A Novel Cyclisation Strategy for the Synthesis of Lactonamycin: A New Route to Highly Functionalised Heterocyclic Rings

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Received 8 September 2006

Abstract: A novel thermal cascade reaction equivalent to the well-known [2+2+2] cycloaddition has been developed which is clean and reliable and does not involve the use of metal ions. This highly efficient method has been used to construct a model for the synthesis of the antibiotic lactonamycin. The utility of this new sequence for the formation of furans is also reported.

Key words: lactonamycin, furan, cascade, cyclisation, thermal

Lactonamycin (**1**) was isolated from *Streptomyces rishiniensis* by Matsumoto et al. in 1996.[1] Lactonamycin (**1**) showed good antimicrobial activity against Gram-positive bacteria including excellent efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[2] Lactonamycin (**1**) was also found to possess antitumour activity, and because of its interesting biological profile[2] and unusual structure it has attracted significant interest from the chemical community. Hitherto four groups have published synthetic work directed towards the construction of lactonamycin (**1**).

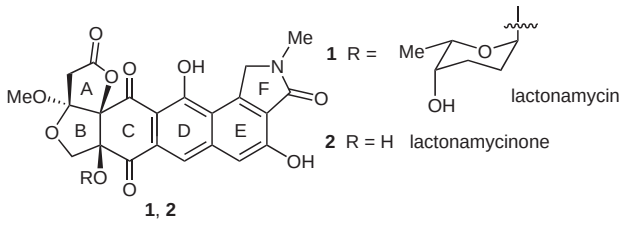
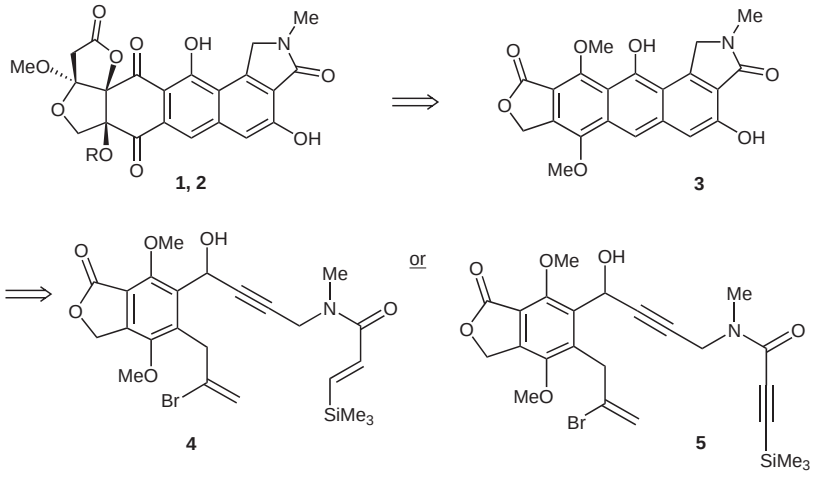


Figure 1

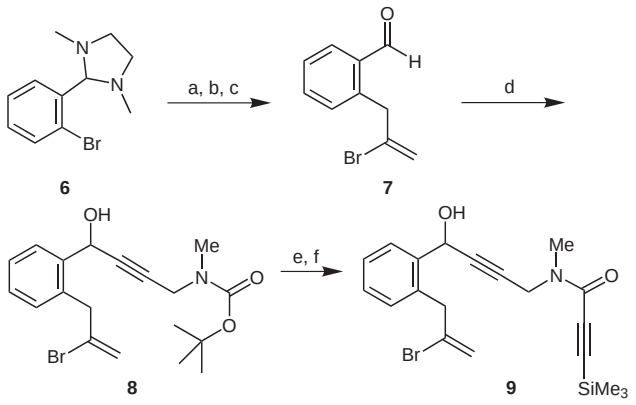
In 2000 and 2001, Danishefsky and Cox reported two different approaches to the ABCD ring system of **1** and later reported a synthetic route to lactonamycinone **2**.[3–6] Behar and Deville reported a route to the CDEF ring system[7] along with Kelly et al.[8] who also reported a synthesis of the chiral AB system.[9] More recently, an approach to the ABCD ring system has been reported by Barrett and coworkers.[10] Our approach to the CDEF ring system differs from all the approaches hitherto reported and is reliant on a cascade sequence.[11] Retrosynthetic analysis of the lactonamycin molecule revealed three new approaches. Herein we report the first of these strategies (Scheme 1).



Scheme 1 Retrosynthesis of lactonamycin

SYNLETT 2006, No. 19, pp 3243–3246
Advanced online publication: 23.11.2006
DOI: 10.1055/s-2006-951542; Art ID: D26606ST

We elected to construct a model system in order to evaluate the palladium[12] or radical-mediated (tin hydride)[13] cyclisation reactions which would afford lactonamycin precursors (Scheme 2).

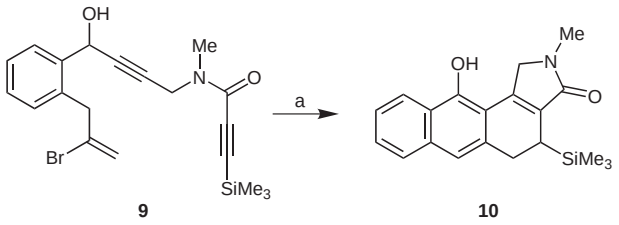


Scheme 2 *Reagents and conditions*: (a) *n*-BuLi (1.05 equiv), THF, –78 °C; (b) CuCN (1.05 equiv), –78 °C to –40 °C; (c) 2,3-dibromopropene (1.2 equiv), THF, –78 °C to r.t. then HCl, H_2O (73% overall); (d) HC≡C–CH_2NMe(Boc), *n*-BuLi (1.05 equiv), THF, –90 °C then *t*-BuBr (2 equiv), –90 °C to r.t. (83% overall); (e) HCl in Et_2O (2 M); (f) Et_3N (2.5 equiv), CH_2Cl_2, trimethylsilylpropioloyl chloride (79%).

Treatment of the aminal **6** with *n*-butyllithium in tetrahydrofuran at –78 °C, followed by the addition of an equimolar amount of cuprous cyanide[14] and then 2,3-dibromopropene, gave upon work-up the aldehyde **7** in good (73%) yield. Careful addition of *n*-butyllithium to *N*-Boc-*N*-methlypropargylamine at –90 °C followed by the addition of aldehyde **7** afforded the alcohol **8** after work-up with *tert*-butyl bromide. The addition of *tert*-butyl bromide as a proton source proved to be essential to avoid dimerisation and the formation of other unwanted impurities.

Reaction of the alcohol **8** with ethereal hydrogen chloride facilitated removal of the *N*-Boc[15] protecting group and addition of trimethylsilylpropioloyl chloride (generated from trimethylsilyl-propiolic acid and oxalyl chloride) in the presence of triethylamine gave the radical cyclisation precursor **9** in 79% yield.[16]

We discovered, however, that when the cyclisation precursor **9** was heated alone in boiling toluene the tetracycle **10** was isolated in 50% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) PhMe, reflux, 2 h, (50%).

In his synthesis of gibberellic acid Corey used epoxypropene as an acid trap.[17] We employed the higher boiling and less volatile 1-epoxyhexene as an acid trap and the yield of **10** was thence improved to an isolated 76%. The X-ray crystal structure of **10** is depicted in Figure 2.

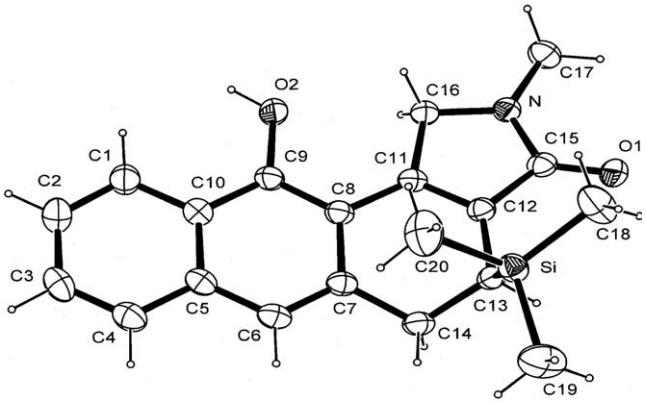
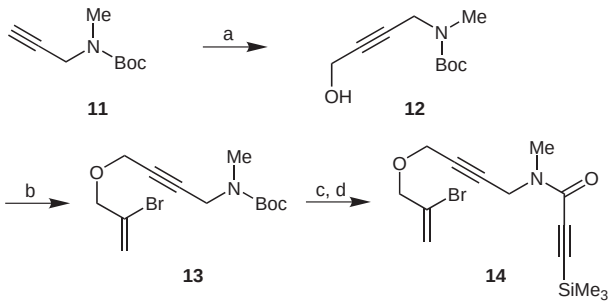


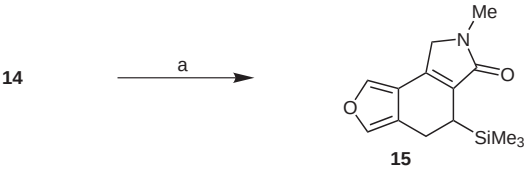
Figure 2 X-ray crystal structure of **10**

In order to extend this finding to the synthesis of other heterocyclic systems we synthesised the ether **14** (Scheme 4).



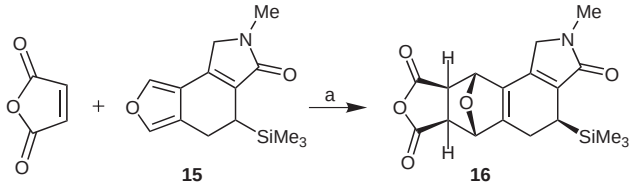
Scheme 4 *Reagents and conditions*: (a) *n*-BuLi (1.05 equiv), $(CH_2O)_n$, THF, –78 °C, (82%); (b) NaH (1.1 equiv), THF, 2,3-dibromopropene (1.05 equiv), (81%); (c) TFA, CH_2Cl_2; (d) trimethylsilylpropioloyl chloride, CH_2Cl_2, Et_3N (2.5 equiv), (82%, 2 steps).

When the ether **14** was heated in boiling toluene-containing 1-epoxyhexene as an acid scavenger, the furan **15** was obtained in 90% yield (Scheme 5).[18]



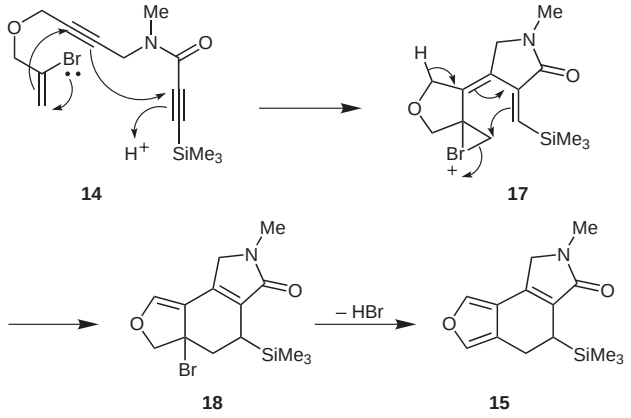
Scheme 5 *Reagents and conditions*: (a) PhMe, reflux, 1 h, 1-epoxyhexene (90%).

Diels–Alder cycloaddition of the furan **15** to maleic anhydride gave the cycloadduct **16**, which demonstrates the utility of this novel strategy for an additional route to lactonamycin (**1**) and its analogues (Scheme 6).



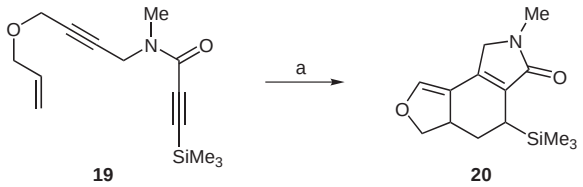
Scheme 6 *Reagents and conditio*ns: (a) Et_2O, r.t., 24 h, (50%).

Initially we wondered if an acid catalysed mechanistic pathway was involved in the cyclisation process (Scheme 7).



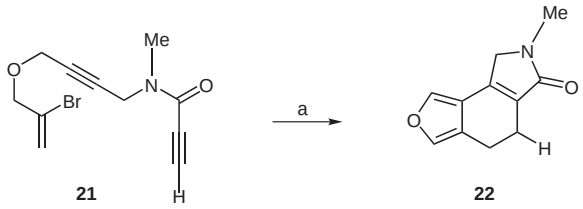
Scheme 7 Possible acid-catalysed mechanism

The mechanism outlined in Scheme 7 is less favoured because the ether **19** was also found to cyclise in boiling toluene to afford the dihydrofuran **20** (Scheme 8).



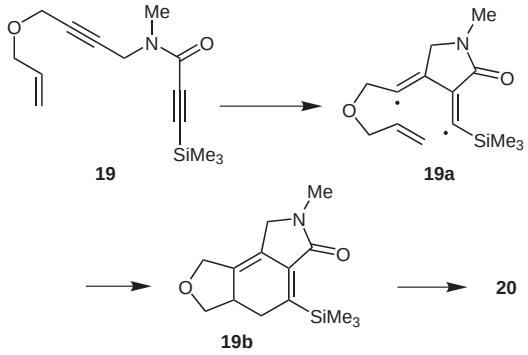
Scheme 8 *Reagents and conditions*: (a) PhMe, reflux, 1 h, (91%).

Of further interest is that when the ene-diyne **21** is heated in boiling toluene the tricycle **22** is formed in 97% yield. The longer reaction time of 13 hours is required to achieve cyclisation in the absence of a trimethylsilyl group (Scheme 9).



Scheme 9 *Reagents and conditions*: (a) PhMe, reflux, 13 h, (97%).

The cyclisation could involve the formation of a diradical intermediate as shown in Scheme 10. Trapping of the diradical **19a** with the pendent double bond would afford the highly strained and unstable cyclohexadiene **19b**, which would undergo double-bond isomerisation to give **20**.



Scheme 10 Suggested radical-based mechanism

We note that addition of tri-*n*-butyltin hydride to the reaction mixture inhibits the formation of **20**, which adds additional support to a radical pathway. Examination of molecular models also shows that the alkynes in **19** are in very close proximity when invoking amide resonance. Bergman et al.,[19] have published extensively on enediyne cyclisations which involve radical intermediates. We are now investigating the scope and limitations of this interesting new cyclisation which we feel will be of general interest in natural product synthesis and will avoid the use of metal catalysts.[20,21]

In summary, we report a reliable and efficient novel cyclisation reaction for the formation of fused ring systems, which is metal-free and hence environmentally friendly.

Acknowledgment

The authors would like to thank the EPSRC, Pfizer Ltd and Glaxo-SmithKline for their generous financial support. Professor Jim Hanson, Dr. Clive Penkett, Dr. Murray, Dr. Pennicott and Mr. Graham Marsh (Sussex University) are gratefully acknowledged for their useful discussions.

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(18) A typical experimental procedure for the thermal cyclisation is shown below.
Synthesis of 6-Methyl-9-trimethylsilanyl-5,6,9,10-tetrahydrofuro[10,11-*e*]isoindol-7-one(15).
To 9-trimethylsilanyl-propynoic acid [4-(bromoallyl-oxy)but-2-ynyl]methyl amide (**14**, 0.342 g, 1.0 mmol) in toluene (10 mL) was added 1-epoxyhexene (1.00 g, 1.21 mL, 10.0 mmol). The solution was stirred at reflux for 1 h, after which time TLC showed the reaction to be complete. Toluene and 1-epoxyhexene were removed in vacuo and the product purified by column chromatography (Et_2O–hexane 7:3) to give the title compound as a bright yellow oil (0.235 g, 0.9 mmol, 90% yield). ^{1}H NMR ($CDCl_3$): δ = 7.31 (s, 1 H, C2), 7.14 (s, 1 H, C12), 4.15–4.24 (d, 1 H, *J* = 18.3 Hz, C5), 3.92–4.01 (m, 1 H, C5), 3.05 (s, 3 H, C13), 2.74–2.91 (m, 2 H, C9, C10), 2.32 (d, 1 H, *J* = 7.0 Hz, C10), –0.11 (s, 9 H, C14, C15, C16). ^{13}C NMR ($CDCl_3$): δ = 173.6 (C7), 139.8 (C2), 138.3 (C4), 138.0 (C12), 137.1 (C8), 123.3 (C3), 121.4 (C11), 54.4 (C5), 32.0 (C13), 24.6 (C9), 21.9 (C10), 0.0 (C14, C15, C16). IR (neat): 3104, 2953, 2235, 1673, 1562, 851 cm^{-1}. MS (ES+): *m/z* = 284 [M + Na].
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