Pergamon

Tetrahedron Letters 42 (2001) 6271–6274

TETRAHEDRON LETTERS

Concise total synthesis of the prolyl endopeptidase inhibitor eurystatin A via a novel Passerini reaction–deprotection–acyl migration strategy†

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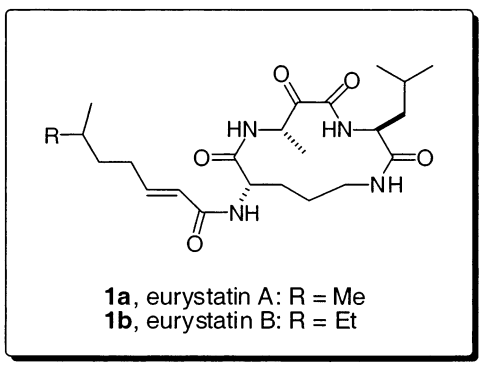
Received 14 June 2001; accepted 16 July 2001

Abstract—The Passerini reaction between suitably protected alaninal, leucine isonitrile, and ornithine components delivered adducts **10a**,**b** in high yield. Orthogonal *N*-deprotection of **10a** led, via a smooth *O*- to *N*-acyl migration, to **11**, which constitutes the entire skeleton of the eurystatins. Subsequent deprotection, macrocyclization, elaboration, and final oxidation steps efficiently afforded eurystatin A **1a** in high overall yield. © 2001 Elsevier Science Ltd. All rights reserved.

Peptidyl and peptidomimetic α-ketoamide scaffolds are useful in small molecule drug discovery programs as transition-state analog (TSA) protease inhibitors.[1] Such covalent inhibitors generally exhibit potent in vitro enzyme inhibitory activity, with sub-nanomolar equilibrium inhibitor constants (K_i) being typical of representative members.[2] Accordingly, they are finding increasing applications as potential therapeutics for important disease indications.[3–6] Eurystatins A (**1a**) and B (**1b**) are 13-membered macrocyclic natural products isolated from *Streptomyces eurythermus* R353-21 featuring leucine, ornithine and α-ketoalaninamide subunits.[7] They are reported to be potent inhibitors of the serine protease prolyl endopeptidase (PEP). Due to their relative structural simplicity, they serve as attractive targets for the development of new α-hydroxy-β-amino amide and α-ketoamide methodologies.

Utilizing the appropriate *N*-α-protected amino aldehydes **2** (Fig. 1), we recently disclosed novel variations of the atom-economical Passerini reaction[8] for the direct production of either α-acyloxy-β-amino amides **3**[1,9] or α-hydroxy-β-amino amide derivatives **4**.[9,10] We observed that orthogonal *N*-deprotection of **3** under mild conditions generates the α-acyloxy-β-amino intermediate **5**, which undergoes a facile *O*- to *N*-acyl shift and delivers the stable adduct **6** in high yield. Intermediates **4** and **6** serve as useful advanced precursors to α-ketoamide derivatives **7** by oxidation, preferably at a very late synthetic stage. The recent report by Banfi et al.[11] on a related process prompts us to disclose our application of the Passerini reaction–deprotection–acyl migration strategy towards a concise total synthesis of eurystatin A (**1a**).



1a, eurystatin A: R = Me
1b, eurystatin B: R = Et

The synthesis of isonitrile and aldehyde intermediates is outlined in Scheme 1.[12] Leucine isonitrile derivatives **8a**,**b** were obtained from the corresponding amino esters via *N*-formylation and dehydration according to Ugi protocols.[13] *N*-Fmoc-alaninal **9** was generated by either LiTEPA reduction of the requisite UNCA precursor[14] or by DIBAL reduction of the corresponding ester.[15] These methods produced crude aldehyde **9** in high chemical and enantiomeric purity (typically >95–97%), which was utilized immediately in the Passerini reactions.

Three-component reaction of leucine isonitriles **8a**,**b**, *N*-α-Fmoc-alaninal **9** and *N*-protected ornithine fragments proceeded under very mild, essentially neutral conditions, and provided the corresponding Passerini adducts **10a**,**b** in high yield and in multigram quantities (Scheme 2).[16] RP-HPLC or chiral HPLC analysis of adducts **10a** or **10b** revealed two peaks in a ratio of ca.

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† Dedicated to the memory of Joseph E. Semple.

PII: S0040-4039(01)01287-4

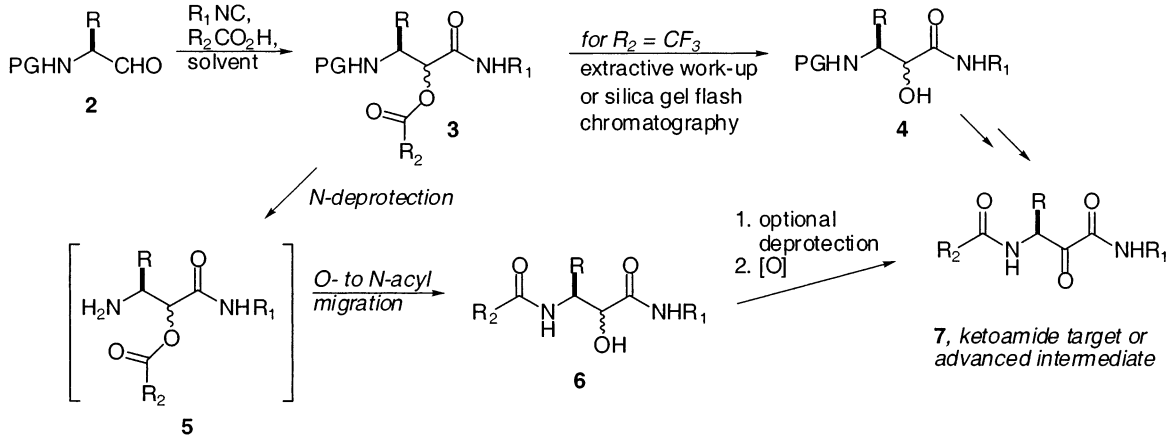
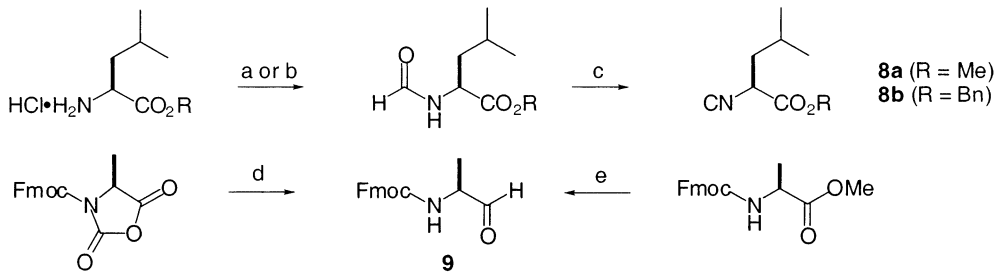
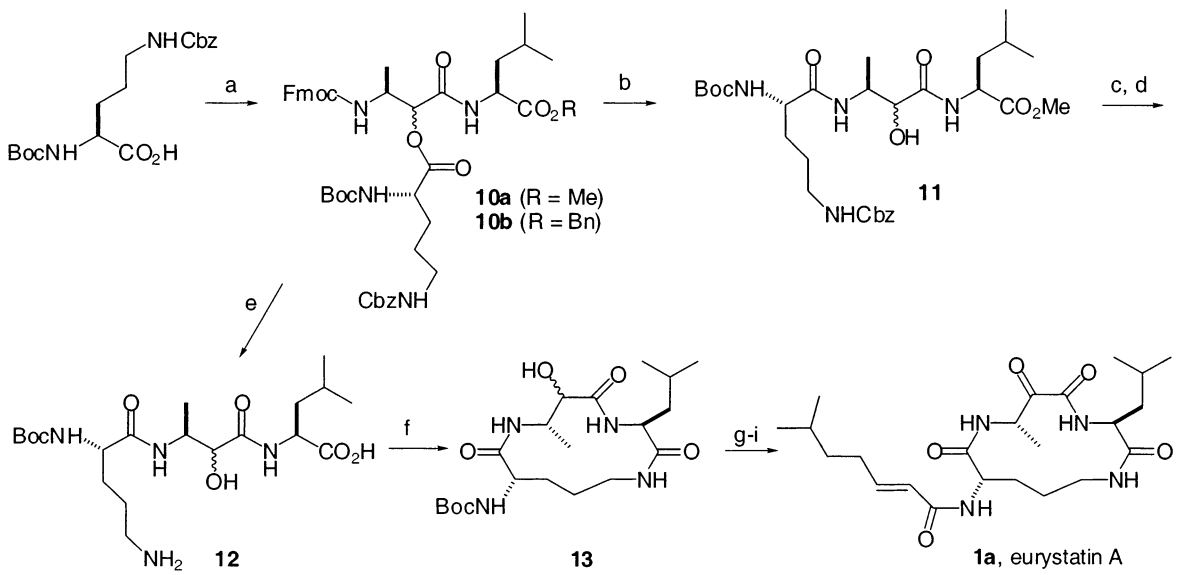


Figure 1. Variations of the Passerini reaction employing α-amino aldehydes. PG = protecting group.



Scheme 1. *Reagents and conditions*: (a) for Me ester: 1. HCO_2H, $NaCO_2H$, 70°C to rt; 2. Ac_2O, 0°C to rt, 70% distilled; (b) for Bn ester: 1. CH_3CO_2CHO, Et_3N, 0°C to rt, ~90%; (c) Cl_3CO_2CCl, NMM, CH_2Cl_2, −40 to −15°C, 86–98%; (d) $LiAl[OC(C_2H_5)_3]_3H$ (LiTEPA), THF, −40 to −5°C; HCl, ~quant.; (e) DIBAL, toluene, −78 to −20°C, 93%.



Scheme 2. *Reagents and conditions*: (a) **8a** or **8b**, **9**, CH_2Cl_2, 0°C to rt, 3–5 days; Me ester **10a**, 75%; Bn ester **10b**, 80%; (b) for Me ester **10a**: Et_2NH, rt, CH_2Cl_2, 12 h, 92%; (c) LiOH, MeOH, H_2O, rt, 95%; (d) H_2, Pd/C, MeOH, 45 psi, 3 days, ~quant. (e) for Bn ester **10b**: 1. Et_2NH, CH_2Cl_2, rt, 75%; 2. H_2, Pd/C, MeOH, 95%; (f) DPPA, DMF, $NaHCO_3$, 0–4°C, 5 days, (0.005–0.01 M), 75–85% or HBTU, HOBt, DMF, rt, 3 days, (0.005 M), 50%; (g) HCl, EtOAc, 0°C to rt, ~quant.; (h) (*E*)-6-methyl-2-heptenoic acid, EDC, HOAt, DMF, rt, 93%; (i) $Pyr{\cdot}SO_3$, DMSO, Et_3N, 5°C to rt, 75%.

1:1.2, confirming retention of the original chirality and formation of one diastereomeric pair at the newly-created α-hydroxy center.[8e,f] Base-catalyzed Fmoc-deprotection of **10a** led, via a smooth *O*- to *N*-acyl migration, to **11** in high yield.[17] Hydrolysis of **11** and subsequent hydrogenolysis afforded advanced intermediate **12**, which constitutes the entire acyclic skeleton of the eurystatins. Deprotection–migration of **10b** followed by global hydrogenolysis provided a more direct route to **12**. Macrocyclization of the ω-amino acid **12** occurred under standard high dilution conditions and delivered the 13-membered macrocycle **13** in respectable yields. Finally, **13** was elaborated to the target eurystatin A **1a** by sequential *N*-Boc deprotection, acylation with (*E*)-6-methyl-2-heptenoic acid, and oxidation to the α-ketoamide. Physical properties of our sample agreed with literature values.[18] It is of interest to note that solubility issues with both **13** and the *N*-acylated penultimate intermediate precluded the use of typical Swern-type oxidation conditions in dichloromethane solvent. However, the oxidation was efficiently and reproducibly executed via the Parikh–von Doering protocol[19] in DMSO.

Our approach to eurystatin A **1a** via the key Passerini reaction–deprotection–acyl migration strategy is convergent and highly efficient. Proceeding over nine to ten steps in 20–26% overall yield from commercially available leucine esters, it compares quite favorably to other current routes.[18,20] Although Wasserman's elegant acyl cyanophosphorane oxidation approach to **1a** proceeded concisely over ten steps, the base-labile α-ketoamide functionality is revealed early in the synthesis sequence.[18] Our experience,[1,2,10] as well as literature precedent,[2c,21] indicates that α-ketoamide racemization issues may arise during completion of such a synthesis. Schmidt's simple Passerini–acyl cleavage method to **1a** proceeded in 14 steps and utilized benzoic acid for adduct formation.[20] The benzoyl moiety was subsequently cleaved and discarded, producing a simpler α-hydroxyamide derivative akin to **4**. We contrast these approaches with our method, whereby a suitably protected ornithine derivative is used as the carboxylic acid component in the key Passerini reaction and is retained throughout the succeeding deprotection–migration stages, ultimately shortening the synthesis of this target by several steps.

In conclusion, the utility of this technology for the rapid assembly of relatively complex α-ketoamide amide-containing natural products is highlighted by a concise total synthesis of eurystatin A (**1a**). The key Passerini reaction, deprotection and acyl migration steps proceed in moderate to high yields and under mild conditions. Other noteworthy features of our methodology include high atom-economy and very late stage oxidation to the reactive α-ketoamide moiety, which minimizes potential stability and racemization issues. Numerous applications to the synthesis of α-ketoamide natural products and protease inhibitors are envisioned and will form the basis of forthcoming publications from our laboratories.

Acknowledgements

Stimulating discussions with T. K. Brunck, K. E. Pryor, J. E. Reiner and O. A. Moreno are gratefully acknowledged.

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16. Experimental for **10a**: A solution of α-*N*-Boc-ω-*N*-Cbz-Orn-OH (10.63 g, 29.0 mmol), isonitrile **8a** (4.50 g, 29.0 mmol) and freshly prepared alaninal **9** (9.10 g, 30.8 mmol) in 60 mL of dry dichloromethane was stirred at rt under nitrogen for 4 days. Solvent was removed and the residue was purified by flash chromatography on silica gel, eluting with a dichloromethane to dichloromethane/isopropanol: 99/1 gradient system to afford 17.65 g (74.5% yield) of **10a** as a pale yellow, viscous oil. TLC (silica, CH_2Cl_2/IPA, 9:1 or EtOAc): two overlapping spots. MS: $[MH]^+$ 817.9, $[MNa]^+$ 839.9. RP-HPLC and ^1H NMR analysis indicated two diastereomers, ca. 1:1.2.
17. Experimental for **11**: To a solution of **10a** (3.44 g, 4.20 mmol) in 20 mL of dry dichloromethane at rt under nitrogen was added Et_2NH (3.07 g, 42.0 mmol, 4.35 mL). After stirring the yellow solution overnight, the solvent was removed and the residue was purified by flash chromatography on silica gel, eluting with dichloromethane/isopropanol, 97:3 to afford 2.30 g (91.6% yield) of **11** as a colorless viscous oil. TLC (silica, CH_2Cl_2/IPA, 4:1): R_f ~0.5, 0.45. MS: $[MH]^+$ 595.7, $[MNa]^+$ 617.7. RP-HPLC analysis indicated two diastereomers ca. 1/1.2. ^1H NMR (CD_3OD, 400 MHz): δ 0.90–1.00 (ov. d, 6H), 1.05–1.25 (m, 3H), 1.45 (s, 9H), 1.50–1.85 (br. m, 7H), 3.1 (m, 2H), 3.65+3.75 (2s, 3H total), 4.00 (br s, 2H), 4.21–4.31 (m, 1H), 4.45–4.55 (m, 1H), 5.11 (s, 2H), 7.25–7.40 (m, 5H).
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