Use of the non-aldol aldol process in the synthesis of the C1–C11 fragment of the tedanolides: use of lactol ethers in place of tetrahydrofurans

Michael E. Jung* and Christopher P. Lee

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, USA

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Abstract

The use of a lactol methyl ether 23 in place of the simple tetrahydrofuran 11 allows for the high yielding non-aldol aldol process to occur without concomitant tetrahydropyran formation (cf. 13) to give the desired product 24 in good yield. © 2000 Elsevier Science Ltd. All rights reserved.

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Tedanolide (1, \( R = \text{OH} \)) was isolated by Schmitz and co-workers in 1984 from the Caribbean sponge *Tedania ignis*.\(^1\) The macrolide demonstrates its high cytotoxicity by displaying ED\(_{50}\)’s of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Seven years after tedanolide’s discovery, Fusetani and co-workers isolated 13-deoxytedanolide (2, \( R = \text{H} \)) from the Japanese sponge *Mycale adhaerens*.\(^2\) This macrolide is also extremely cytotoxic, exhibiting an IC\(_{50}\) of 94 pg/mL against P388 murine leukemia. Due to its powerful antitumor activity and complex structure, tedanolide has garnered considerable synthetic interest,\(^3\) including that of our group which uses the non-aldol aldol process.\(^4\)

Disconnecting the tedanolide backbone retrosynthetically is quite straightforward, beginning with cleavage at the lactone moiety and at the C12–C13 bond, which could be formed in the forward sense by an aldol reaction for 1 or an alkylation for 2, either prior to a macrolactonization or after simple ester formation. Thus in this analysis both tedanolide and 13-deoxytedanolide have common intermediates in fragments 3 and 4. Recently we published an approach to the C1–C11 fragment 4 which used several non-aldol aldol processes.\(^4i\) However that route had a serious drawback in one of the key non-aldol aldol steps. We report herein a solution to this problem which utilizes a lactol ether rather than a tetrahydrofuran.
Although the simple non-aldol aldol reaction can be easily accomplished, the presence of an 
ethereal oxygen (including a silyl ether) five atoms away from the electrophilic tertiary site of the 
epoxide allows for attack of the oxygen atom before the internal hydride shift takes place. Thus 
when the tertiary epoxy silyl ether 5 was subjected to standard non-aldol aldol conditions, the 
silyl ether oxygen opened the epoxide to give the bis-tetrahydrofuran 6 and not the aldehyde 7.

We had already recognized this problem and had developed methods to overcome it, namely 
the use of a mesylate protecting group. Thus while treatment of the simple epoxy bis-silyl ether 
8a under normal conditions gave a high yield of the tetrahydrofuran 9, treatment of the mesylate 
silyl ether 8b under very similar conditions gave a high yield of the desired non-aldol aldol 
product 10. However, application of this technique to avoid participation of the oxygen five 
atoms away to the desired substrate analogous to 5, e.g. 11, resulted in a problem of a different 
sort, namely undesired nucleophilicity of the tetrahydrofuran oxygen to afford, after Stille–
Wittig reaction and separation, an 80% yield of a 1:1 mixture of the desired non-aldol aldol 
product 12 and the tetrahydropyran 13. Thus the ethereal oxygen six atoms away now partici-
pated in the formation of the tetrahydropyran at the same rate as the internal hydride trans-
fer. What was needed was a ‘protecting group’ for the tetrahydrofuran which would decrease 
the nucleophilicity of the ring oxygen but still allow for conversion of the bromotetrahydro-
furan system into a trisubstituted alkene at the end of the synthesis. We report the successful 
use of a lactol ether in this regard.
The first protected tetrahydrofuran examined was the lactone, since clearly the nucleophilicity of the ring oxygen would be expected to be quite low with the lone pair being tied up in resonance with the lactone carbonyl. Treatment of the tetrahydrofuran 15 (prepared in a few steps from the commercially available hydroxy ester 14) with RuCl₃ and NaIO₄ gave the lactone 16 in 70% yield.⁴ Nevertheless, the lactone moiety acidified the adjacent hydrogen atom so that β-elimination became a problem either during removal of the TBS group with TBAF (to give 17, although the silyl protecting group could be liberated under acidic HF conditions) or the subsequent Swern oxidation to give a similar furan-2-one.

The solution lay in the expectation that the inductive electron-withdrawing effect of an alkoxy group α to the ring oxygen, as in a lactol ether, would decrease the nucleophilicity enough to allow the internal hydride transfer to occur selectively. One could argue, a priori, that an α alkoxy group might increase the nucleophilicity of the ring oxygen due to a resonance effect. However, a search of the Cambridge Structure Database indicated that the length of the O1–C2 bond in tetrahydrofuran systems decreased from an average of 1.449 Å in the tetrahydrofuran to 1.417 Å in the lactol methyl ether to 1.347 Å in the lactone.⁶ Therefore we reduced the lactone 16 with DIBAL to give in 84% yield a 1:1 ratio of the lactols 17ab which were converted into a 1:1 mixture of the mixed cyclic methyl acetals 18ab in 95% yield. The acidic methanol conditions not only protected the lactol but also deprotected the TBS ether and allowed for the chromatographic separation of diastereomers. The 11R diastereomer 18a was taken on through the steps shown in Scheme 1 to test the key non-aldol aldol reaction. Swern oxidation, olefination, and reduction gave the allylic alcohol 19 in 81% overall yield. Epoxidation of this allylic alcohol by the method of Sharpless,⁸ followed by silyl ether protection afforded the first rearrangement substrate 20 in 90% yield over two steps in an 8:1 diastereomeric ratio favoring the isomer shown. The first non-aldol aldol reaction was accomplished with TMSOTf and Hünig’s base at −78°C, yielding the desired aldehyde as the only diastereomer observed. Immediate Wittig olefination and deprotection of the silyl ether furnished the syn aldol product 21 in 86% yield over three steps. This compound was shown to be a 3:1 mixture of the original diastereomer at C11 along with its epimer. The isomerization occurs during the first step, presumably due to reversible TMSOTf-catalyzed loss of the methoxy group. A longer reaction time for this rearrangement step causes increased epimerization and affords diastereomeric ratios as high as 1:1.
Protection of the C7 hydroxyl group with an electron-withdrawing mesylate functionality was carried out in 98% yield using recrystallized methanesulfonic anhydride and subsequent DIBAL-H reduction to give the protected allylic alcohol 22 quantitatively. This intermediate was epoxidized with tBuOOH and VO(acac)$_2$ and protected with TBSCl to furnish the second rearrangement substrate 23 in 87% yield over three steps as a 3:1 ratio of epoxide diastereomers.

The key non-aldol aldol reaction of the lactol ether 23 was accomplished as before with TMSOTf and Hünig’s base but required a somewhat higher temperature (−42°C) to afford the desired syn aldol product 24 in 84% yield and a 6:1 Z:E ratio after a Stille–Wittig olefination and deprotection of the silyl ether. Thus the lactol ether decreased the nucleophilicity of the ring oxygen enough to allow for complete internal hydride transfer without any competing tetrahydropyran formation.

In conclusion, we have shown that the inductive effect of the methoxy group in lactol methyl ethers is enough to reduce the nucleophilicity of the ring oxygen atom so that it does not participate via anchimeric assistance in the opening of a tertiary epoxide six atoms away, and therefore the internal hydride transfer necessary for the non-aldol aldol process occurs in excellent yield, e.g. 23 gives 24 in high yield. We are currently attempting to convert these intermediates, e.g. 24, into the final protected materials for coupling to give tedanolide and 13-deoxytedanolide.

Acknowledgements

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References


6. Groups of twenty compounds containing tetrahydrofuran, 2-methoxytetrahydrofurans, and 4,5-dihydro-2[H]-furanones were selected randomly and the O1-C2 bond distances were averaged to produce the numbers given. The standard deviations were: THF’s, 0.018 Å; 2-OMe THF’s, 0.008 Å; lactones, 0.023 Å. For comparison, three sets of ten 6-membered ring compounds were also analyzed with the following results for the O1-C2 bond distances: tetrahydropyrans, 1.448 Å (0.006 Å); 2-OMe THP’s, 1.416 Å (0.010 Å); lactones, 1.338 Å (0.011 Å). Thus the trend is general for 5- and 6-membered compounds.

7. The stereochemistry at the methoxy carbon, which is unimportant since it is lost later in the synthetic scheme, was determined during an X-ray analysis carried out on the final compound 23.


9. Both the relative and absolute stereochemistry of 23 were proven by a single crystal X-ray analysis, the details of which will be reported later.
