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# Stereoselective route to mitosanes via tricarbonyl $\eta^6$ arene chromium complexes

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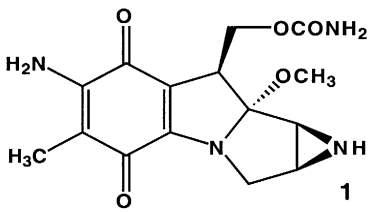
**Abstract**

Stereoselective reduction followed by metalation of a $\eta^6$ arene chromium tricarbonyl complex allows rapid access to substituted mitosanes, whose skeleton mimics the mitomycin family of antitumour agents. 

The mitomycin family of antitumour antibiotics have attracted considerable attention due to their unique chemical structures and observed antiproliferative activity.[1] Mitomycin C **1** (isolated from *Streptomyces caespitosus*) is employed clinically for the treatment of a variety of solid tumors, and a number of other closely related naturally occurring structures also display antitumoral activity, including mitomycin K **2**.[2] A common feature of this interesting class is the pyrrolo[1,2-*a*]indole skeleton **3**, and numerous approaches for the synthesis and functionalization of this system have been explored.[3] The antiproliferative activity of the mitomycins stems from their ability to undergo covalent cross linking of DNA, via generation of two reactive intermediates. This involves nucleophilic opening of the aziridine ring and is then followed by side chain alkylation, which in the case of **1** results from expulsion of the carbamate group, yielding an exomethylene iminium ion which undergoes alkylation. Both processes are influenced by the quinone subunit, which functions as a bioreductive triggering mechanism, similar to that found in the enediyne natural product, dynemicin A.[4]

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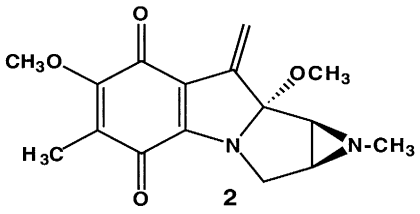


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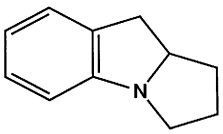


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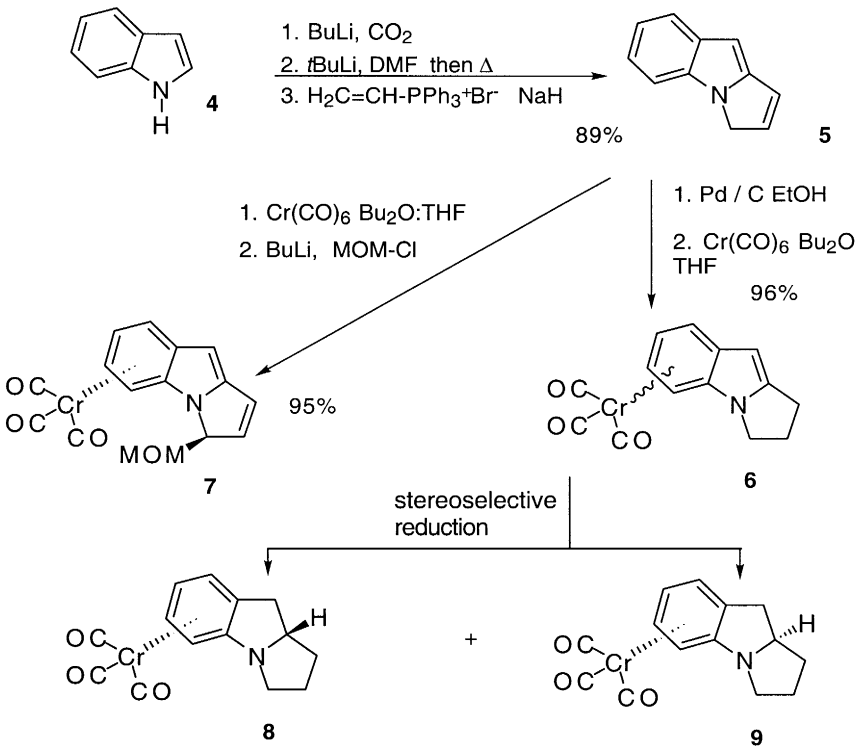
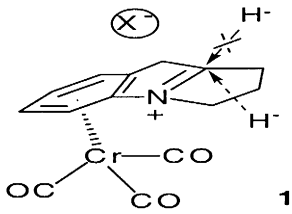
Due to its strategic importance, an efficient means was thus sought to assemble and functionalize the core unit of this important class of DNA interactive agent. Based on prior experience, we envisioned that an appropriately functionalized $\eta^6$ arene chromium carbonyl complex might serve as a versatile building block for the construction of derivatives of **3**, since they are known to undergo a range of reactions with high levels of stereocontrol.[5] Accordingly, tricyclic mitosene **5** was prepared from indole **4** via the Katritzky metalation procedure,[6] followed by intramolecular cyclization (Scheme 1).[7] Reduction of the pyrrolo vinyl group followed by direct complexation gave **6** in excellent yield. Alternatively, direct complexation of **5** could also be effected in high yield. This complex allowed the influence of the metal carbonyl group on the stereochemistry of allylic functionalization to be probed. Accordingly, metalation followed by addition of methoxymethyl chloride resulted in exclusive formation of *exo* product **7**, a presumed consequence of the metal carbonyl group encumbering the approach of the electrophile from the $\alpha$ face.[8]




Scheme 1. Preparation and reduction of $\eta^6$ arene mitosene complexes

X-Ray determination of the tricarbonyl chromium complex of **5** was possible, and supported the observed outcome of the allylic alkylation reaction.[9] Furthermore, the overlay of the tricarbonyl chromium tripod suggested that, under acidic conditions, stereoselective reduction of the indolyl $C_2$–$C_3$ bond may be possible, since the associated counterion would be expected to reside *anti* to the metal carbonyl tripod, encouraging *endo* hydride approach **10**.



**10**

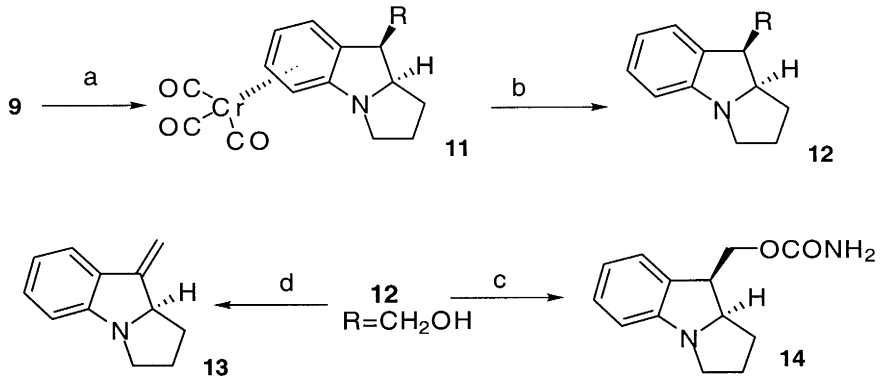
Stereoselective reduction of the critical indolyl $C_2$–$C_3$ bond was thus investigated using a variety of methods. Tandem reductions of either **7** or the tricarbonyl chromium complex of **5** gave intractable mixtures of products; however, **6** proved an amenable substrate for study. The corresponding mitosanes **8**/**9** were formed in moderate to good yield and with a marked degree of stereocontrol in many cases. As predicted by conformational analysis (**10**), the product of *endo* addition (**9**) predominates in most cases (Table 1), a result consistent with the work of Pigge, who has reported a similar outcome with substituted indoles and carbazoles.[10] Optimal conditions involve sodium cyanoborohydride as reductant and trifluoroacetic acid as proton source, with pronounced reduction in both chemical yield and stereocontrol observed with alternate combinations. Though the origin of the *endo* addition product is presumed to be a function of counterion bulk presented in iminium ion **10**, no clear trend based on either electronic or steric factors emerges, indicating the intriguing possibility of a cooperative mechanism for hydride delivery which directly involves the metal carbonyl group.

Table 1
Stereoselective reduction of **6**[a]

| Entry | Reductant | Acid | (pKa) | %Yield | Ratio **8**:**9** |
|---|---|---|---|---|---|
| 1 | $NaCNBH_3$ | $CH_3COOH$ | (4.7) | <5 | - |
| 2 | $NaCNBH_3$ | $PhCOOH$[b] | (4.2) | 38 | 10:90 |
| 3 | $NaCNBH_3$ | $HCOOH$ | (3.8) | <5 | - |
| 4 | $NaCNBH_3$ | $HCCl_2COOH$ | (1.3) | 63 | 13:87 |
| 5 | $NaCNBH_3$ | $CF_3COOH$ | (0.3) | 92 | 5:95 |
| 6 | $Et_3SiH$ | $CF_3COOH$ | " | <5 | - |
| 7 | $NaBH_4$ | $CF_3COOH$ | " | 21 | 32:68 |
| 8 | $LiAlH_4$ | $CF_3COOH$ | " | 28 | 54:46 |
| 9 | $NaHB(OMe)_3$ | $CF_3COOH$ | " | 40 | 15:85 |
| 10 | $NaHB(OAc)_3$ | $CF_3COOH$ | " | 50 | 8:92 |

[a] all reactions conducted at –10°C / 60 min. in neat acid [b] conducted in THF solution

With a high yielding and stereoselective route to mitosanes developed, we wished to demonstrate the capacity for functionalization of the skeleton (Scheme 2). Lithiation at the benzylic position, quenching with the appropriate electrophile, followed by in situ decomplexation gave ready access to a variety of building blocks **12** in good yield (Table 2). The exclusive *anti* geometry of the products was confirmed by comparison with authentic material.[11] Subsequent transformations on **12** ($R{=}CH_2OH$) lead to the formation of mitomycin K and C skeletons **13**, **14**.[1,11] As a consequence of the planar chirality inherent to arene chromium carbonyl complexes, the stereoselective route described could potentially be used for enantioselective synthesis. In this regard, separation of **6** was effected using chiral chromatography, providing access to either enantiomeric series as desired.[12] The combination of this powerful methodology, in tandem with directed metalation strategies (on e.g. **7** and **9**), can now be applied to the synthesis of mitomycin analogues, and will be reported in due course.[13]




Scheme 2. Stereoselective functionalization of $\eta^6$ arene complexed mitosene. (a) *s*BuLi, THF then $E^+$; (b) h$\nu$/$Et_2O$ (>90%); (c) PhOCOCl, $NH_3$ (85%); (d) $PhSO_2Cl$, lutidine (73%)

Table 2
Stereoselective functionalization of mitosanes

| Entry | E | R | %**11** |
|---|---|---|---|
| 1 | $(CH_2O)_n$ | $CH_2OH$ | 90 |
| 2 | MeI | $CH_3$ | 87 |
| 3 | EtI | $C_2H_5$ | 78 |
| 3 | PhCHO | CH(OH)Ph | 97 |
| 4 | ethylene oxide | $CH_2CH_2OH$ | 93 |
| 5 | BnBr | $CH_2Ph$ | 58 |

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8. Relative stereochemistry assigned. For comparison, a mixture of $\alpha/\beta$ isomers was prepared via decomplexation (h$\nu$/$Et_2O$) then recomplexation ($CrCO_6$/*n*$Bu_2O$:THF). All new compounds gave satisfactory spectroscopic and analytical data.
9. We thank Professor William T. Pennington (Clemson University) for this determination.
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11. Dijksman, W. C.; Verboom, W.; Egberink, R. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1985**, *50*, 3791.
12. Daicel OD column, 10% IPA 90% hexanes eluent, 254 nM detection, 1.5 ml/min flow rate: *ent* 1 $t_R$=20.4 min, *ent* 2 $t_R$=46.8 min. $[\alpha]_D$: *ent* 1= +886° (c=0.1, $CHCl_3$), *ent* 2= −813° (c=0.1, $CHCl_3$).
13. Research supported by grants from the NIH [RO1GM57123] and PRF [33920AC-1].