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Formal synthesis of (+)-lactacystin based on a novel radical cyclisation of an α-ethynyl substituted serine

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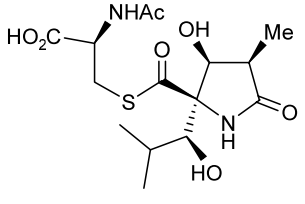
Abstract—A diastereoselective 5-*exo*-dig radical cyclisation of the bromoamide **7** produced from the enantiopure α-ethynyl substituted amino alcohol **5** led to the pyrrolidinone **8** (2:1 α:β epimers) in 70% yield. Oxidative cleavage of the alkene bond in **8**, followed by a stereoselective α-methylsulfanylation of the resulting 4-keto derivative **9**, next led to the methylsulfanyl derivative **10**. Finally, the pyrrolidinone derivative **10** was converted into the key intermediate **12** used previously in an enantioselective synthesis of (+)-lactacystin.

Lactacystin **1** is a novel biologically important pyrrolidinone-based secondary metabolite isolated from the culture broth of *Streptomyces sp*. OM-6519.[1] The compound exhibits significant neurotrophic activity due to its ability to inhibit mammalian 20S proteasomes.[2] The 20S proteasome is essential for the turnover of cellular proteins and for removing damaged, misfolded and mistranslated proteins in cells. It also plays a vital role in the turnover of many regulatory proteins that control cell growth and metabolism.[3] These features have led to speculation that lactacystin may have a therapeutic use in the treatment of debilitating conditions such as arthritis, asthma and Alzheimer's disease.[4] Not surprisingly therefore, lactacystin has been an attractive target for the synthetic chemist, and several total syntheses of the metabolite have now been published,[5] in addition to a number of formal and/or partial synthesis.[6] In this letter we describe a conceptually distinct synthetic approach to lactacystin based on a novel 5-*exo*-dig radical cyclisation of a chiral ethynyl substituted serine derivative, leading to a functionalised pyrrolidinone, which can be elaborated efficiently to key intermediates in earlier total syntheses of (+)-lactacystin.



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Thus, a Sharpless epoxidation of the 2-ethynylpropenol **2**[7] using (+)-DIPT, $Ti(O^iPr)_4$ in DCM at −10°C[8] first gave the chiral epoxide **3** (66% and 90% ee), which was next converted into the oxazoline **4a** by cyclisation of the corresponding trichloromethylacetamidate intermediate **3b**[9] in the presence of Et_2AlCl. Treatment of the alcohol **4a** with TBSOTf (DCM, 0–25°C) gave the crystalline TBS–ether **4b** (92%) whose stereochemistry was confirmed by X-ray crystallography.[10] When a solution of the 2-trichloromethyl substituted oxazoline **4b** in THF was treated with 1 M aqueous HCl, the 2-ethynyl-2-amino alcohol **5** was released which was then immediately converted into a mixture of methyl epimers of the amide **6** on acylation with 2-bromopropionoyl chloride (76% over two steps). The hydroxymethyl unit in **6** was next converted into the corresponding methyl ester **7** in three steps (i.e. Dess–Martin periodinane, then $NaClO_2$, NaH_2PO_4 and finally Me_3SiCHN_2) and in 60% overall yield (Scheme 1).

When a solution of the bromoamide **7** in toluene under reflux was treated with a solution of Bu_3SnH (1:1 equiv.) and AIBN (catalytic) in toluene over 30 min and the resulting mixture was heated under reflux for 2 h, work-up gave the corresponding pyrrolidinone **8** in 70% yield.[11] The pyrrolidinone **8** results from a facile 5-*exo*-dig cyclisation of the ethynyl substituted bromoamide **7** and was produced as a 2:1 mixture of α- and β-methyl epimers.[12] Ozonisation of the alkene **8** in MeOH at −78°C followed by a reductive work-up using

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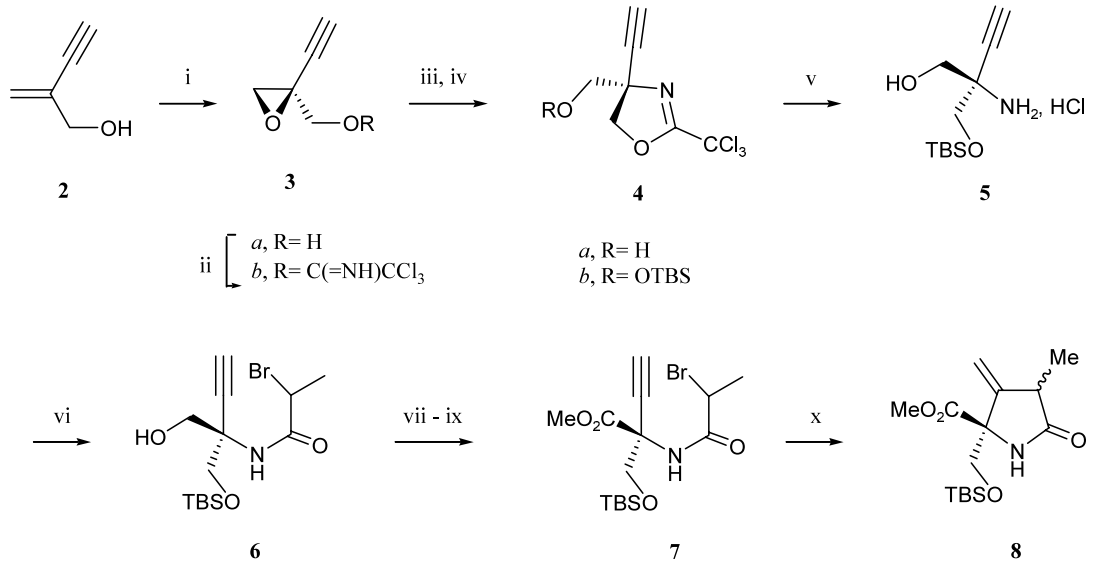
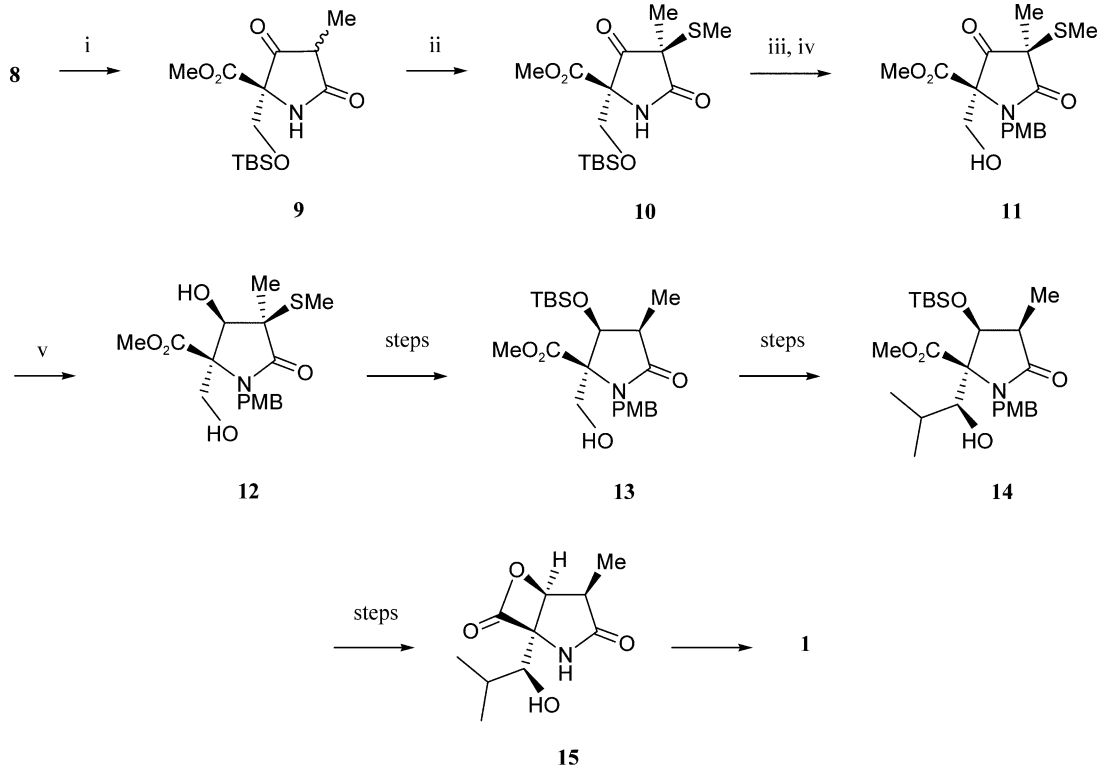


Scheme 1. *Reagents and conditions*: (i) L(+)DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, DCM, −10°C, 66%, 90% ee; (ii) Cl_3CCN, DBU, 0°C, 65%; (iii) Et_2AlCl, DCM, 0°C→rt, 75%; (iv) TBSOTf, 2,6-lutidine, DCM, 0°C→rt, 92%; (v) aq. HCl (1 M), THF, rt; (vi) $CH_3CH(Br)COCl$, $NaHCO_3$, DCM, rt, 76% (two steps); (vii) Dess–Martin periodinane, DCM, 0°C; (viii) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, 2-methyl-2-butene, rt; (ix) TMS–CHN_2, MeOH, benzene, rt, 60% (three steps); (x) Bu_3SnH, AIBN, toluene, reflux, 70%, 2:1 mixture of α- and β-Me epimers.

Me_2S (−78°C to rt) next gave the corresponding 4-ketopyrrolidinone **9** with no evidence of the co-isolation of the tetramic acid tautomer. Similar to **8**, the 4-ketopyrrolidinone **9** was isolated as a 2:1 mixture of C-3 methyl epimers with the β-epimer required for elaboration to lactacystin **1** as the minor isomer. We were disappointed to find that under a range of conditions we were not able to epimerise the C-3 centre in **9** and secure the β-methyl epimer exclusively.[13] To overcome this synthetic problem, we treated the 4-ketopyr-



Scheme 2. *Reagents and conditions*: (i) O_3, MeOH, −78°C, 15 min then Me_2S, −78°C→rt, 75%, 2:1 mixture of α- and β-Me epimer; (ii) $TolSO_2SMe$, Et_3N, DCM, rt, 78%; (iii) PMBBr, NaH, DMF, THF, 0°C→rt; (iv) HF, pyridine, THF, rt, 40% (two steps); (v) $NaBH(OAc)_3$, AcOH, rt, 90%.

rolidinone **9** with methylsulfanyl tolylsulfonate in the presence of Et_3N[14] at rt which, to our pleasure, was stereoselective and led to the 3-methylsulfanyl derivative **10** with the α-methyl stereochemistry at C-3 (ca. 10% of the C-3 β-methyl epimer was also isolated).[15] We presume this stereochemical outcome is determined by the proximity of the bulky α-orientated CH_2OTBS group at C-5 in **9** which screens methylsulfanylation from the α-face at C-3 (Scheme 2).

Protection of the nitrogen centre in **10** as its PMB derivative, followed by deprotection of the silyl ether group next led to the known substituted pyrrolidinone **11**. Finally, reduction of the 4-keto group in **11**, using sodium triacetoxyborohydride at rt, gave the pyrrolidinone derivative **12**[16] which is a key intermediate in Corey's total synthesis of (+)-lactacystin.[5e] Both of the pyrrolidinones **11** and **12** displayed NMR spectroscopic data together with mass spectrometric and optical rotation data which were identical with those reported by Corey et al. Lactacystin has been synthesized from the pyrrolidinone **12** by: (i) protection of the alcohol group followed by a novel diastereoselective desulfurisation with Raney nickel producing **13**; (ii) oxidation of the primary alcohol group in **13** and addition of 2-propenylmagnesium bromide followed by hydrogenation leading to **14**; and finally (iii) conversion of **14** into the β-lactone **15** and addition of *N*-acetylcysteine.[17]

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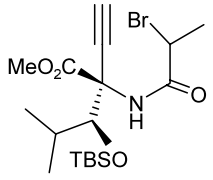
12. PMR data for **8** (360 MHz, $CDCl_3$): α-methyl epimer: δ 6.29 (1H, br. s, N*H*), 5.43 (1H, app. d, *J* 2.8, C=CH*H*), 5.19 (1H, app. d, *J* 2.3, C=CH*H*), 4.23 (1H, d, *J* 9.4, C*H*HOTBS), 3.75 (3H, s, OCH_3), 3.47 (1H, d, *J* 9.4, CH*H*OTBS), 3.08–3.00 (1H, app. m, C*H*CH_3), 1.30 (3H, d, *J* 7.4, CHCH_3), 0.85 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); β-methyl epimer: δ 6.26 (1H, br. s, N*H*), 5.50 (1H, app. d, *J* 2.7, C=CH*H*), 5.19 (1H, app. d, *J* 2.3, C=CH*H*), 4.14 (1H, d, *J* 9.4, C*H*HOTBS), 3.76 (3H, s, OCH_3), 3.55 (1H, d, *J* 9.4, CH*H*OTBS), 3.08–3.00 (1H, app. m, C*H*CH_3), 1.30 (3H, d, *J* 7.4, CHCH_3), 0.85 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$) ppm. The stereochemistries of the separated pyrrolidinones were confirmed by selective NOE enhancements.

13. For related epimerisation studies of 3-substituted pyrrolidinones, see: Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139–2140; Charrier, J.-D.; Duffy, J. E. S.; Hitchcock, P. B.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2367–2371; Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 80–90.
14. cf. Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343–348; Bateson, J. H.; Quinn, A. M.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 1151–1152.
15. PMR data for **10** (360 MHz, $CDCl_3$): δ 6.54 (1H, br. s, N*H*), 4.11 (1H, d, *J* 10.0, C*H*HOTBS), 3.97 (1H, d, *J* 10.2, CH*H*OTBS), 3.82 (3H, s, OCH_3), 2.08 (3H, s, SCH_3), 1.50 (3H, s, CH_3), 0.86 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$) ppm.
16. Data for **12**: $[\alpha]_D^{22} = -42.0$ (*c* 0.13, $CHCl_3$) (lit.[5e] $[\alpha]_D^{23} = -41.8$ (*c* 0.10, $CHCl_3$)), δ_H (500 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.6, Ar*H*), 6.87 (2H, d, *J* 8.6, Ar*H*), 5.16 (1H, d, *J* 15.3, PhCH*H*), 4.15 (1H, d, *J* 7.9, C*H*OH), 4.03 (1H, d, *J* 15.3, PhCH*H*), 3.82–3.80 (2H, m, CH_2OH), 3.80 (3H, s, $PhOCH_3$), 3.79 (3H, s, OCH_3), 3.63 (1H, d, *J* 8.2, CHO*H*), 2.16 (3H, s, SCH_3), 1.63 (3H, s, CH_3), 1.06 (1H, dd, *J* 5.7, 8.5, CH_2OH); δ_C (125 MHz) 173.5 (s), 171.6 (s), 159.5 (s), 129.7 (s), 129.5 (2d), 114.6 (2d), 76.7 (d), 72.4 (s), 62.5 (t), 55.4 (q), 53.4 (s), 52.9 (q), 44.8 (t), 22.9 (q), 12.4 (q) ppm. The stereochemistry was confirmed by selective NOE enhancements.
17. In contemporaneous studies we also examined the radical cyclisation of the ethynyl bromoamide **16** containing additional substitution by an *iso*-propyl, with the idea of securing a concise synthesis of a more advanced precursor to **14**, i.e. **17**. However, this particular reaction failed and instead led to the product of reduction of the C–Br bond in **16**, possible as a result of facile intramolecular 1,6- or 1,5-H abstraction from the 2-methylpropanol unit in the substrate.



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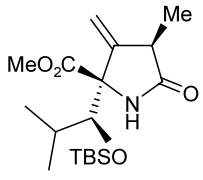

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