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Asymmetric synthesis of a tetracyclic model for the aziridinomitosenes

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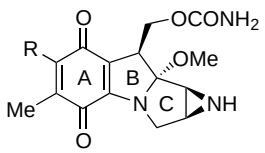
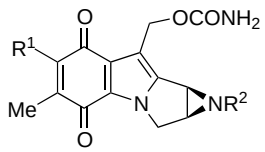
Abstract—The conversion of (−)-2,3-*O*-isopropylidene-D-erythronolactone (**9**) into the *N*-phosphorylated aziridine **20**, a model for the fundamental structure of aziridinomitosenes, has been accomplished in 11 steps by way of the vinylogous urethane **13**. Key steps include the preparation of **13** by a Reformatsky reaction on a thiolactam precursor, Heck cyclisation of **13** to form the indole ring, and aziridine synthesis via a cyclic sulfite. © 2001 Published by Elsevier Science Ltd.

The mitomycins, e.g. mitomycins A (**1**) and C (**2**), are a group of *Streptomyces* metabolites having pronounced antibacterial and antitumour activity.[1] Considerable effort has been devoted to the synthesis of these clinically useful antibiotics and their bioactive degradation products, the aziridinomitosenes (e.g. **3**). Common to these compounds is a tricyclic 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core, the construction of which has been approached in numerous ingenious ways.[2,3] However, fusing the aziridine ring onto the tricyclic nucleus is a more challenging synthetic problem, since many simple routes to pyrrolo[1,2-*a*]indoles either do not have the flexibility to handle the additional functionality required in the target system, or make little provision for the requisite stereocontrol.[4]



1 R = OMe
2 R = NH_2



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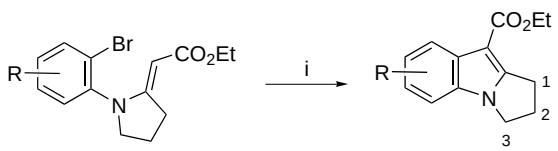
We previously reported[5] a synthesis of pyrrolo[1,2-*a*]indoles **4**, the key-step of which involved the construction of ring B by intramolecular Heck reaction[6] of ethyl 2-[*N*-(2-bromoaryl)pyrrolidin-2-ylidene]acetates **5** (Scheme 1). This Heck reaction, unusual in involving an enamine component, tolerated a variety of substituents on the aromatic ring, including electron-donating groups such as methoxy; but in these cases it was necessary to use a stoichiometric quantity of palladium(II) acetate and the hindered ligand tri(*o*-tolyl)phosphine in order to achieve reasonable yields. A similar intramolecular Heck reaction featured in a mitosene synthesis by Luly and Rapoport,[7] who cyclised an *N*-(2-bromobenzoquinone) analogue of **5** to give the quinone version of the pyrrolo[1,2-*a*]indole system directly.

The synthesis of aziridinomitosenes themselves requires that the reaction sequence be modified by the introduction of functional groups at the positions destined to become C-1 and C-2 of the condensed system **4**. The timing of the construction of the potentially labile aziridine is obviously a critical feature in the synthetic plan. We envisaged a late-stage construction of the strained ring from a precursor of the form **6** (Scheme 2) once the pivotal intramolecular Heck reaction had been accomplished on a vinylogous urethane **7**. The stereochemistry of substituents X and Y thus assumes prime importance, but the numerous published routes to aziridines from 1,2-difunctionalised precursors offer opportunities to explore methods involving both reten-



5 **4**

Scheme 1. *Reagents and conditions*: (i) $Pd(OAc)_2$ (0.2–1.0 equiv.), PPh_3 or $P(o\text{-Tol})_3$, MeCN, reflux.

Keywords: aziridinomitosene; thiolactams; Reformatsky reaction; enaminones; Heck reaction.

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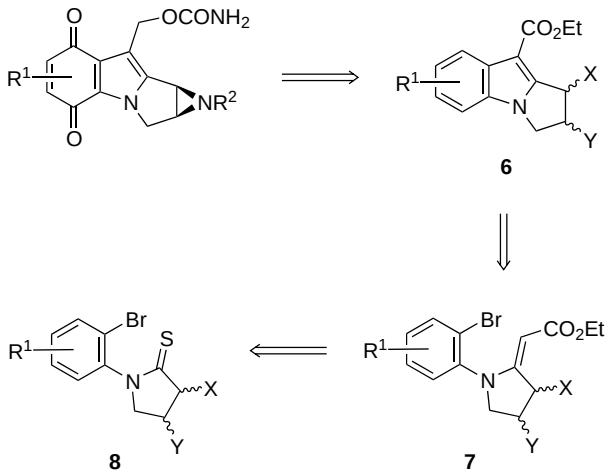
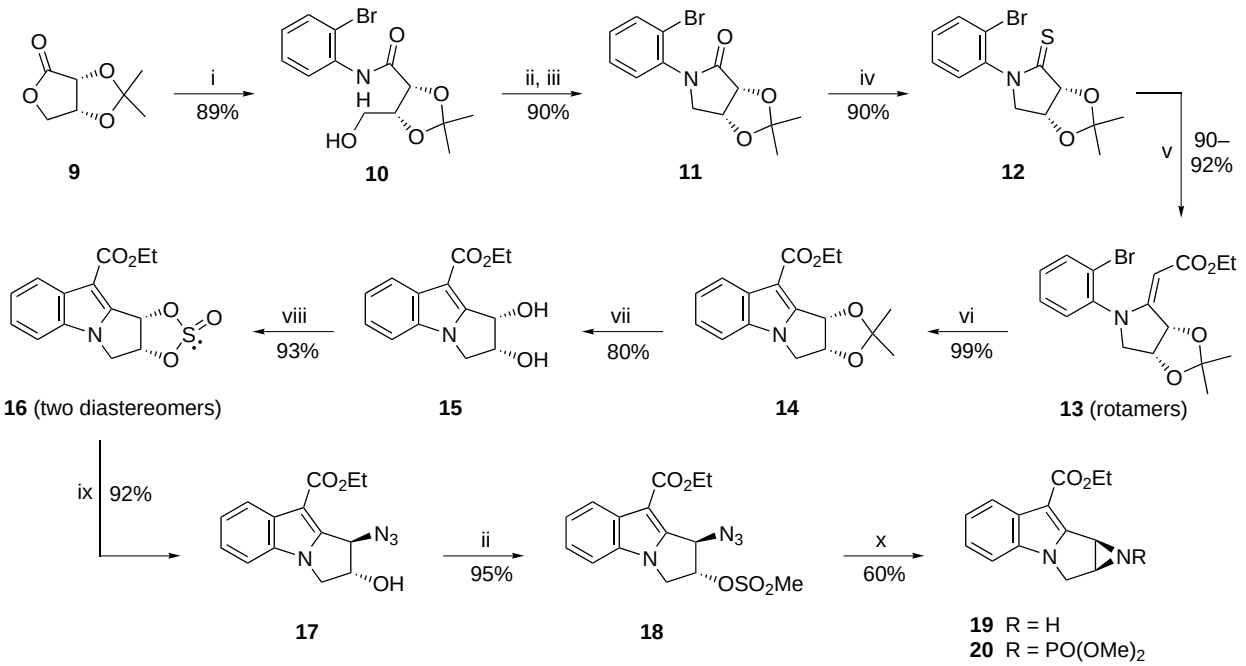


Scheme 2. Retrosynthetic plan for constructing the tetracyclic core of aziridinomitosenes.

tion and inversion of configuration.[8] In line with methods that we routinely use for preparing enaminones related to **5**,[9] we chose to investigate routes that proceeded through non-racemic 3,4-disubstituted pyrrolidine-2-thione intermediates of general structure **8**.

The precursor of choice proved to be the 'chiral pool' compound (−)-2,3-*O*-isopropylidene-D-erythronolactone (**9**), readily prepared in 77% yield by a published method that entails oxidative cleavage of the relatively cheap D-isoascorbic acid with hydrogen peroxide, followed by ketal exchange with 2,2-dimethoxypropane.[10] Lactone **9** has been used by others as a chiral building block for the synthesis of unsubstituted and *N*-alkyl 3,4-difunctionalised pyrrolidin-2-ones,[11] but not for the preparation of analogous *N*-arylated lactams. We found that **9** reacted poorly with 2-bromoaniline, our model substrate, even with prolonged heating. However, the lactone ring could be opened by treatment with the anion of 2-bromoaniline (Scheme 3). Although several bases could be used for making the anion (e.g. potassium hexamethyldisilazide, trimethylaluminum), the most convenient for larger-scale operation (ca. 5 g scale) was ethylmagnesium bromide. Yields of the amido alcohol **10** were consistently around 90%. Mesylation of **10** followed by cyclisation of the intermediate with sodium hydride in THF gave the *N*-(2-bromophenyl) lactam **11** in a yield of 90% for the two-step procedure. Thionation of this product with Lawesson's reagent completed the synthesis of the substituted pyrrolidine-2-thione **12** in 90% yield.

The transformation of thiolactam **12** into the vinylogous urethane **13** was problematic. When standard Eschenmoser sulfide contraction[12] and related condensation methods failed, we turned to an atypical application of the Reformatsky reaction that we[13] and others[14] have exploited in several rather specific cases involving the thiocarbonyl group as the electrophilic partner. Heating **12** at reflux in THF with an excess (3 equiv.) of the organozinc reagent formed by sonicating activated zinc powder with ethyl bromoacetate in THF in the presence of iodine as catalyst afforded the desired product **13** in reproducibly good yields of above 90%. On the NMR spectroscopic timescale at ambient temperature, this compound exists as an equal mixture of two rotamers about the N–aryl bond, but signals were shown to coalesce at higher temperatures. The crucial



Scheme 3. *Reagents and conditions*: (i) 2-bromoaniline, EtMgBr, THF, −78°C; (ii) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0°C to rt; (iii) NaH, THF, rt; (iv) Lawesson's reagent, toluene, reflux; (v) Zn (5 equiv.), $BrCH_2CO_2Et$ (3 equiv.), I_2 (0.2 equiv.), THF, ultrasound, then add **15**, THF, reflux; (vi) $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.4 equiv.), KOAc (7.5 equiv.), Bu_4NBr (2.5 equiv.), DMF–MeCN–H_2O (1:1:0.2), 100°C, 5 h; (vii) TFA, THF–H_2O (1:1), rt; (viii) $SOCl_2$, NEt_3, CH_2Cl_2, −15°C; (ix) NaN_3, DMF, 55°C, then aq. H_2SO_4; (x) $P(OMe)_3$, THF, reflux, then NaH, rt.

intramolecular Heck cyclisation of **13** under conditions that we had employed for the model systems (cf. Scheme 1) gave disappointing yields of the ketal-protected pyrrolo[1,2-*a*]indole **14** (<30%). However, by a judicious combination of solvent, base, ligand and additive[15] (Scheme 3), an almost quantitative yield of **14** could be obtained even when the reaction was performed on a 2 g scale. The corresponding methyl and menthyl esters, made by quite different routes, have been reported by Sulikowski and co-workers.[3e]

With several methods available for the transformation of 1,2-diols into aziridines,[8] our immediate task was to remove the protecting group from **14**. This simple transformation proved troublesome, because under standard conditions with aqueous mineral acid, or with iodine in methanol,[16] competing eliminations and reactions in which one or both hydroxy groups were displaced were found to occur. However, with trifluoroacetic acid in a mixture of THF and water, diol **15** could be obtained in 80% yield. We chose to effect the double S_N2 displacement of the OH groups with a nitrogen nucleophile via a cyclic sulfate, an approach that has precedent for the synthesis of aziridines.[17] Accordingly, diol **15** was treated with thionyl chloride and triethylamine in dichloromethane[18] to produce a 1:1 mixture of the two separable cyclic sulfite diastereomers **16** in 93% yield. It was all the more disappointing, therefore, that we were never able to oxidise the sulfites to the desired sulfate under the Sharpless conditions (catalytic ruthenium trichloride with sodium periodate as oxidant[18]). However, we fortuitously discovered that the diastereomeric mixture of sulfites underwent efficient nucleophilic ring opening when treated with sodium azide in DMF—an unusual, but not unprecedented,[19] transformation. After acidic work-up, the azidoalcohol **17** was isolated in 92% yield. The regiochemistry and stereochemistry of the reaction was confirmed by an X-ray crystal structure determination on compound **17**.

The Staudinger reaction of azides with phosphorus(III) reagents gives iminophosphorane intermediates that can displace adjacent leaving groups to yield aziridines.[4d,20] In preparation for applying this methodology, we converted **17** into the corresponding azidomesylate **18** (95% yield). When **18** was treated with triphenylphosphine, the unstable unprotected aziridine **19** was formed in poor yield (ca. 30%). Among other decomposition products was a dimeric compound in which the two moieties were apparently linked by a piperazine ring. However, treatment of **18** with trimethyl phosphite in boiling tetrahydrofuran yielded an isolable dimethyl phosphoramidate intermediate, which was immediately cyclised with sodium hydride in tetrahydrofuran to give the *N*-phosphorylated mitosene analogue **20** in 60% yield.

In summary, we have achieved an enantioselective synthesis of an advanced tetracyclic model for the aziridinomitosenes that has the advantage of using inexpensive reactants and reagents as well as relatively straightforward transformations. The route is comparatively short (11 steps based on the D-erythronolactone derivative **9**), the yields of individual steps are generally good, and extension to the synthesis of aziridinomitosenes themselves can readily be envisaged. We are currently investigating the preparation of 2-bromoanilines that contain the characteristic ring A substitution patterns of mitomycins as well as functionality that will favour oxidation of the ring to the quinone level found in the target systems.

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