Tandem Radical Cyclisation and Translocation Approaches to Biologically Important Mitomycin Ring Systems

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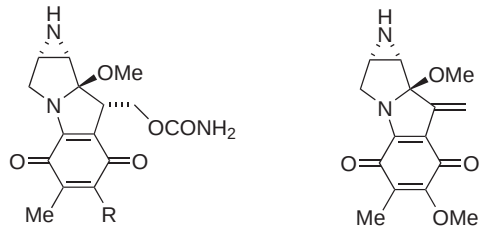
Abstract: New free-radical cyclisation and translocation approaches to the tricyclic mitomycin ring system have been developed. These convergent approaches involve either a tandem 5-*endo*/5-*exo* radical cyclisation or alternatively, a 1,6-hydrogen-atom transfer followed by 5-*exo* cyclisation sequence.

Key words: cyclisations, mitomycin, radical reactions, tandem reactions, tin

The mitomycins, which include mitomycin A **1**, C **2** and K **3**, are a family of naturally occurring compounds which were first isolated from *Streptomyces verticillatus* in the 1960's.[1] These compounds have attracted considerable medical interest due to their pronounced antibiotic and antitumour activities. They are active against both Gram-positive and -negative bacteria and also several kinds of tumours. Although numerous synthetic approaches to the mitomycins have been reported,[2,3] the development of a direct, versatile, diastereo- and enantio-selective approach to these synthetically challenging compounds is still lacking. As a consequence, we have investigated concise synthetic approaches to the core tricyclic ring system of these compounds using novel tandem radical cyclisation reactions. These approaches were designed to afford not only naturally occurring mitomycins but also a range of biologically important analogues including BMY-25067 **4** (Figure).[4]

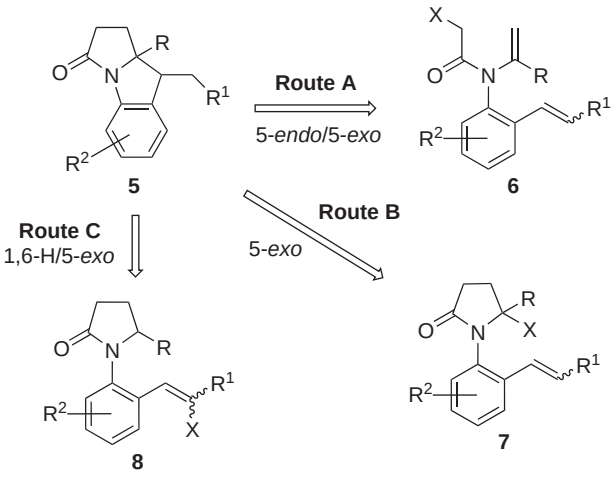


1; R = OMe
2; R = NH_2
4; R = $NH(CH_2)_2SS$-(4-NH_2)-Ar

3

Figure Mitomycins **1**, **2**, **3** and **4**

The development of novel cascade (or domino) radical reactions is an active area of current research[5] and our initial approach to the mitomycin ring system focused on the application of an unusual 5-*endo* followed by 5-*exo* tandem radical cyclisation sequence (Scheme 1, Route A). Tricycles of type **5** have previously been elaborated to mitomycins[2] and so an efficient and concise approach to this ring system, from diene **6**, was first investigated. The proposed tandem cyclisation of halide **6** followed on from related studies within our group, which has shown that haloenamides can undergo sequential 5-*endo*/5-*exo* reactions to form pyrrolizidinones in the presence of triphenyl- or tributyl-tin hydride.[6] This required a radical stabilising group, namely an ester, on the second acceptor double bond (i.e. $R^1 = CO_2R$ in **6**) so as to prevent a reversible cyclisation leading to the thermodynamically favoured indolizidinone ring system (derived from a 5-*endo*/6-*endo* cyclisation).



Scheme 1

Hence our studies began by the synthesis of a suitable unsaturated ester (of type **6**) starting from 2-nitrobenzaldehyde **9** (Scheme 2). Initially, a Wittig reaction followed by selective reduction of the nitro group afforded aniline **10** in good yield.[7] Subsequent condensation of **10** with a ketone was expected to afford an intermediate imine/enamine, which on N-acylation would yield a variety of enamide precursors (with various R groups, Scheme 1). Unfortunately, this reaction proved problematic and the desired enamide was only formed in good to reasonable yield when using acetophenone followed by chloroacetyl chloride. This gave enamide **11**, which was then reacted with triphenyltin hydride and AIBN (added over 1 h) in boiling toluene to initiate free-radical cyclisation. Follow-

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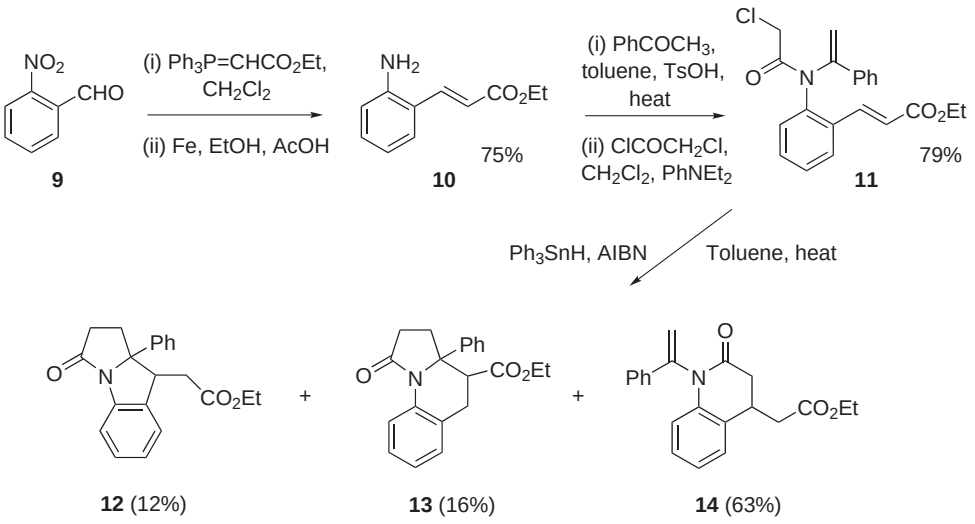
ing work-up and column chromatography, three lactam products were isolated from the reaction. The desired tricycle **12** was formed as a single diastereoisomer as indicated by the ^{1}H NMR spectrum[8] but only in 12% yield. A competitive 5-*endo*-6-*endo* tandem cyclisation was also observed to give tricycle **13** (as a single diastereoisomer)[8] in 16% yield. The ^{1}H NMR spectrum of **13** showed a distinctive doublet at 9.02 ppm for the aromatic H-1 hydrogen, which is characteristic of this type of 5,6,6-ring system.[9] The fact that a 6-*endo* cyclisation takes place presumably reflects the stability of the intermediate pyrrolidinone radical; this radical is mesomerically stabilised by both the amide nitrogen atom and the phenyl ring. This ensures reversible 5-*exo* ring-closure leading to the formation of the thermodynamically favoured 5,6,6-ring system. However, the major product from this reaction was the piperidinone **14**. This was derived from a competitive 6-*exo* cyclisation of the intermediate carbamoyl radical directly on to the unsaturated ester double bond. Reaction of the corresponding iodide, under the same reaction conditions, gave similar yields of **12** and **13** (overall 20%), and once again, the 6-*exo* product **14** was the major compound isolated (in 36% yield).

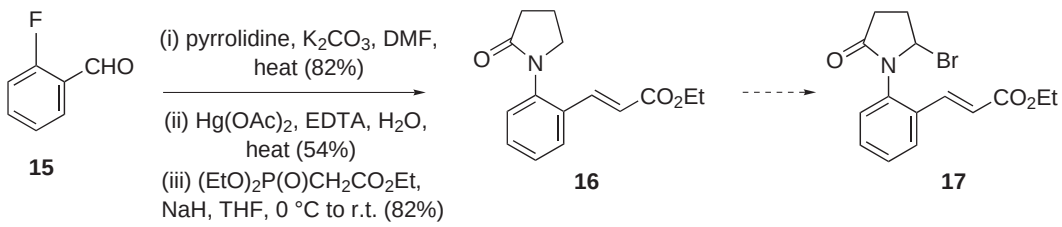
Thus, although the desired 5,5,6-ring system was formed, the yield of the product was modest because of competing free-radical cyclisations. In order to avoid the formation of a piperidinone our attention turned to the cyclisation of a 5-halopyrrolidinone of type **7** (Scheme 1, Route B). In this case, cyclisation of the intermediate pyrrolidinone radical on to an unsaturated ester double bond (**7**, $R^1 = CO_2R$) was expected to afford the desired 5,5,6-ring system. It should be noted that a competitive 6-*endo* cyclisation of **7** is also possible, particularly if a radical stabilising group (e.g. **7**, R = phenyl) is present at the site of radical generation. So, to minimise 6-*endo* cyclisation, reaction of the parent pyrrolidinone (**7**, R = H) was investigated.

The synthesis of a suitable 5-halopyrrolidinone precursor started from 2-fluorobenzaldehyde **15** (Scheme 3). Nucleophilic aromatic substitution in the presence of pyrrolidine was followed by oxidation of the pyrrolidine ring[10] to afford the corresponding pyrrolidinone. Olefination of the aldehyde using a Horner–Wadsworth–Emmons type reaction then afforded the expected *E*-alkene **16** in good overall yield. However, problems arose with the introduction of a halogen atom at the 5-position of the pyrrolidinone ring. Hence, for example, attempted bromination of **16** to give **17** using NBS in the presence of AIBN gave rise to a number of products in low yield. This may reflect the instability of the bromopyrrolidinone **17**[11] and/or competing reactions involving NBS and the alkene double bond of **16**.

An alternative cyclisation approach was then devised using a related vinyl halide precursor of type **8** (Scheme 1, Route C). In this case, the required pyrrolidinone radical was expected to be formed from a 1,6-hydrogen atom

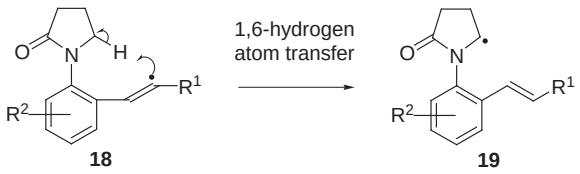


Scheme 2



Scheme 3

transfer reaction.[12] Hence, reaction of **8** (R = H) with the tributyltin radical should produce reactive vinyl radical **18**, which could undergo a rearrangement reaction so as to form the more stable pyrrolidinone radical **19** (Scheme 4).



Scheme 4

The required *Z*-vinyl bromide precursor **20** was prepared in a similar manner to pyrrolidinone **16**, but using the bromophosphonate $(EtO)_2P(O)CHBrCO_2Et$[13] in the Horner–Wadsworth–Emmons step (Scheme 5). Following reaction of **20** with tributyltin hydride and AIBN (added over 2 h), the desired 5,5,6-tricycle **21** was isolated in 64% yield as a 1.4:1 mixture of diastereoisomers. It was pleasing to see that the 6-*endo* product **22** was formed in only 6% yield (as a single diastereoisomer) and that no simple reduced product was isolated. Whereas the ^1H NMR spectra for the two diastereoisomers of **21** showed signals at 4.81–4.75 and 4.34–4.30 ppm for the NCH hydrogen,[14] the corresponding NCH hydrogen in **22** was shifted to 4.07–3.97 ppm.[15]

A similar cyclisation reaction was observed when using the dimethoxyaryl analogue **24** (Scheme 6). Nitration (HNO_3/SiO_2) of commercially available 2,5-dimethoxybenzaldehyde gave **23** in 76% yield, which was then elaborated to vinyl bromide **24** in four steps.[16] On reaction of **24** with tributyltin hydride (added over 2 h) the 5,5,6-tricycle **25** was isolated as the major product in 50% yield (as a 7.3:1 mixture of isomers) together with the 6-*endo* product **26** (as a single isomer) in 20% yield. Interestingly, no products derived from simple reduction or 1,6-hydrogen atom transfer from the methoxy group were isolated.

This work has shown that the 5,5,6-ring system present in mitomycins can be prepared, for the first time, via tandem radical cyclisation sequences. The mild cyclisation conditions and convergent approach offers a potentially flexible approach to these types of biologically important compounds. The ability to control the ratio of 5-*exo*/6-*endo* radical cyclisation pathways by appropriate substitution of the precursor is of particular mechanistic interest as is the novel 1,6-hydrogen atom transfer reaction. This is shown to afford an elegant approach to an intermediate pyrrolidinone radical, which proved impossible to access from a classical halogen-atom transfer route because of the difficulty in preparing the requisite 5-halopyrrolidinone precursor.

Acknowledgement

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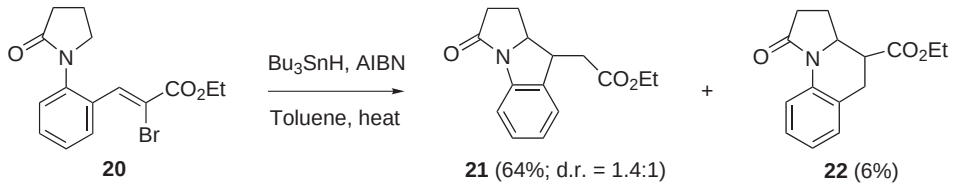
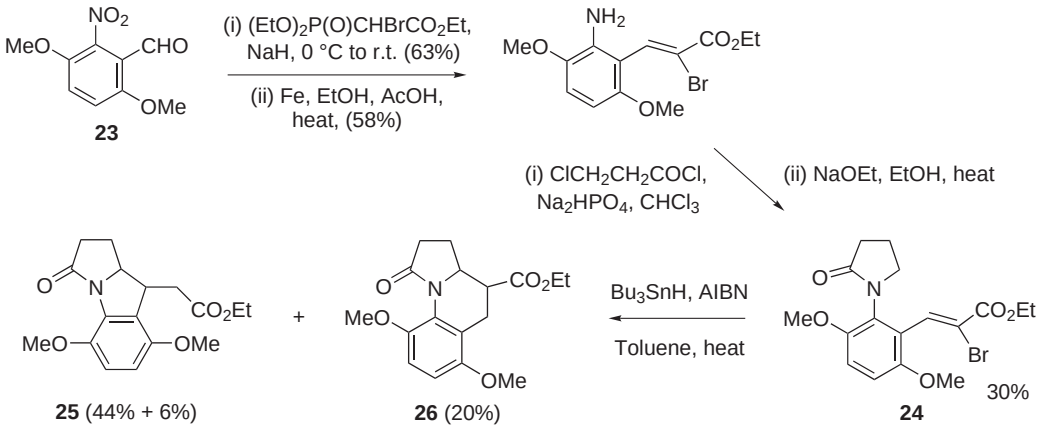


Scheme 5



Scheme 6

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(7) All new compounds exhibited satisfactory spectral and analytical (high-resolution mass) data.

(8) Tricycle **12**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.80 (1 H, d, *J* = 8 Hz, H-1 aromatic), 7.53–6.97 (8 H, m, aromatic), 4.26 (2 H, q, *J* = 7 Hz, CO_2CH_2), 3.78 (1 H, dd, *J* = 11 and 4.5 Hz, $CHCH_2CO_2$), 2.75 (1 H, dd, *J* = 17.5 and 11 Hz, $CHCO_2$), 2.62–2.15 (5 H, m, $CHCO_2$, $NCOCH_2$ and $NCOCH_2CH_2$) and 1.32 (3 H, t, *J* = 7 Hz, $CO_2CH_2CH_3$). MS (CI, NH_3): *m/z* (%) = 336 (100) [M + H$^+$]. Found (CI, NH_3): 336.1598 [M + H$^+$]. $C_{21}H_{21}NO_3$ requires for [M + H$^+$], 336.1600. Tricycle **13**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.02 (1 H, d, *J* = 8.2 Hz, H-1 aromatic), 7.46–6.99 (8 H, m, aromatic), 4.36–4.26 (2 H, m, CO_2CH_2), 3.03 (1 H, dd, *J* = 13.3 and 4.1 Hz, $CHCHCO_2$), 2.89–2.30 (6 H, m, $CHCHCO_2$, $NCOCH_2$ and $NCOCH_2CH_2$) and 1.36 (3 H, t, *J* = 7 Hz, $CO_2CH_2CH_3$). MS (CI, NH_3): *m/z* (%) = 336 (100) [M + H$^+$]. Found (CI, NH_3): [M + H$^+$] 336.1599. $C_{21}H_{21}NO_3$ requires for [M + H$^+$] 336.1600.

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(15) 5,5,6-Tricycle **21**. Diastereoisomer 1: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (1 H, d, *J* = 7.8 Hz, H-1 aromatic), 7.27–7.18 (2 H, m, aromatic), 7.05–7.01 (1 H, m, aromatic), 4.81–4.75 (1 H, m, NC*H*), 4.17 (2 H, q, *J* = 7.1 Hz, CO_2CH_2), 3.74–3.69 (1 H, m, $CHCH_2CO_2$), 2.90–2.82 (1 H, m, NCOC*H*), 2.63–2.57 (2 H, m, $CHCO_2$ and NCOC*H*), 2.43 (1 H, dd, *J* = 16.8 and 5.7 Hz, $CHCO_2$), 2.19–2.14 (1 H, m, $NCOCH_2CH$), 2.00–1.91 (1 H, m, $NCOCH_2CH$) and 1.26 (3 H, t, *J* = 7 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 170.7 (NCO and CO_2), 138.0, 137.0 (2 × *C*=CH aromatic), 128.4, 125.2, 124.3, 114.5 (4 × C=*C*H aromatic), 65.0 (NCH), 60.9 (CO_2CH_2), 38.3 ($CHCH_2CO_2$), 36.4, 36.2 ($CHCH_2CO_2$ and $NCOCH_2$), 23.3 ($CH_2CH_2CH_2$), 14.2 ($CO_2CH_2CH_3$). MS (CI, NH_3): *m/z* (%) = 260 (100) [M + H$^+$]. Found (CI, NH_3): [M + H$^+$] 260.1290. $C_{15}H_{17}NO_3$ requires for [M + H$^+$] 260.1287. Diastereoisomer 2: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (1 H, d, *J* = 7.8 Hz, H-1 aromatic), 7.41–7.04 (3 H, m, aromatic), 4.34–4.30 (1 H, m, NCH), 4.25–4.16 (2 H, m, CO_2CH_2), 3.60–3.55 (1 H, m, $CHCH_2CO_2$), 3.03 (1 H, dd, *J* = 16.4 and 4.4 Hz, $CHCO_2$), 2.86–2.78 (1 H, m, NCOCH), 2.61–2.51 (3 H, m, $CHCO_2$, NCOCH and $NCOCH_2CH$), 2.15–2.06 (1 H, m, $NCOCH_2CH$) and 1.30 (3 H, t, *J* = 7 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 171.6 (NCO and CO_2), 139.1, 136.3, 128.4, 124.4, 123.9, 115.0 (*C*=*C*H aromatic), 69.8 (NCH), 60.9 (CO_2CH_2), 44.8 ($CHCH_2CO_2$), 37.8, 36.1 ($CHCH_2CO_2$ and $NCOCH_2$), 29.2 ($CH_2CH_2CH_2$), 14.4 ($CO_2CH_2CH_3$). MS (CI, NH_3): *m/z* (%) = 260 (100) [M + H$^+$]. Found (CI, NH_3): [M + H$^+$] 260.1288. $C_{15}H_{17}NO_3$ requires for [M + H$^+$] 260.1287. 5,6,6-Tricycle **22**. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.70 (1 H, d, *J* = 9.1 Hz, H-1 aromatic), 7.27–7.04 (3 H, m, aromatic), 4.26 (2 H, q, *J* = 7.2 Hz, CO_2CH_2), 4.07–3.97 (1 H, m, NC*H*), 3.14–3.09 (2 H, m, $CHCHCO_2$ and CH_2CHCO_2), 2.74–2.33 (4 H, m, $NCOCH_2$, $CHCHCO_2$ and $NCOCH_2CH$), 1.93–1.77 (1 H, m, $NCOCH_2CH$) and 1.32 (3 H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 172.6 (NCO and CO_2), 136.0, 128.9, 127.4, 124.0, 123.9, 119.1 (*C*=*C*H aromatic), 61.2 (CO_2CH_2), 58.9 (NCH), 45.4 ($CHCO_2$), 31.9, 31.5 ($NCOCH_2$ and CH_2CHCO_2), 24.0 ($CH_2CH_2CH_2$), 14.3 (CH_2CH_3). Found (CI, NH_3): [M + H$^+$] 260.1285. $C_{15}H_{17}NO_3$ requires for [M + H$^+$] 260.1287.

(16) The low yield (30%) for the N-acylation/cyclisation reactions (to form the pyrrolidinone ring) was due to the formation of an alkyne in 55% yield, which resulted from dehydrobromination of vinyl bromide **24** by ethoxide.