purified by column chromatography over silica gel using hexane/EtOAc (1:20) as eluent.

General Procedure for Nickel-Catalyzed Cross-Coupling of 11-(Methylsulfanyl)indolo[2,3-*b*]quinolines 7a and 14a with Methyl/phenyl Grignard Reagents. A solution of appropriate Grignard reagent [MeMgI or PhMgBr (0.10 mmol)] in THF was added dropwise to a stirring suspension of $(Ph_3P)_2$-$NiCl_2$ (30 mol %, 0.19 g) in 25 mL of dry benzene under argon atmosphere, and the reaction mixture was refluxed for 15 min. It was then immediately added to the preformed suspension of lithio salt of **7a** or **14a** [prepared by addition of *n*-BuLi (1.0 mmol, 0.62 mL, 1.6 M in hexane) to a solution of **7a** or **14a** (1.0 mmol) in dry benzene (10 mL)] followed by further addition of Grignard reagent [MeMgI or PhMgBr (1.90 mmol)]. The reaction mixture was then refluxed for 5−6 h (monitored by TLC), cooled, and poured into saturated NH_4Cl solution (100 mL) followed by extraction with $CHCl_3$ (3 × 50 mL). The organic layer was dried (anhydrous Na_2SO_4) and evaporated to give crude products **13a**, **15a**, and **16**, which were purified by column chromatography over silica gel using hexane/EtOAc (5:1) as eluent.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for compounds **6a**,**b**, **7a**,**b**, **8a**,**b**, **9a**, **10**, **12**, **13a**, **14a**, **15a**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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