Anti Aldol Selectivity in a Synthetic Approach to the C₁−C₁₂ Fragment of the Tedanolides

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ABSTRACT

In a synthetic approach to the completely protected C₁−C₁₂ fragment of the macrocyclic cytotoxic agent tedanolide 1, we carried out the tin-catalyzed Mukaiyama aldol reaction between the 2,3-dialkoxypropanal 5 and the silyl enol ether 6 derived from the ketone 7, which gave, unexpectedly, the anti aldol isomer, rather than the expected syn isomer 4, as the major diastereomer formed.

In 1984, Schmitz and co-workers (1) isolated tedanolide 1 from the Caribbean sponge Tedania ignis and reported that it showed very high cytotoxicity, with ED₅₀ values of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Seven years later, Fusetani isolated 13-deoxytedanolide, which also displayed very potent cytotoxic effects. (2) Owing to its structural complexity and biological activity, tedanolide has generated considerable synthetic interest, (3) including two total syntheses and significant synthetic work. Over the past few years, we have employed the non-aldol aldol process (4) in several approaches to tedanolide and its analogues. By using a straightforward retrosynthetic disconnection of the tedanolide skeleton involving cleavage at the lactone moiety and scission at the C₁₂−C₁₃ bond, we were able to generate the precursors 2 and 3 (Scheme 1). Recently, we reported two approaches to the C₁−C₁₂ fragment of tedanolide 2, both of which used the non-aldol aldol process and either a highly stereoselective

syn aldol reaction or a stereoselective vinyl lithium addition coupled with a stereoselective hydroboration—protonation scheme. While these routes are quite efficient, we nevertheless also investigated concurrently other possible routes to prepare the same “top half” fragment of tedanolide since this piece is a common intermediate for both tedanolide and 13-deoxytedanolide. We now report an attempted synthesis of this unit in which a novel anti-selective tin-catalyzed Mukaiyama aldol reaction was revealed.

We thought that 2 could be prepared in a few steps from the silyl ether 4, which could be formed by a route using as the key constructive step the Mukaiyama aldol reaction between the 2,3-dialkoxypropanal 5 and the silyl enol ether 6, the latter easily prepared from the ketone 7 (Scheme 2).

Thus the commercially available optically pure ester 9 was converted in 13 steps to 8 by our earlier method. This ketone was prepared from the bromo-tetrahydrofurfuryl aldehyde 8, the preparation of which we have reported previously, by a four-step route using straightforward chemistry. The ketone 7 has all the carbons from C4 to C11 and the three correct chiral centers at C6, C7, and C10 of tedanolide. To synthesize the top fragment efficiently, a syn selective aldol or Mukaiyama aldol reaction of the enolate or the enol ether derived from 7, e.g., 6, with the aldehyde 5 was required. The results of our study of that condensation follow.

Before proceeding with the reaction of the enol ether 6 of the complex ketone 7 with the aldehyde 5, we first examined the reaction of simpler ketones with 5. Literature reports of such reactions of simple silyl enol ethers with R-alkoxy aldehydes indicated that, depending on the exact case and conditions, predominantly the syn aldol product was obtained. Thus reaction of the known Z-trimethylsilyl enol ether 11,9 effected by treatment of ethyl phenyl ketone 10 with lithium diphenylamide and the silyl chloride, with the aldehyde 5 under Mukaiyama conditions, namely in the presence of stannic chloride in dichloromethane, afforded, in 89% yield, mainly the desired syn aldol diastereomer 12 with essentially none of the anti isomer 13 (Scheme 3). This result agrees well with the report of Reetz on a very similar system. The structure of 12 was proven (Scheme 4) by reduction of the ketone with DIBAL to give a mixture of diols which were cyclized to the acetonide 14, using 2,2-dimethoxypropane (DMF) and camphorsulfonic acid (CSA), which was purified by preparative TLC. The very small coupling constants of Hα and Hc and Hb and Hc (J 2.0 Hz) in the proton NMR indicated that all three protons were cis and that we had indeed obtained the syn isomer 12.10 However, when the known Z-trimethylsilyl enol ether 16, prepared from diethyl ketone 15 with trimethylsilyl iodide and triethylamine, was reacted under the same conditions with 5, a 93% yield of a >10:1 ratio favoring the anti product 18 over the syn 17 (Scheme 5) was obtained. Thus the two analogous cases proceed to give the opposite diastereoselectivity. The structure of 18 was proven by the following

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(7) Ethylmagnesium bromide was added to the aldehyde 8 followed by Dess–Martin oxidation to the ketone. Reductive ring-opening with zinc in acetic acid and silylation of the diol with TBSCl gave 7.

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two routes (Scheme 6). DIBAL reduction and acetonide formation with TLC separation afforded the acetonide 19. Proton coupling analysis indicated that protons H\textsubscript{a} and H\textsubscript{c} were trans diaxial (J = 10.5 Hz) while protons H\textsubscript{b} and H\textsubscript{c} were cis (J = 1.5 Hz). The differences in the NMR spectra of 14 and 19 were very clear. The syn relationship between the benzyloxy group and the alcohol was shown by preparing the second acetonide 20 via first protection of the alcohol as the TBS ether, reduction of the ketone with DIBAL, and protection of the resulting alcohol as the methyl ether. Removal of the two silyl groups (TBAF), acetonide formation, and finally separation afforded 20, in which protons H\textsubscript{a} and H\textsubscript{b} showed a small coupling (J = 1.5 Hz) therefore indicating they were cis.

Next, we investigated the condensation of the silyl enol ethers 22a–d prepared from a series of ethyl alkyl ketones 21 with the aldehyde 5 in the presence of stannic chloride (Scheme 7). Whereas the TMS enol ether 22a gave relatively poor selectivity (1:2), the corresponding TBS enol ether 22b gave a 1:9 ratio favoring the anti diastereomer 24a in 71% yield. Likewise the cyclohexyl TMS enol ether 22c gave a 1:5 ratio favoring the anti isomer 24c in 82% yield while the TBS enol ether 22d gave a higher 1:7 ratio again favoring the anti isomer 24c.

The structures of the two major diastereomeric products 24ac were proven via the coupling constant analysis of the acetonides as described in detail above.

Interestingly, additional stereocenters in the ethyl ketone fragment do not disturb the anti selectivity. Thus the known\textsuperscript{(12)} silyl enol ether 26, prepared from the ketone 25, reacted with the aldehyde 5 to give an 88% yield of only the anti diastereomer 28 (Scheme 8). Similarly treatment of the silyl enol ether 29, derived from a two-step silylation of the ethyl ketone 18, which was prepared as in Scheme 5, with the aldehyde 5 afforded only the anti diastereomer 30 in 83% yield (Scheme 9). The stereochemistry of 30 was easily assigned by silylation of the free alcohol to give the C\textsubscript{2} symmetric ketone 31.

Finally, even though it was apparent that anti selectivity would be observed, nonetheless we tried the requisite key step for the synthesis of 4, namely the Mukaiyama aldol condensation of the silyl enol ether 6 (prepared from the ketone 7) with the aldehyde 5 in the presence of stannic chloride (Scheme 10). The condensation afforded, in 78% isolated yield, the anti diastereomer 32 as the major product, which is the epimer of the desired syn diasteromer 4 at C4.

The following reasons may be postulated for the observed selectivity. Theoretical calculations indicate that the two Z

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(10) Extensive decoupling experiments were carried out to ensure the identity of the indicated protons in all the acetonides.


transition states suggested by Heathcock,\textsuperscript{8a} namely the Z-A\textsuperscript{3} and the Z-S\textsuperscript{1} transition states, have very different energies depending on whether the substituent is an ethyl or a phenyl group. Thus B3LYP/6-31G(d) level calculations\textsuperscript{13} give the differences shown in Figure 1, specifically the anti transition state A (Heathcock’s Z-A\textsuperscript{3}) is calculated to have a lower $\Delta G$ than that of the opposite syn transition state B (Heathcock’s Z-S\textsuperscript{1}) by roughly 2.4 kcal/mol. That energy difference is in good agreement with the product ratios observed. However the situation changes with the phenyl substituent: the syn transition state D is calculated to have a lower $\Delta G$ than that of the opposite anti transition state C by roughly 0.7 kcal/mol. Here, although the magnitude of the energy difference does not correspond to the ratio seen (all syn), the trend is at any rate in the right direction. Compared to A, the syn TS B is disfavored, mainly due to repulsion between the alkyl group R and the chiral C2 carbon of the aldehyde. However, the reasons for the smaller difference in energy between the phenyl substituted case, D and C, are less obvious. From a careful examination of the transition structures, it can be seen that in C, the silyl enol ether rotates from a perfectly staggered conformation to avoid interaction between the phenyl and a chloride on the tin, which introduces steric repulsion between the methyl and again the chiral C2 carbon of the aldehyde. This causes this normally favored transition state now to be higher in energy than its syn counterpart. Further theoretical studies will be needed to gain more insight into this difference.

In conclusion, we have observed a novel change in the diastereoselectivity of the tin-catalyzed Mukaiyama aldol reaction between an $\alpha$-alkoxy aldehyde and the Z trialkylsilyl enol ether of ethyl ketones from completely syn when the opposite group is phenyl to mainly or completely anti when the opposite group is alkyl. This effect is seen even when the opposite group is a relatively large alkyl unit and has additional alkyl or oxygen stereocenters. Finally, we have carried out theoretical calculations which provide some rationale for this novel switch in the diastereoselectivity. Further developments toward the total synthesis of tedanolide will be published in due course.

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Supporting Information Available: Experimental procedures and spectral data (proton and carbon NMR, IR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) These calculations were done on a simpler model system where the enol silyl ether was replaced by an enol, the OTBDPS group by an OH, and the OBN by an OMe group with the R group being ethyl ($R = Et$).