Pergamon

Tetrahedron Letters 41 (2000) 9719–9723

TETRAHEDRON LETTERS

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

Received 15 August 2000; accepted 18 September 2000

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.

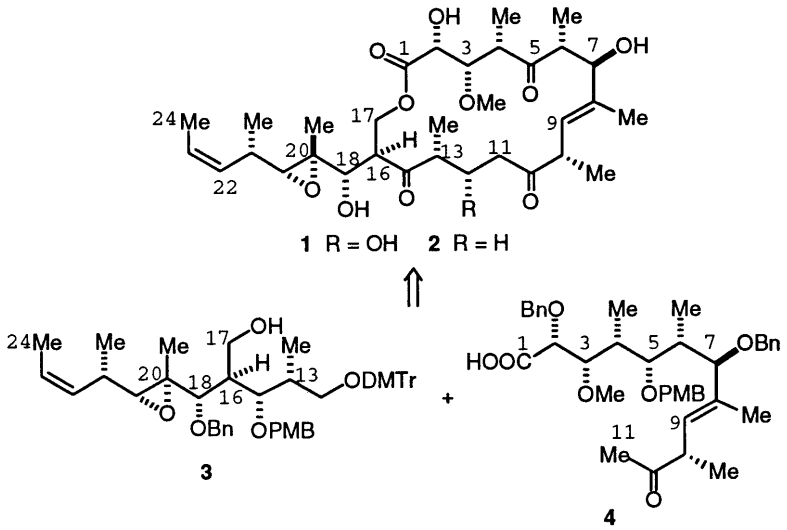
Keywords: non-aldol aldol; polypropionate synthesis; lactol methyl ethers.

Tedanolide (**1**, R = 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 = 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]

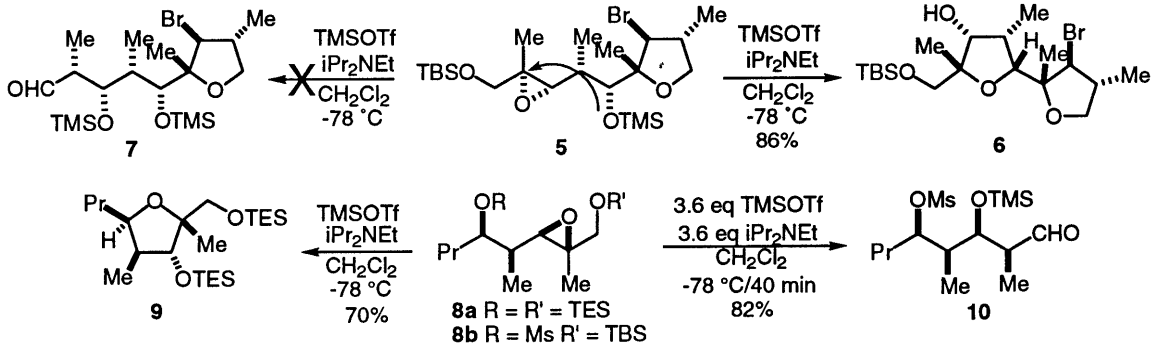
Disconnecting the tedanolide backbone retrosynthetically is quite straightforward, beginning with cleavage at the lactone moiety and at the C12–C13 bond, which could be formed in the forward sense by an aldol reaction for **1** or an alkylation for **2**, either prior to a macrolactonization or after 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.

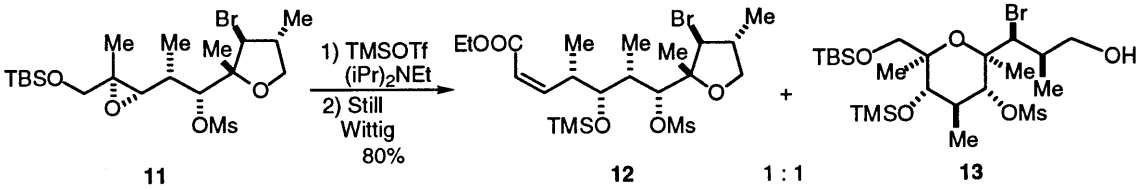
* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01726-3



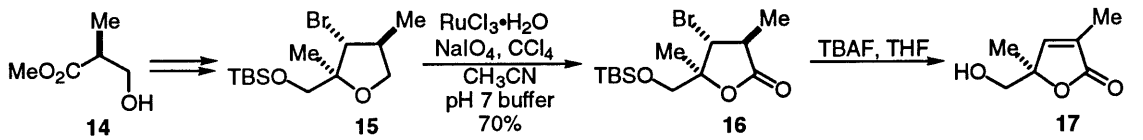
Although the simple non-aldol aldol reaction can be easily accomplished, the presence of an ethereal oxygen (including a silyl ether) five atoms away from the electrophilic tertiary site of the epoxide allows for attack of the oxygen atom before the internal hydride shift takes place. Thus when the tertiary 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,[4e] 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 participated in the formation of the tetrahydropyran at the same rate as the internal hydride transfer. 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 bromotetrahydrofuran system into a trisubstituted alkene at the end of the synthesis.[4d] We report the successful use of a lactol ether in this regard.





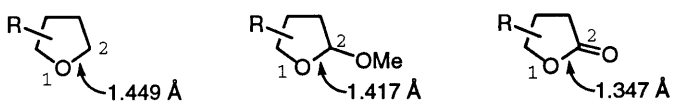
11 12 13

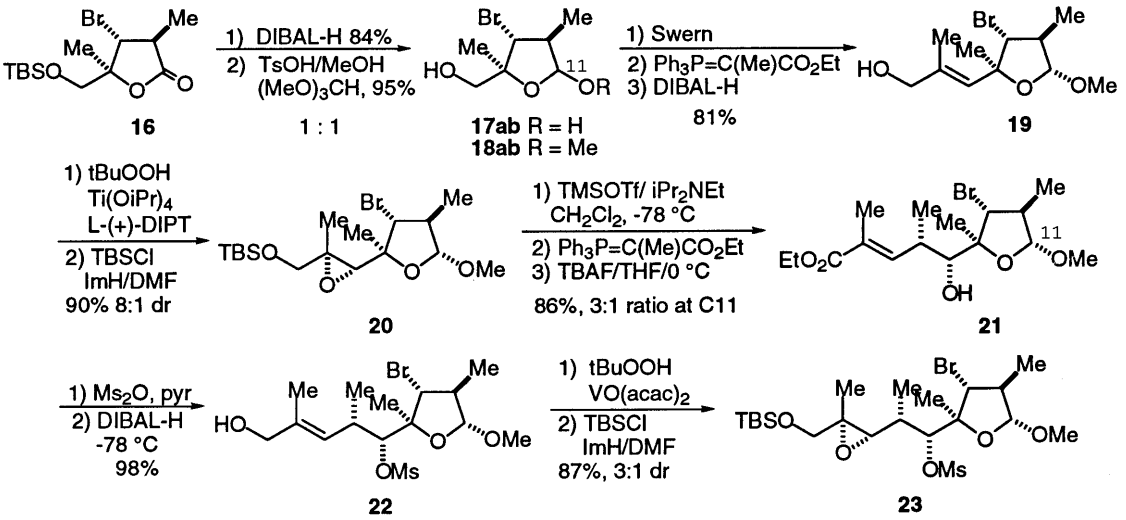
The first protected tetrahydrofuran examined was the lactone, since clearly the nucleophilicity of the ring oxygen would be expected to be quite low with the lone pair being tied up in resonance with the lactone carbonyl. Treatment of the tetrahydrofuran **15** (prepared in a few steps from the commercially available hydroxy ester **14**) with $RuCl_3$ and $NaIO_4$ gave the lactone **16** in 70% yield.[4g,5] However, 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.



14 15 16 17

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 11*R* diastereomer **18a**[7] 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.

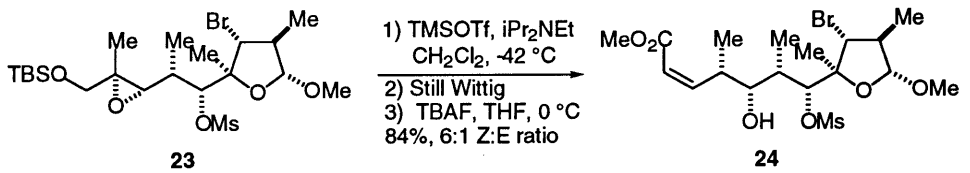




Scheme 1.

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 *t*BuOOH and $VO(acac)_2$ and protected with TBSCl to furnish the second rearrangement substrate **23**[9] 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[10] 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.[11]

Acknowledgements

We thank the National Institutes of Health (CA72684) for generous financial support.

References

1. Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.
2. Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1991**, *56*, 4971.
3. (a) Yonemitsu, O. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 946. (b) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 185. (c) Matsushima, T.; Mori, M.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (d) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H. Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (e) Matsushima, T.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, *6*, 780. (f) Liu, J.-F.; Abiko, A.; Pei, Z. H.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (g) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361. (h) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (i) Smith III, A. B.; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249.
4. (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208 and references cited therein. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) D'Amico, D. C. Ph.D. Thesis, UCLA, 1995. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307. (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343. (g) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663. (h) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (i) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669.
5. (a) Smith III, A. B.; Scarborough, R. M. *Synth. Commun.* **1980**, *10*, 205. (b) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
6. Groups of twenty compounds containing tetrahydrofuran, 2-methoxytetrahydrofurans, and 4,5-dihydro-2[3*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**.
8. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
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.
10. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
11. See Jung, M. E.; Lee, C. P. *Organic Letters*, submitted.