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Synthesis of Bisbenzannulated Spiroketals—Model Studies for a Modular Approach to Rubromycins

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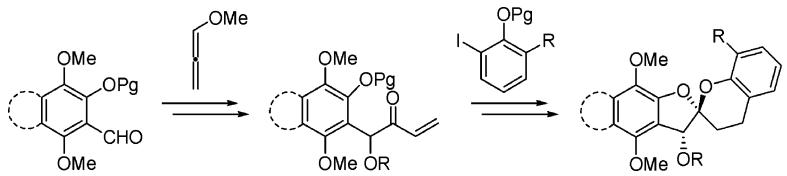
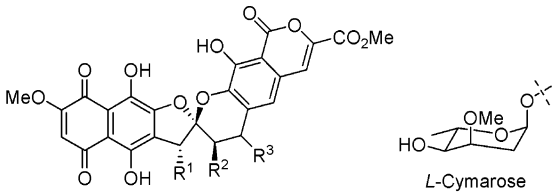
ABSTRACT



A highly flexible synthesis of bisbenzannulated spiroketals is described with additions of lithiated methoxyallene to aryl aldehydes and Heck reactions as key steps. Subsequent hydrogenations and ketalizations afforded the desired spiroketals in good yields and with predominating *trans*-configuration. With model compound 30, already bearing the fully substituted naphthyl core of rubromycins, the ketalization proceeded efficiently providing the expected product 31 and the isopropoxy compound 32. Both products are advanced model compounds of heliquinomycin.

Rubromycins, such as γ-rubromycin **1**,[1] purpuromycin **2**,[2] and heliquinomycin **3**,[3] are structurally related pigments, which display a broad range of biological activity (Figure 1). While γ-rubromycin **1** is a potent inhibitor of DNA polymerase (a reverse transcriptase of HI-virus type 1),[4] purpuromycin **2** displays activity against bacteria and fungi[2] and is a potential topical agent for vaginal infections.[5] In contrast, heliquinomycin **3** proved to be a selective inhibitor of DNA helicase.[3]



γ-Rubromycin **1**: $R^1 = R^2 = R^3 = H$
Purpuromycin **2**: $R^1 = R^2 = H$, $R^3 = OH$
Heliquinomycin **3**: R^1 = *O*-Cymarose, $R^2 = OH$, $R^3 = H$
Heliquinomycinone **4**: $R^1 = R^2 = OH$, $R^3 = H$

Figure 1. Compounds of the rubromycin family.

The basic structure of the rubromycins combines a naphthoquinone moiety with a 5,6-spiroketal fused to an isocoumarin unit. Despite the interesting biological properties and the intriguing molecular architecture of these natural products, apart from several model studies[6] and preliminary

(1) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Tetrahedron Lett.* **1966**, 3525.

(2) (a) Coronelli, C.; Pagani, H.; Bardone, M. R.; Lancini, G. C. *J. Antibiot.* **1974**, *27*, 161. (b) Coronelli, C.; Zerilli, L. F.; Bardone, M. R.; Martinelli, E. *Tetrahedron* **1974**, *30*, 2747.

(3) (a) Chino, M.; Nishikawa, K.; Umekita, M.; Hayashi, C.; Yamazaki, T.; Tsuchida, T.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 752. (b) Chino, M.; Nishikawa, K.; Tsuchida, T.; Sawa, R.; Nakamura, H.; Nakamura, K.; Muraoka, Y.; Ikeda, D.; Naganawa, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 143. (c) Chino, M.; Nishikawa, K.; Sawa, R.; Hamada, M.; Naganawa, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 781. (d) Chino, M.; Nishikawa, K.; Yamada, A.; Ohsono, M.; Sawa, T.; Hanaoka, F.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 480.

(4) Goldman, M. E.; Salituro, G. S.; Bowen, J. A.; Williamson, J. M.; Zink, L.; Schleif, W. A.; Emini, E. A. *Mol. Pharmacol.* **1990**, *38*, 20.

(5) Trani, A.; Dallanoce, C.; Panzone, G.; Ripamonti, F.; Goldstein, B. P.; Ciabatti, R. *J. Med. Chem.* **1997**, *40*, 967.

(6) (a) Greul, V. Ph.D. Dissertation, Universität Göttingen, 1971. (b) Capecchi, T.; de Koning, C. B.; Michael, J. P. *Tetrahedron Lett.* **1998**, *39*, 5429. (c) Capecchi, T.; de Koning, C. B.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2681. (d) Tsang, K. Y.; Brimble, M. A.; Bremner, J. B. *Org. Lett.* **2003**, *5*, 4425. (e) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365.

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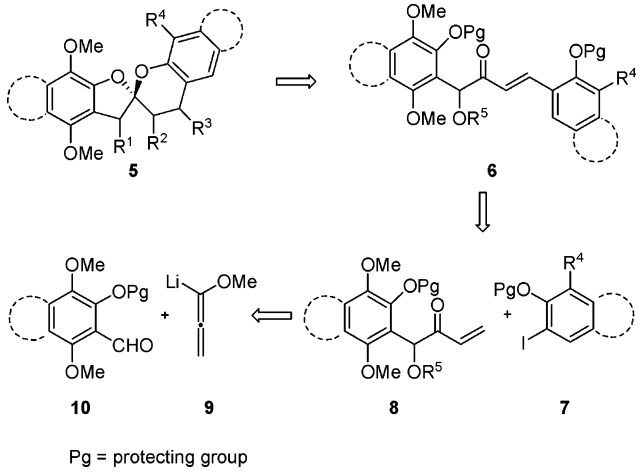
investigations toward the synthesis of purpuromycin,[7] only the synthesis of racemic heliquinomycinone **4**[8] (the aglycon of heliquinomycin **3**) has so far been reported.

Herein we present our investigations regarding the construction of bisbenzannulated spiroketals suitable for a modular approach to rubromycins. Our retrosynthetic analysis (Scheme 1) envisages enones **6** to serve as precursors for

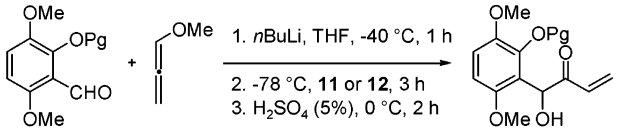
Scheme 1



the synthesis of model spiroketals **5**. These highly substituted enones would be accessible via Heck reactions of iodinated benzene derivatives **7** (acting as isocoumarin model compounds)[9] with α-hydroxy enone derivatives **8**. The synthesis of the required enones **8** should be accomplished by addition of lithiated methoxyallene **9** to functionalized benz- or naphthaldehyde derivatives **10** (Scheme 1) followed by acidic hydrolysis of the alkoxyallene moiety.[10]

Substituted α-hydroxy enones **13** and **14** were prepared by addition of lithiated methoxyallene to the corresponding aryl aldehydes **11** or **12** (Scheme 2). Subsequent hydrolysis

Scheme 2



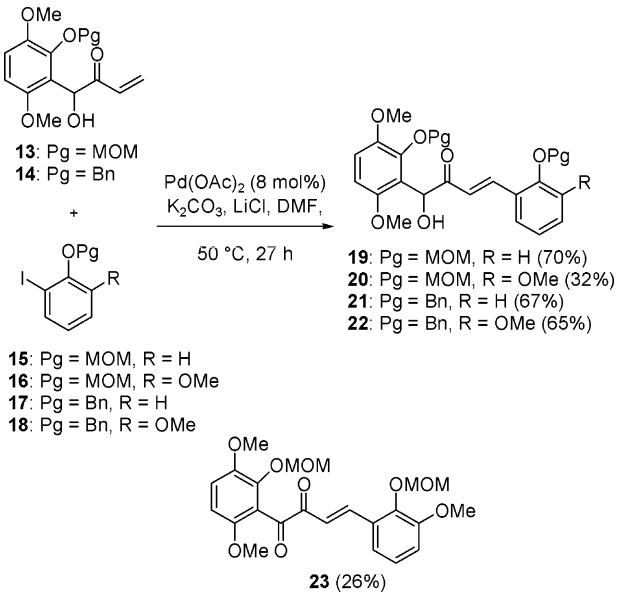
of the intermediate allene adducts with acid furnished the required enones **13** and **14** in excellent overall yields.

(7) (a) Waters, S. P.; Fennie, M. W.; Kozlowski, M. C. *Tetrahedron Lett.* **2006**, *47*, 5409. (b) Waters, S. P.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 3243.

(8) (a) Qin, D.; Ren, R. X.; Siu, T.; Zheng, C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4709. (b) Siu, T.; Qin, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4713.

(9) For a synthesis of an appropriate isocoumarin building block, see: (a) Brasholz, M.; Reissig, H.-U. *Synlett* **2004**, 2736. (b) Brasholz, M.; Luan, X.; Reissig, H.-U. *Synthesis* **2005**, 3571.

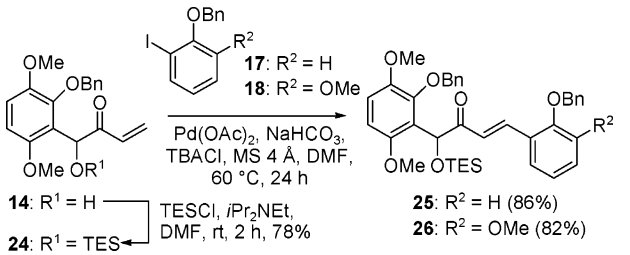
Scheme 3



Compounds **13** and **14** were then used in the Pd-catalyzed coupling with aryl iodides **15**/**16** (MOM-protected) or **17**/**18** (Bn-protected) employing a modified Jeffery protocol (Scheme 3).[11] The corresponding α,β-unsaturated enones **19**−**22** were obtained in good yields. However, a side reaction partially oxidized the α-hydroxy group to the corresponding diketone in varying amounts which made this transformation less efficient. For the conversion of **13** and **16** into enone **20**, the corresponding diketone **23** was isolated in an almost equal yield of 26% (Scheme 3). During synthesis of **21** and **22**, the corresponding diketones were obtained in 7% yield and trace amounts, whereas **19** gave no side product at all. Although we applied various conditions, we were not able to completely suppress this side reaction.

Thus, we slightly modified our sequence by protecting the α-hydroxy function of enone **14** prior to the Heck coupling. Among the protecting groups examined,[12] the TES group proved to be most suitable. Subsequent coupling of protected enone **24** with iodobenzene derivatives **17** and **18** smoothly afforded the corresponding enones **25** and **26** in good yield (Scheme 4) without formation of side products.

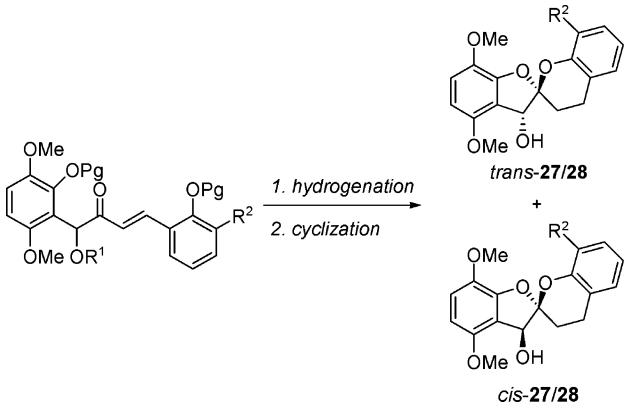
Scheme 4



We then turned our attention toward the final construction of the desired spiroketals. Hydrogenation of the precursor

compounds should result in both saturation of the double bond, as well as the benzyl protecting group removal. Subsequent acidic treatment should then induce cyclization. For MOM-substituted precursors, the removal of the protecting group should only occur under treatment with acid. As shown in Table 1, hydrogenation followed by treatment with

Table 1. Formation of Spiroketals **27** and **28** from Enone Precursors



entry	enone	Pg	R^1	R^2	product	[%][e]	*trans*:*cis*
1[a]	**19**	MOM	H	H	**27**	51	59:41
2[b]	**21**	Bn	H	H	**27**	83	62:38
3[c]	**25**	Bn	TES	H	**27**	76	100:0
4[a]	**20**	MOM	H	OMe	**28**	43	100:0
5[d]	**22**	Bn	H	OMe	**28**	54	100:0
6[c]	**26**	Bn	TES	OMe	**28**	65	100:0

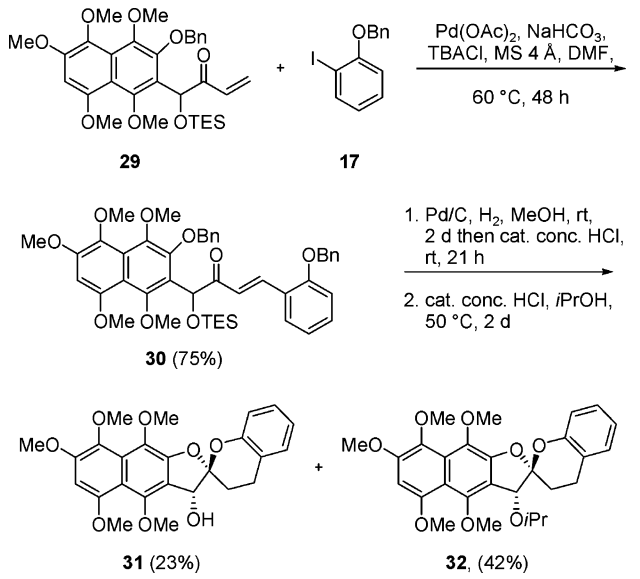
[a] (1) Pd/C, H_2, EtOAc, rt, 2 h; (2) cat. concn HCl, *i*PrOH, 50 °C, 16−24 h. [b] Pd/C, H_2, MeOH/$CHCl_3$, rt, 2 days. [c] (1) $Pd(OH)_2$/C, H_2, C_6H_{10}, EtOH, rt, 18−23 h; (2) cat. concn HCl, *i*PrOH, 50 °C, 1−3 days. [d] $Pd(OH)_2$/C, H_2, C_6H_{10}, EtOH, rt, cat. concn HCl, 24 h. [e] Yields refer to isolated material after column chromatography.

acid worked well in most cases, resulting in the formation of the corresponding spiroketals in good to excellent yields. The TES-protected compounds (Table 1, entries 3 and 6) were desilylated under these reaction conditions.

Diastereomeric mixtures[13] of spiro compound **27** were obtained for precursors with substituent R^2 = H when ketalization was performed at room temperature or with insufficient exposure to higher temperatures (Table 1, entries 1 and 2). However, elevated temperatures (50 °C) and longer reaction times exclusively led to the formation of *trans*-spiroketal **27**,[14a] probably due to thermodynamic control (Table 1, entry 3). With substituent R^2 = OMe, only *trans*-configured product **28** was obtained even at room temperature (Table 1, entries 4−6).[14b]

With these promising model reactions in hand, we studied the more complex enone **29** which was analogously accessible by addition of lithiated methoxyallene to 3-benzyloxy-1,4,5,6,8-pentamethoxynaphthalene-2-carbaldehyde followed by acid treatment and protection.[15] Pd-catalyzed coupling with iodobenzene derivative **17** afforded the required spiroketal precursor **30** in 75% yield (Scheme 5). Hydrogenation of

Scheme 5



enone **30** and treatment with acid at 50 °C led to formation of *trans*-configured spiroketals. However, not only the expected product **31** was obtained in 23% yield but also isopropoxy-substituted compound **32** was isolated in 42% yield. Its formation may be explained by a S_N1-type solvolysis via a carbenium ion which is highly stabilized due to the very electron-rich naphthalene core. This transformation has to be taken into consideration in further studies dealing with the synthesis of heliquinomycin. However, the naphthalene moiety of both spiro compounds **31** and **32** already fully corresponds to a protected version of the naphthoquinone moiety present in rubromycins (Figure 1).

In conclusion, a novel protocol for the diastereoselective formation of functionalized bisbenzannulated spiro[4.5]-ketals has been presented, applying the addition of lithiated methoxyallene to suitably substituted aryl aldehydes as well as a Heck coupling reaction as key steps. This protocol could also be successfully employed using naphthyl-substituted enone **30**, thus giving rise to more complex spiroketals. Our strategy not only places the 3′-hydroxy function in the benzo- or naphthofuran moiety but also will enable further functionalization of the pyran ring by taking

(10) (a) Clinet, J. C.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, *19*, 1137. (b) Clinet, J. C.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, *21*, 3987. For reviews, see: (c) Zimmer, R. *Synthesis* **1993**, 165. (d) Zimmer, R.; Reissig, H.-U. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 425.

(11) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(12) The following protecting groups were tested: TMS, TES, TIPS, TBDMS, TBDPS, THP.

(13) The *trans* describes the configuration of the 3′-hydroxy group relative to the C−O bond of the pyran ring. This configuration is also found in natural occurring heliquinomycin.

(14) For X-ray analyses of compounds *trans*-**27** and *trans*-**28**, see: (a) Azap, C.; Luger, P.; Reissig, H.-U.; Wagner, A. *Z. Kristallogr. NCS* **2004**, *219*, 492. (b) Azap, C.; Luger, P.; Reissig, H.-U.; Wagner, A. *Z. Kristallogr. NCS* **2004**, *219*, 495.

(15) Sörgel, S.; Azap, C.; Reissig, H.-U. *Eur. J. Org. Chem.* **2006**, 4405.

advantage of the enone function in spiroketal precursors **6** (see Scheme 1). Furthermore, the use of chiral alkoxyallenes[16] will allow for the preparation of enantiomerically enriched or pure intermediates of type **8**. Studies toward the synthesis of heliquinomycin and other members of the rubromycin family are currently underway and will be reported in due course.

(16) (a) Rochet, P.; Vatèle, J.-M.; Goré, J. *Synlett* **1993**, 105. (b) Surivet, J.-P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 14877. (c) Hausherr, A.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2001**, 1377. (d) Kaden, S.; Brockmann, M.; Reissig, H.-U. *Helv. Chim. Acta* **2005**, *88*, 1826.

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Supporting Information Available: Detailed description of typical experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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