A Kiyooka Aldol Approach for the Synthesis of the C(14)−C(23) Segment of the Diastereomeric Analog of Tedanolide C

ARTICLE *in* ORGANIC LETTERS · NOVEMBER 2011

Impact Factor: 6.36 · DOI: 10.1021/ol202515x · Source: PubMed

4 AUTHORS, INCLUDING:

Arun Naini
Helmholtz Centre for Infection Research
5 PUBLICATIONS **5** CITATIONS

ORGANIC LETTERS

2011
Vol. 13, No. 22
6038–6041

A Kiyooka Aldol Approach for the Synthesis of the C(14)–C(23) Segment of the Diastereomeric Analog of Tedanolide C

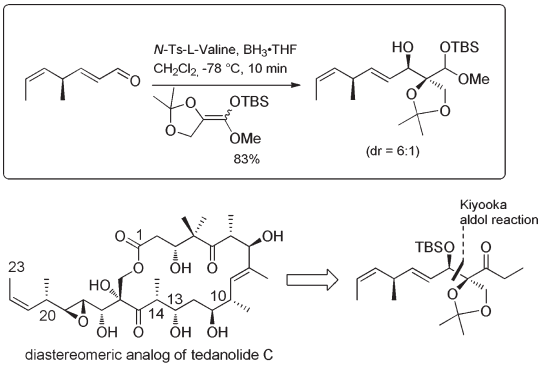
Leila Bülow, Arun Naini, Jörg Fohrer, and Markus Kalesse*

Centre for Biomolecular Drug Research, Leibniz Universität Hannover, 30167 Hannover, Germany

Markus.Kalesse@oci.uni-hannover.de

Received September 16, 2011

ABSTRACT



The challenging synthesis of a quaternary center within the highly oxygenated setting of tedanolide C can be performed via a Kiyooka aldol reaction. Here, the diastereomeric analog of tedanolide C with the configurations between C10 and C20 opposite compared to the proposed structure was chosen as the synthetic target. The tetra-substituted silyl ketene acetal provides the southern hemisphere of tedanolide C in useful selectivities, and the absolute configuration of the newly generated quaternary center was determined by NOE experiments of the corresponding acetonide.

In 2005 Ireland and co-workers isolated tedanolide C (**1**) from the marine sponge *Ircinia sp.*[1] It belongs to the family of the tedanolides which includes, up to now, five members[2–4] which have attracted considerable synthetic interest.[5] Tedanolide C (**1**) exhibits potent cytotoxicity against HCT-116 cells *in vitro* with an IC_{50} of 57 ng/mL. Subsequent cell cycle analysis showed that treatment of HCT-cells with 0.2 μg/mL tedanolide C (**1**) resulted in a strong accumulation of cells in the S-phase. These results indicate that tedanolide C (**1**) could be a promising lead compound for the inhibition of protein biosynthesis.[6]

Tedanolide C (**1**) contains a highly functionalized 18-membered macrolactone displaying 12 stereogenic centers (Figure 1). The side chain, which bears an epoxide, is characteristic for all members of the tedanolide family.[7]

(1) Ireland, C. M.; Aalbersberg, W.; Andersen, R. J.; Ayral-Kaloustian, S.; Berlinck, R.; Bernan, V.; Carter, G.; Churchill, A. C. L.; Clardy, J.; Concepcion, G. P.; Dilip De Silva, E.; Discafani, C.; Fojo, T.; Frost, P.; Gibson, D.; Greenberger, L. M.; Greenstein, M.; Harper, M. K.; Mallon, R.; Loganzo, R.; Nunes, M.; Poruchynsky, M. S.; Zask, A. *Pharm Biol.* **2003**, *41*, 15.

(2) Tedanolide: Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

(3) 13-Deoxytedanolide: Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1991**, *56*, 4971.

(4) Candidaspongiolide: Meragelman, T. L.; Willis, R. H.; Woldemichael, C. M.; Heaton, A.; Murphy, P. T.; Snader, K. M.; Newman, D. J.; van Soest, R.; Boyd, M. R.; Cardellina, J. H.; McKee, T. C. *J. Am. Prod.* **2007**, *70*, 1133. (b) Whitson, E. L.; Pluchino, K. M.; Hall, M. D.; McMahon, J. B.; McKee, T. C. *Org. Lett.* **2011**, *13*, 3518.

(5) (a) Smith, A. B.; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (b) Smith, A. B.; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042. (c) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, 127. (d) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038. (e) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *Chem.—Eur. J.* **2008**, *14*, 2232. (f) Dunetz, J. R.; Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 16407.

(6) Tedanolide, C; Chevallier, C.; Bugni, T. S.; Feng, X.; Harper, M. K.; Orendt, A. M.; Ireland, C. M. *J. Org. Chem.* **2006**, *71*, 2510.

(7) (a) Taylor, R. E. *Nat. Prod. Rep.* **2008**, *25*, 854. (b) Roy, M.; Kalesse, M. *Nat. Prod. Rep.* **2008**, *25*, 862.

10.1021/ol202515x
Published on Web 10/25/2011

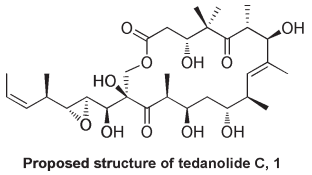


Figure 1. Proposed structure of tedanolide C, **1**.

Its carbon skeleton was elucidated via NMR spectroscopy whereas the relative configuration was deduced from a combination of molecular modeling and DFT calculations which in turn were based on the observed coupling constants.

The presence of a chiral quaternary center requires substantial modifications for its synthetic startegy to construct the southwest fragment as compared to tedanolide itself. Recently, an elegant approach involving a Baylis–Hillman reaction and a Sharpless dihydroxylation was put forward by Roush et al.[8]

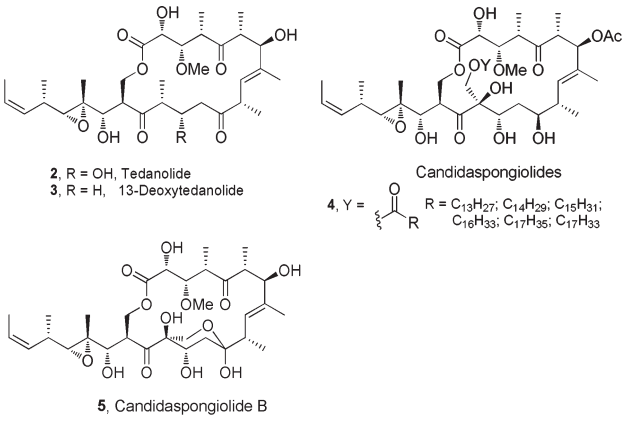


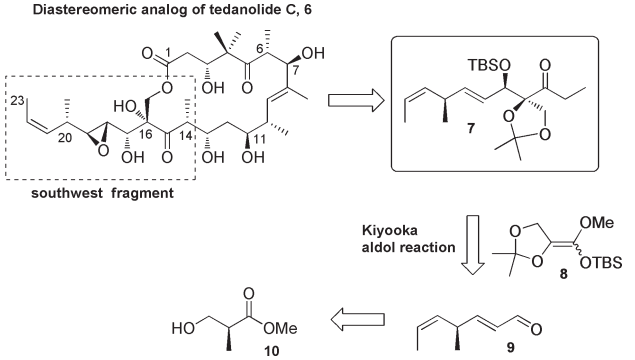
Figure 2. Members of the tedanolide family.

Due to the differing configurations in the southern hemisphere of tedanolide C (**1**) compared to other members of the tedanolide family (Figure 2), we planned on the synthesis of the diastereomeric analog of tedanolide C (**6**) as our synthetic target. Our retrosynthetic analysis divides tedanolide C into equally complex northern and southern fragments. Focusing on the southwest fragment **7**, the synthetic plan requires the construction of a quarternary center as the key step (Scheme 1).

To generate one additional stereogenic center at C-17 a Kiyooka aldol reaction[9] between aldehyde **9** and silyl ketene acetal **8** was envisioned to provide the desired aldol product with concomitant protection of the hydroxyl group at the secondary alcohol. Examples in which two

(8) Barth, R; Roush, W. R. *Org. Lett.* **2010**, *12*, 2342.
(9) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276.

Scheme 1. Retrosynthetic Analysis of Southwest Fragment **7**

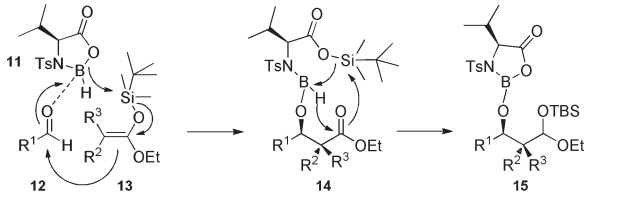


continuous chiral centers of which one is quaternary are constructed within the same C–C bond forming reaction are rare.

In 2002 Hayashi and co-worker used a tetra-substituted ketene acetal for the pivotal step in the synthesis of azaspirene.[10] However, here we had to establish a protocol that would allow for the construction of the absolute configuration independently of the directing effects of the inherent chiral center since we expected that this center would not contribute significantly to the stereochemical outcome of this transformation. Our experience with the Kiyooka aldol reaction as the ideal transformation to establish a secondary alcohol next to a quarternary center was based on the synthesis of a simplified disorazole analog.[11] Even with this state of knowledge it was not obvious if the Kiyooka aldol reaction would be suited to establishing the chiral quaternary center and thus remained as the pivotal transformation during this synthesis.

The proposed mechanism involves the complex generated from *N*-Ts-L-valine and BH_3 to generate a chiral oxazaborolidinone *in situ*. This chiral Lewis acid induces the selective aldol process and leads to reduction of the nascent ester moiety (Scheme 2). It is noteworthy to point out that the use of a TBS-protected silyl ketene acetal favors the reductive acetal formation (**15**) as a consequence of their superior transition state stabilization, whereas TMS-protected ketene acetals lead to the corresponding β-hydroxyl esters.

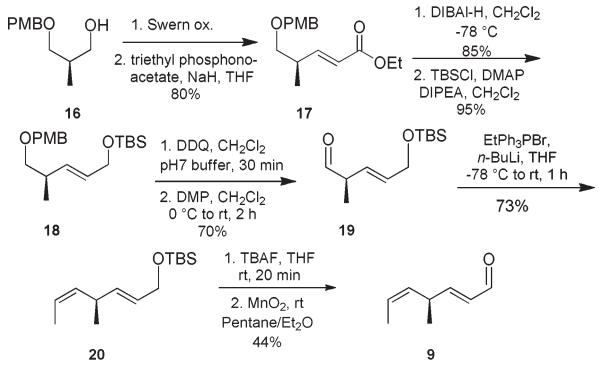
Scheme 2. Proposed Mechanism for the Kiyooka Aldol Reaction



The aldehyde required for the construction of the southwest fragment is derived from alcohol (**16**) which can be

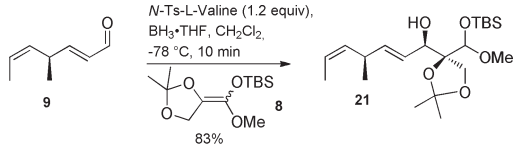
obtained by standard transformations from the corresponding Roche ester. The subsequent steps utilize the Swern protocol and a Wittig–Horner olefination[12] to install the *E*-configurated α,β-unsaturated ester **17**. Reduction to the allylic alcohol and a sequence of protecting group manipulations were completed by Dess–Martin oxidation. The so-obtained aldehyde is sensitive to epimerization and was therefore immediately subjected to a Wittig olefination,[13] to provide skipped diene **20**. Finally, TBAF mediated TBS deprotection and MnO_2 oxidation established unsaturated aldehyde **9** (Scheme 3).

Scheme 3. Synthesis of Aldehyde **9**



This volatile aldehyde (**9**) is then used in the pivotal Kiyooka aldol reaction, with silyl ketene acetal **8** to afford β-hydroxy acetal **21** in good yields (Scheme 4).[9] Silyl ketene acetal **8** in turn was derived from the corresponding ester in one step using LiHMDS, TBSCl, and HMPA.[14] Gratifyingly, the Kiyooka aldol reaction generated the desired product in good selectivities. The sterically demanding quarternary center is obtained in a highly diastereoselective manner (vide infra).

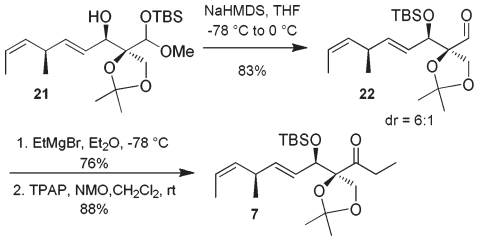
Scheme 4. Kiyooka Aldol Reaction



Based on theory, the use of *N*-Ts-L-valine as the source of chirality should lead to *R*-configured secondary alcohols which was confirmed for the configuration at C17 using the Mosher ester method and showed that the transformation proceeded in an enantiomeric ratio > 10:1.[15]

To complete the synthesis of ethyl ketone **7**, β-hydroxy acetal **21** was treated with NaHMDS to induce a 1,5 O→O silyl migration followed by elimination of the methoxy group to provide aldehyde **22**. At this stage the selectivity of the Kiyooka aldol reaction became apparent and could be identified based on their ^{1}H NMR signals to be 6:1.[16] The final two steps include a Grignard addition using EtMgBr followed by a TPAP oxidation to establish southwest fragment **7** (Scheme 5).

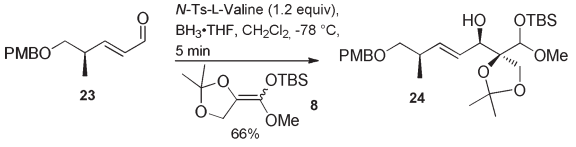
Scheme 5. Synthesis of Ethyl Ketone **7**



In conclusion, fragment **7** could be obtained in 15 steps and good selectivities taking advantage of the Kiyooka adol reaction as the pivotal transformation.

The following studies confirmed the relative configuration at the quarternary center. This particular structural motif was without literature precedent to which it could have been compared to. We therefore decided to restrict the conformational flexibility of the Kiyooka product through acetonide formation and to deduce the relative conformation from its NOE contacts. Since we had previously assigned the absolute configuration of the secondary alcohol at C17 using the Mosher method we would obtain all the remaining chiral information from NMR experiments in correlation to the secondary alcohol.[17] For practical reasons we performed the synthesis of the bisacetonide on aldehyde **23** (Scheme 6).

Scheme 6. Synthesis of Kiyooka Aldol Product **24**



β-Hydroxy acetal **24** was obtained following the Kiyooka protocol and then carefully treated with TBAF to yield aldehyde **25** (Scheme 7). The Kiyooka aldol reaction using aldehyde **23** could be performed at an even higher diastereomeric ratio of 10:1. Reduction of aldehyde **25** with DIBAl-H to the corresponding diol followed by acetalization with

(10) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078.

(11) Schäckel, R.; Hinkelmann, B.; Sasse, F.; Kalesse, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1619.

(12) Jiao, L.; Yuan, C.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 4421.

(13) Ehrlich, G.; Kalesse, M. *Synlett* **2005**, *4*, 655.

(14) Chen, C.; Namba, K.; Kishi, Y. *Org. Lett.* **2009**, *11*, 409.

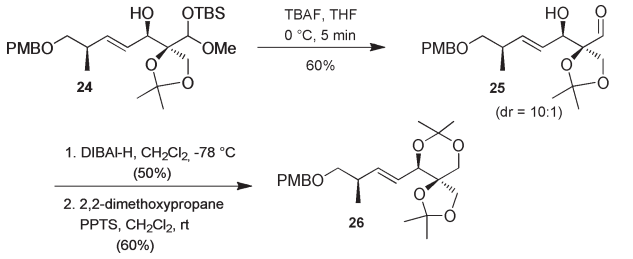
(15) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(16) Hillier, M. C.; Meyers, A. T. *Tetrahedron Lett.* **2001**, *42*, 5145.

(17) Kiyooka, S.-I.; Shahid, K. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1537.

2,2-dimethoxy propane generated acetonide **26** which was used for NOE studies.

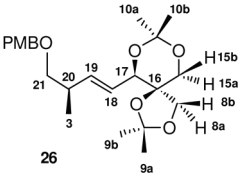
Scheme 7. Synthesis of Acetonide **26**



The observed NOE contacts are shown in Table 1 and allow the unambiguous assignment of the relative configuration of the quarternary center.

Table 1. Indicative NOE Contacts (displayed in red)[a]

Proton	NOE contacts
H-17	H-19, H-18, H-15a, Me-10a, H-8a, H-8b
H-15a	H-17, Me-10a, H-8b
H-15b	Me-10b, Me-9a, H-8b
H-8a	H-19, H-18, H-17, Me-9
H-8b	H-17, H-15a/b, Me-9
Me-9	H-18, H-15, H-8a, H-8b
Me-10a	H-17, H-15a
Me-10b	H-15b

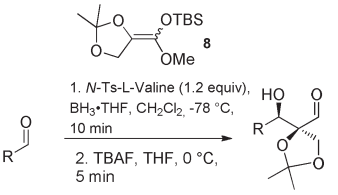


[a] Tedanolide C numbering is used.

It can be seen that proton H-17 has contact with proton H-15a and with both protons H-8a, H-8b) at the CH_2-group of the five-membered acetonide. Proton H-8b shows contacts to proton H-17 and to the CH_2-protons H-15a and H-15b. In contrast proton H-8a has NOE contacts to the protons H-19, H-18, H-17, and Me-9. All these contacts can be rationalized with the C16–C17 *syn* relationship of the diol moiety. In the case of the *anti* isomer the protons H-8a and H-8b should not exhibit NOE contacts to H-17. Additionally, these results are consistent with the configurational analysis reported by Kiyooka et al.[17]

To show that this is a general protocol allowing for the generation of a variety of different tertiary alcohols, aliphatic, unsaturated, and aromatic aldehydes were employed as well (Table 2). It became apparent that the diasteriomeric ratios range from 6:1 to 10:1 as observed in the two above-mentioned cases and the enantiomeric ratio was higher than 10:1.[18]

Table 2. Kiyooka Protocol Using Different Aldehydes



entry	R	yield (%)	dr	er
1	Phenyl	**83**	6:1	>10:1
2	Cinnamyl	**80**	10:1	>10:1
3	Valeryl	**40**	10:1	>10:1

In summary, we developed a diastereoselective synthesis of the southwest fragment of tedanolide C in 15 steps, involving the construction of the quarternary center and the adjacent secondary alcohol. Among the different conditions validated in the pivotal aldol step, the Kiyooka protocol not only provided the highest yields and selectivities but also allowed for the efficient assembly of the ethyl ketone, required for further transformations.

Supporting Information Available. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) See Supporting Information.