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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7683–7686

Stereoselective synthesis of the 6,6-spiroketal core of CP-61,405 (routiennocin)

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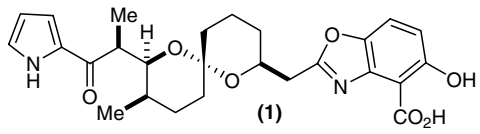
Received 19 July 2007; revised 21 August 2007; accepted 23 August 2007
Available online 29 August 2007

Abstract—A convergent and efficient synthesis of the 6,6-spiroketal core of the ionophore antibiotic CP-61,405 (routiennocin) is described. The synthesis required 10 steps from *N*-propionyl oxazolidinone (*S*)-**8** and produced the desired spiroketal in 36% overall yield.

1. Introduction

The carboxylic acid ionophore antibiotic CP-61,405 (routiennocin) (**1**) was isolated in 1985 from a microbial fermentation of *Streptomyces routiennii Huang sp. Nov. (ATCC 39446)* (Fig. 1).[1] This compound is a member of the family of pyrrolylcarbonyl spiroketal ionophore antibiotics, and other members are calcymycin (A-23187),[2] cezomycin,[3] X-14885A[4] and AC7230.[5] These compounds are able to effect proton-cation exchange across biological membranes as they have the ability to form lipophilic complexes with divalent cations like Ca^{2+} and Mg^{2+} as well as with monovalent cations like Li^{+}, Na^{+}, K^{+}, and Rb^{+}.[6,7] Because of their involvement in calcium sequestration in cellular processes, they are very useful probes for biological mechanisms.[6] In addition, recent studies demonstrate that promising pharmacological effects (such as phosphatase inhibition, modulation of tubulin cytoskeleton of breast cancer cells, and cytotoxity against tumor cell lines) can be achieved through construction and screening of simple spiroketals.[7,8]



(1)

Figure 1. CP-61,405 (routiennocin).

Keywords: Spiroketal; Ionophore antibiotic; Aldol reaction.
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doi:10.1016/j.tetlet.2007.08.087

The relative and absolute stereochemistry for routiennocin have been confirmed by total synthesis.[9]

As the natural supply is extremely restricted, and attracted by the promising anticancer activity of the corresponding analogues, we initiated a project directed toward the total synthesis of routiennocin and derivatives. An efficient and flexible synthesis of the spiroketal fragment is essential to provide further material for more extensive biological studies, along with access to novel analogues.[9,10]

2. Results and discussion

Our disconnection strategy summarized in Figure 2 shows that routiennocin might arise from spiroketal **2**, which contains the five stereogenic centers of routiennocin.[11]

Our synthetic strategy for the 6,6-spiroketal system, having the functional groups for the synthesis of **1** and additional analogues, was based on the treatment of ketone **3** under acidic conditions (Fig. 2). Ketone **3** may be further dissected in a straightforward manner to give ketophosphonate **4** and aldehyde **5**. Of the available options, we speculated that the desired *syn* stereocenters at C17 and C18 in **4** might be established through a boron enolate-mediated aldol reaction and that the stereocenter at C10 in **5** might arise from a symmetry breaking opening reaction of anhydride **7**.

Our approach began with an asymmetric aldol addition of the boron enolate derived from oxazolidinone **8** with

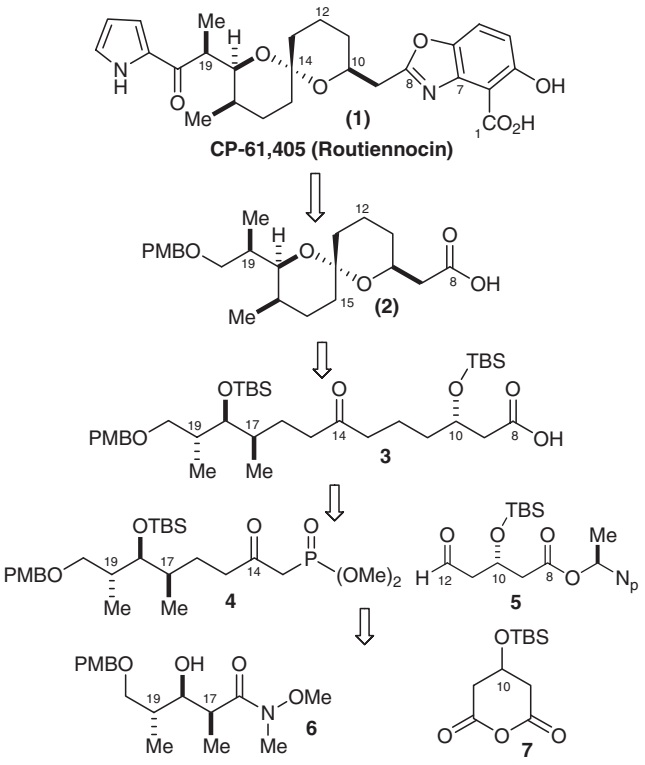
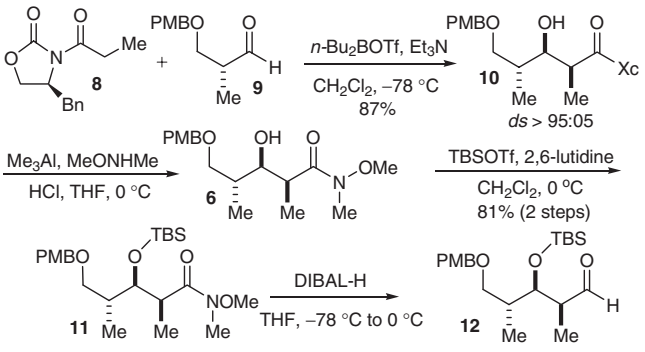


Figure 2. Retrosynthetic analysis.

chiral aldehyde **9** to give aldol adduct **10** in 87% isolated yield and with excellent diastereoselectivity (ds > 95:5) (Scheme 1).[12,13] This aldol adduct possesses the *syn–anti* stereochemistry concerning the three contiguous stereocenters and this result illustrates that the chiral auxiliary is effective in controlling the stereoselectivity of the reaction, even overriding the facial bias of chiral aldehyde **9** for Felkin addition.

Exchange of the oxazolidinone auxiliary in the *syn*-aldol **10** with *N*,*O*-dimethylhydroxyamine generated Weinreb amide **6**, purification of which was done by the isolation of the recyclable oxazolidinone chiral auxiliary from the reaction mixture.[14,15] Recovery of the oxazolidinone auxiliary in this reaction is nearly quantitative. Protection of the OH-function as its TBS ether gave Weinreb amide **11** in 81% yield (over two steps, transamidation and TBS protection). This amide was smoothly reduced



Scheme 1. Preparation of aldehyde **12**.

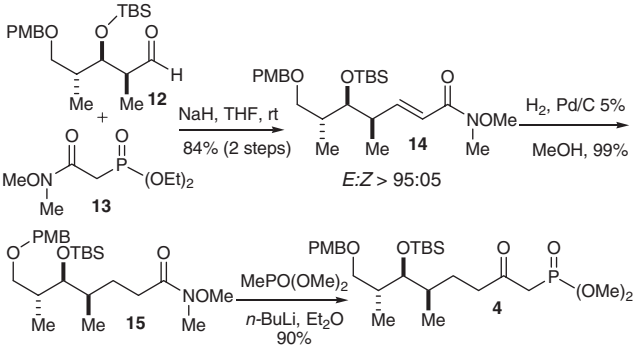
to aldehyde **12** in 92% yield on the treatment with diisobutylaluminum hydride in THF (Scheme 1).[16]

This intermediate aldehyde was directly submitted to a Horner–Wadsworth–Emmons homologation with the requisite stabilized reagent **13** to give the corresponding α,β-unsaturated amide **14** (*E*:*Z* > 95:5) in 84% yield for the two-step sequence (Scheme 2).[17] Catalytic hydrogenation[18] followed by the treatment of Weinreb amide **15** with the lithium anion generated from dimethyl methylphosphonate and *n*-BuLi led to ketophosphonate **4** in 90% yield.[17b,c]

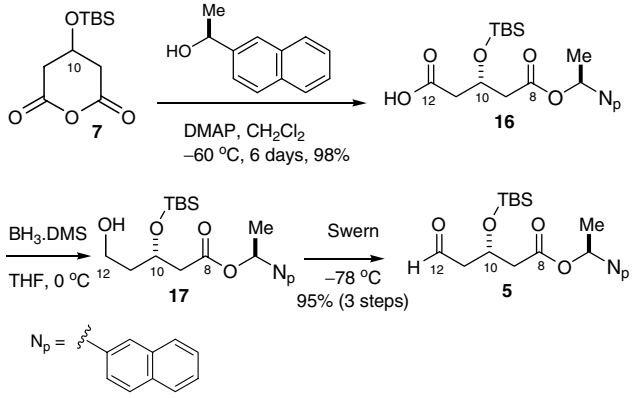
In order to prepare aldehyde **5**, we started with the symmetry-breaking enantioselective transesterification study of Heathcock and co-workers (Scheme 3).[19]

By using this methodology, *meso*-anhydride **7** was opened with (*S*)-naphthylethanol to give carboxylic acid **16** in 98% yield and 31:1 diastereoselectivity. Borane reduction of acid **16** provided primary alcohol **17**, which after Swern oxidation gave aldehyde **5** in 95% yield for the three-step sequence.[20]

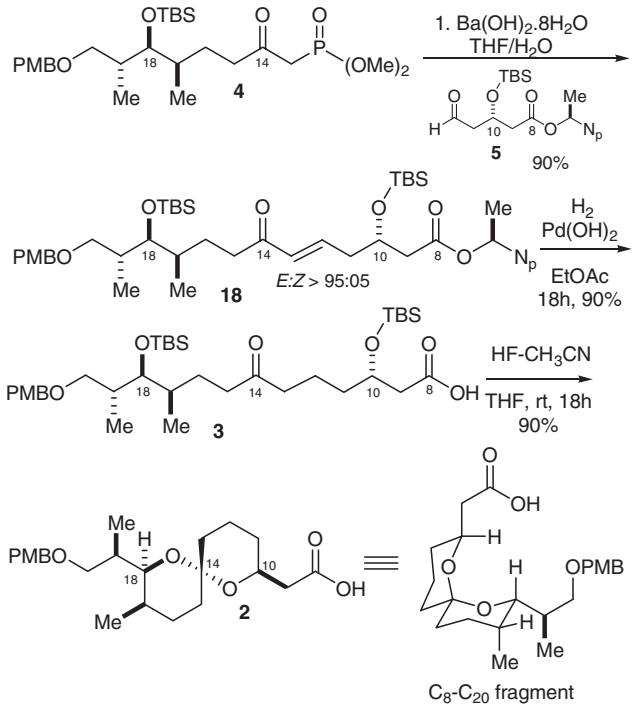
A Barium hydroxide promoted HWE homologation reaction of ketophosphonate **4** with aldehyde **5** gave α,β-unsaturated ketone **18** in 90% yield (*E*:*Z* > 95:5) (Scheme 4).[17b,c]



Scheme 2. Preparation of ketophosphonate **4**.



Scheme 3. Preparation of aldehyde **5**.



Scheme 4. Synthesis of spiroketal **2**.

Hydrogenation of the double bond (H_2, $Pd(OH)_2$, EtOAc, 18 h) with concomitant hydrogenolysis of the ester function at C8 provided carboxylic acid **3** in 90% yield, leaving the PMB group intact.[18] All that remained was to carry out the necessary spiroketalization.[21] Treatment of ketone **3** with HF–CH_3CN in THF at rt occurred with efficient removal of both TBS protecting groups positioned at C10 and C18, followed by cyclization to give spiroketal **2** in 90% isolated yield, after purification by silica-gel column chromatography.

It is noteworthy that under these conditions, spiroketal **2**, with two anomeric stabilizations, was isolated as the only observed isomer.[21] The relative stereochemistry for spiroketal **2** was confirmed by NMR analysis (Scheme 4). For spiroketal **2** (needed for the synthesis of routiennocin), the ^{13}C chemical shift of the spiro carbon C14 (96.4 ppm) was typical for a bis-axial orientation with two anomeric stabilizations. In addition, the ^{13}C chemical shift of the methyl group at C17 (12.7 ppm) was typical for axial position.[22,23]

3. Conclusions

We described here an asymmetric total synthesis of the spiroketal core of the ionophore antibiotic routiennocin. Notable features of this approach include a high yielding *syn* aldol reaction, a very efficient and diastereoselective Horner–Wadsworth–Emmons coupling between ketophosphonate and an aldehyde, followed by spiroketalization under acidic conditions. The route to the spiroketal core of routiennocin described here might easily afford access to additional analogues with potential relevance to biological studies. The results will be described in a full account of this work.[24]

Acknowledgments

We are grateful to FAEP-UNICAMP, FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) for financial support. We also thank Professor Carol H. Collins for helpful suggestions about English grammar and style.

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22. Analysis of some previously published results shows that it is possible to make a distinction between the spiroketal that presents double anomeric stabilization and that which presents single anomeric stabilization, based on chemical shifts of the spiroketal carbon. See Ref. 21b.
23. Spiroketal **2**: TLC (EtOAc–hexanes, 10:90) R_f 0.46; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.98 (d, *J* 6.5 Hz, 2H), 6.64 (d, *J* 6.5 Hz, 2H), 4.19 (s, 2H), 3.95–4.05 (m, 2H), 3.85 (dd, *J* 10.6, 2.1 Hz, 1H), 3.60 (dd, *J* 11.2, 4.7 Hz, 1H), 3.17 (s, 3H), 2.28 (dd, *J* 16.2, 10.2 Hz, 1H), 2.00 (m, 1H), 1.85 (dd, *J* 16.2, 2.3 Hz, 1H), 1.67 (m, 1H), 1.55 (m, 1H), 1.46 (m, 1H), 1.00–1.50 (m, 8H), 0.82 (d, *J* 7.0 Hz, 3H), 0.70 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 134.0, 128.4, 127.6, 114.0, 96.4, 72.5, 66.6, 65.5, 64.8, 54.7, 40.4, 37.5, 35.3, 30.6, 30.2, 27.8, 26.7, 19.6, 12.7, 10.4.
24. New compounds and the additional isolated intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.