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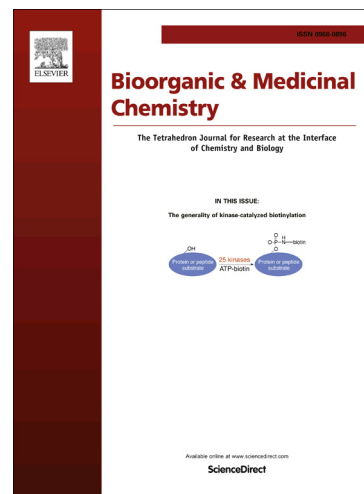
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## Practical synthesis of capromorelin, a growth hormone secretagogue, via a crystallization-induced dynamic resolution

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### Abstract

A practical synthesis of capromorelin (**1**), a growth hormone secretagogue, is described that utilizes as a key step a crystallization-induced dynamic resolution (CIDR) of ( $\pm$ )-3a-benzyl-2-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3(3aH)-one [( $\pm$ )-**2**] by (*L*)-tartaric acid salt formation, yielding (*R*)-**2.L-tartaric acid** in high chemical yield (>85%) and with diastereomeric excess (de) of ~98%. Treatment of (*R*)-**2.L-tartaric acid** with ammonium hydroxide provided (*R*)-**2** without loss of chiral purity. In situ generated (*R*)-**2** was coupled with (*R*)-3-(benzyloxy)-2-(2-(tert-butoxycarbonyl)-2-methylpropanamido)propanoic acid [(*R*)-**3**] to give predominantly a single diastereomer of N-Boc-protected capromorelin [(1*R*,3*aR*)-**4**]. This process was used to prepare bulk quantities of capromorelin from ( $\pm$ )-**2** to support preclinical toxicology studies.

### Keywords

Capromorelin

Crystallization-induced dynamic resolution

Growth hormone secretagogue

GHS-R1a

Ghrelin mimetic

### 1. Introduction

Capromorelin (2-amino-N-[(1*R*)-2-[(3*aR*)-2,3,3*a*,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methylpropanamide; **1**) is an orally active growth hormone secretagogue and small molecule mimetic of ghrelin, a hormone that plays a critical role in the regulation of energy homeostasis.<sup>1</sup> Capromorelin (in the form of its (*L*)-tartrate salt) was initially studied in human clinical trials as a treatment for frailty in elderly adults. Only modest improvements in various measures of physical performance were observed after one year in a Phase II clinical trial, insufficient to justify further clinical investment.<sup>2</sup>

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