Gold-Catalyzed Cycoisomerization of α-Hydroxyallenes: Synthesis of Novel Furanomycin Derivatives.

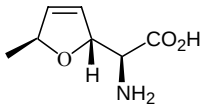
Jörg Erdsack, Norbert Krause†

UNIVERSITÄT DORTMUND

Introduction

The nonproteinogenic α-amino acid (+)-furanomycin (Figure 1) is one of very few natural products containing a 2,5-dihydrofuran ring. It was first isolated in 1967 by Katagiri et al.[1] from *Streptomyces threomyceticus* and it is one of the smallest antibiotic natural products, inhibiting bacterial protein synthesis by mimicking isoleucine.[2] Due to its activity and moderate chemical complexity, several syntheses of furanomycin[3] and derivatives thereof[4] have been disclosed, often using sugars as the starting material.

By taking advantage of the high reactivity and axial chirality of allenes,[5] we have recently established an efficient and stereoselective synthesis of 2,5-dihydrofurans by gold-catalyzed cycloisomerization of α-hydroxyallenes.[6] The utility of the method was demonstrated by the first total synthesis of the β-carboline alkaloids (–)-isocyclocapitelline and (–)-isochrysotricine.[7] In the course of our investigations on target-oriented synthesis towards furanomycin derivatives,[8] we became interest in a diastereoselective α-hydroxyallene synthesis by indium-promoted allenylation[9] of Garners's aldehyde *(S)*-1[10] . This provides an efficient access to isomerical pure target molecules; this would broaden the scope of the gold-catalyzed cyclization of functionalized allenes.

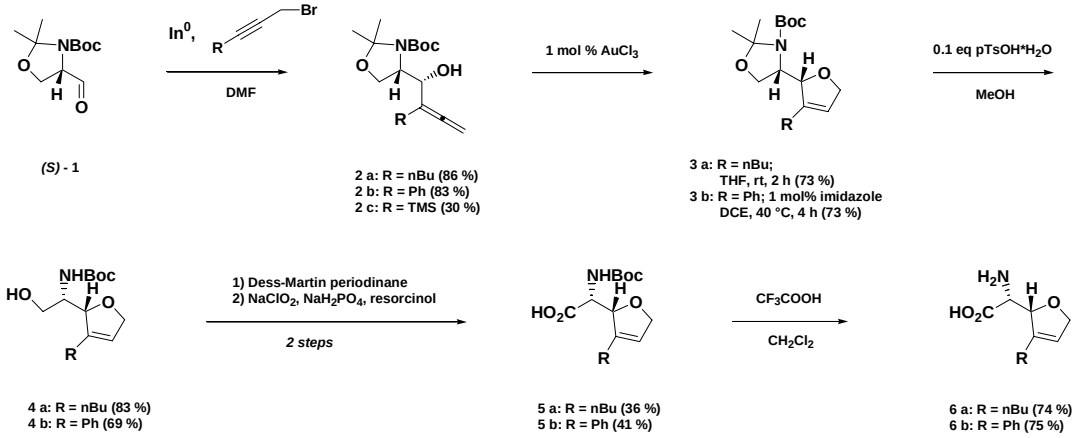


(+)-furanomycin

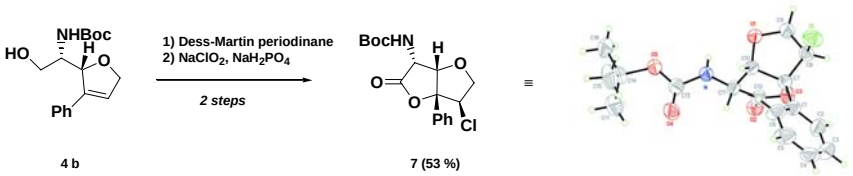
Results

In accordace with our plan, indium promoted allenylation of (S)-**1** with different propargylic bromides proceeds well in a regioselective and stereoselective fashion to the give α-hydroxyallenes **2a** and **2b** in 86 and 83 % yield, respectively (scheme 1). As an exception, in case of the silylated compound **2c** the yield was diminished to 30 % because the isomeric homopropargylic alcohol was formed as a byproduct in considerable yield (33 %). Apparently, there is an electronic influence of the silylic substituent.[11] Exposure of **2a** to $AuCl_3$ (1 mol%) in THF[12] gave the desired 2,5-dihydrofuran **3a** (73 %), whereas in case of **3b** the presence of an organic nitrogen base (imidazol) was necessary, otherwise lower yield and acetal cleavage[13] were observed due to the Lewis acidity of Au.[8] Acetal cleaveage under mild protic conditions ($pTsOH*H_2O$, MeOH, r.t.) affords the hydroxycarbamates **4 a/b** in 83 and 69 % yield, respectively.

The following two step oxidation with Dess-Martin Periodinane[14] and Pinnick oxidation of the aldehyde intermediate with $NaClO_2$ in buffered solution in the presence of 2-methyl-2-butene[15] was insufficient, because chlorolactonization of the boc-protected amino acids by hypochloric acid, the degradation product of the oxidant, takes place. In a control experiment, the oxidation in the absence of any scavenger for electrophilic chlorine affords the expected lactone **7a** in 53 % yield (scheme 2).[16a] Single crystals of the bicyclic lactones were used for establishment of the stereochemistry[16a,b] to prove the *anti* selectivity of the allenylation step **1 a/b** → **2 a/b** (scheme 2). Replacement of 2-methyl-2-butene by resorcinol (scheme 1) and an improved work-up procedure developed by us[8] affords the acids **5 a/b** in 36 and 41 % yield, respectively, which gave after deprotection with trifluoracetic acid the amino acids **6 a/b** in good yield.



Scheme 1 Synthesis of the furanomycin derivatives **6a/b** by gold-catalyzed cycloisomerization of α-hydroxyallenes **2 a/b**.



Scheme 2 Chlorolactonization of the hydroxycarbamate **4 b** and X-ray structure of lactone **7**.

The results shows that the gold-catalyzed cycloisomerization of α-hydroxyallenes is a powerful tool in multistep synthesis. In conjunction with the allenylation of carbonyl compounds we are able to synthesize quickly a wide range of natural product derivatives, which may find application in pharmaceutical screening programs.

In our working group, we are currently involved in the extension of this method to cyclizise the correspondending α-aminoallenes which provides an access to nitrogen-containing derivatives ("Azafuranomycin"). The results from these research will be published elsewehre.

References

†Dortmund University, Organic Chemistry II, D-44221 Dortmund, Germany
(e-mail: norbert.krause@uni-dortmund.de).

(1) Katagiri, .; Tori, K.; Kimura, Y.; Yoshida, T.; Nagasaki, T.; Minato, H. *J. Med. Chem* *10*, 1149.
(2) Von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem. I* **2006**, *45*, 5072; *Angew. Chem.* **2006**, *118*, 5194.
(3) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102* (b) Kang, S. H.; Lee, S. B. *Chem. Commun.* **1998**, 761. (c) Zhang, J. .; Clive, D. L. J. *Chem.* **1999**, *64*, 1754. (d) VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 7 Zimmermann, P. J.; Blanarikova, J.; Jäger, V. *Angew. Chem. Int. Ed.* **2000**, *39*, 910; *A Chem.* **2000**, *112*, 936.
(4) (a) Kazmaier, U.; Pählер, S.; Endermann, R.; Häbich, D.; Kroll, H.-P.; Riedl, P. *Bioorg Chem.* **2002**, *10*, 3905. (b) Jirgenson, A.; Marinozzi, M.; Pellicciari, R. *Tetrahedron* *61*, 373. (c) Lee, J. Y.; Schiffer, G.; Jäger, V. *Org. Lett.* **2005**, *7*, 2317. (d) Chattopadh K.; Sarkar, K.; Karmakar, S. *Synlett* **2005**, 2083.
(5) *Modern Allene Chemistry* (Hrsg.: N. Krause, A.S.K. Hashmi) *Wiley-VCH* **2004**.
(6) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537.
(7) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519.
(8) Erdsack, J.; Krause, N. *Synthesis* **2007**, 3741.
(9) Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 13326; and references cited therein.
(10) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31.
(11) Lin, M.-J.; Loh, T.-P.; J. *Am. Chem. Soc.* **2003**, *125*, 13042.
(12) Deutsch, C.; Gockel, B.; Hoffmann-Röder, A.; Krause, N. *Synlett* **2007**, 1790.
(13) Erdsack, J.; Schürmann, M.; Preut, H.; Krause, N. *Acta Cryst.* **2007**, *E63*, o664.
(14) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Boeckmann, R. K. Jr.; Shao, P.; Mullins, J. J. *Org. Synth. Coll. Vol. X*; John Wiley & Sons: London **2004**, 696.
(15) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(16) (a) Erdsack, J.; Schürmann, M.; Preut, H.; Krause, N. *Acta Cryst.* **2007**, *E63*, o3371. (b) Erdsack, J.; Schürmann, M.; Preut, H.; Krause, N. *Acta Cryst.* **2007**, *E63*, o3372.