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Studies towards the synthesis of tedanolide C. Construction of the C13-*epi* C1–C15 fragment†

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The preparation of an advanced intermediate on route towards the synthesis of tedanolide C is reported here. It is based on the coupling of two fragments of similar size and complexity, which in turn are prepared by highly stereoselective substrate-controlled titanium-mediated aldol reactions from chiral ketones.

Tedanolides are a family of structurally complex natural marine products that feature *in vitro* cytotoxicities in the nanomolar to picomolar range.[1] The combination of this biological activity and their unique structure have led to considerable efforts to synthesize them, which have resulted in the completion of several total tedanolide synthesis (Fig. 1).[2,3] However, and in sharp contrast to the other efforts to date, no total synthesis and only a few approaches towards small fragments of tedanolide C (Fig. 1) have been reported so far.[4]

Tedanolide C, isolated by Ireland in 2005 from a marine sponge of the *Ircinia* species found in Papua New Guinea,[5] exhibits potent cytotoxic activity against HCT-116 cells *in vitro* and produces important S-phase arrest. These remarkable properties grant it a prominent position among the lead compounds for the inhibition of protein biosynthesis. Structurally, tedanolide C resembles other members of the tedanolide family since a side chain bearing an epoxide and an alkene is attached to a highly oxygenated 18-membered macrolactone from a primary alcohol. In turn, it is distinguished by a geminal dimethyl group and eight stereocentres, including a tertiary alcohol. This structure and the relative stereochemistry shown in Fig. 1 have been determined by NMR studies, molecular modelling and DFT calculations, but its absolute configuration is still unknown. In fact, this has often been called into question and most of the synthetic studies reported to date target the enantiomer or any of its epimers.[4]

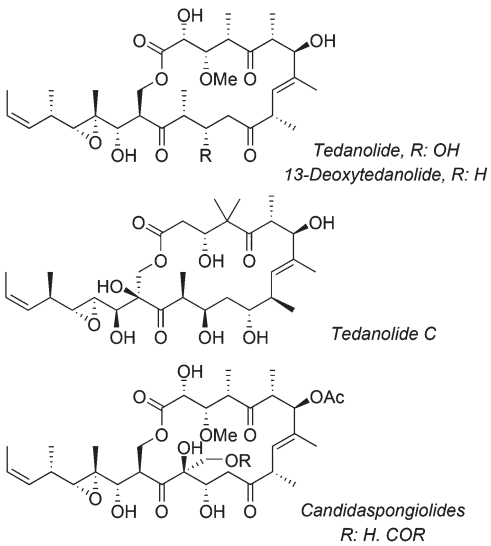

Fig. 1 Tedanolides.

Given this uncertainty and considering the need for efficient routes to tedanolide C, we launched a project devoted precisely to the synthesis of such a challenging structure. Initially, we planned to synthesize an advanced C1–C15 intermediate by coupling two fragments, which in turn might result from the novel and highly stereoselective substrate-controlled aldol reactions developed by our group.[6,7] Such an approach entailed the opposite configuration for the C13 stereocentre; but we were first interested in testing the synthetic potential of our basic methods and exploring the feasibility of the overall strategy. As represented in Scheme 1, our retrosynthetic analysis for the C13-epimeric C1–C15 fragment of tedanolide C (**1**) hinges on the disconnection of the C7–C8 bond, which yields two fragments of similar size and complexity. The synthesis of the C1–C7 northern fragment takes advantage of a titanium-mediated aldol reaction based on a chiral isopropyl ketone;[6] whereas the C8–C15 southern fragment results from the aldol reaction of a chiral methyl ketone with a

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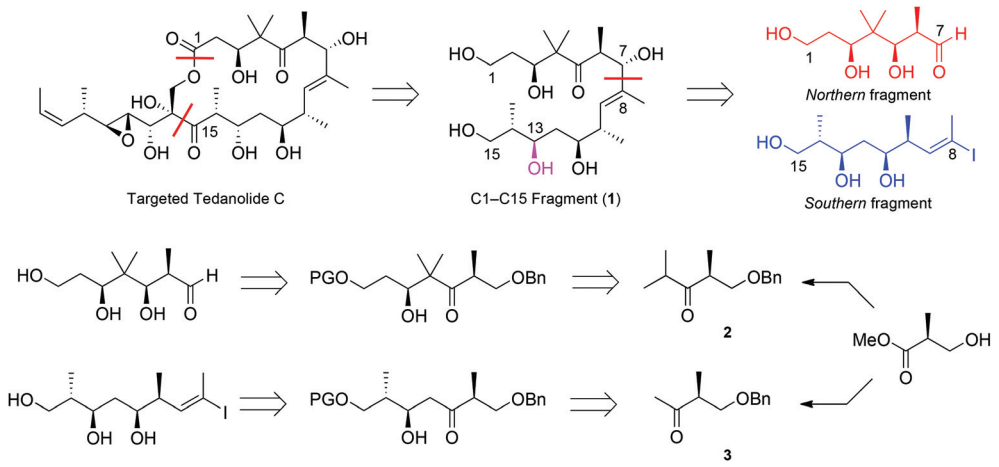
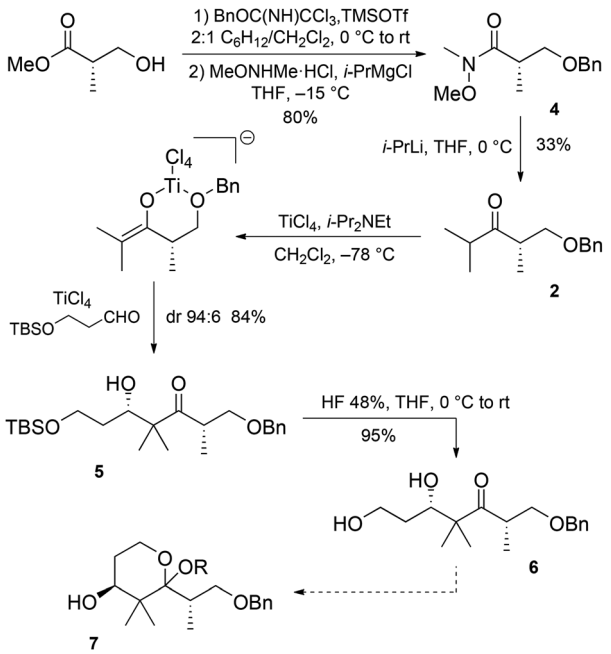


Scheme 1 Retrosynthetic analysis of tedanolide C.

chiral aldehyde.[7] Interestingly, both ketones may be prepared from the same starting material: the methyl (*S*)-Roche ester, which is the single chiral source for all the stereocentres.

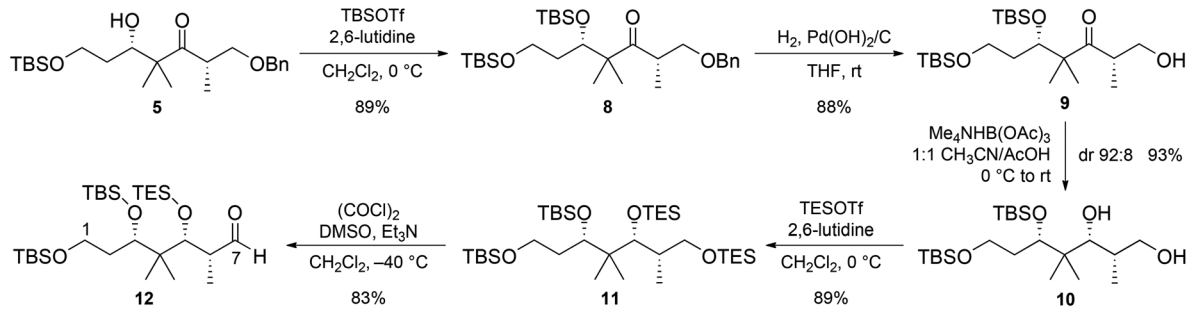
According to this plan, the chiral isopropyl ketone **2** required for the construction of the C1–C7 fragment was prepared in a three-step sequence from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate by standard transformations (Scheme 2).[6] A quick glance at **2** indicated that the enolization would be troublesome due to the close similarity of the two α-positions flanking the carbonyl bond. Contrary to what might be expected, the chelating capacity of $TiCl_4$ permitted outstanding regioselective enolization and the subsequent Lewis acid-mediated aldol addition to 3-*tert*-butyldimethylsilyloxypropanal proceeded smoothly to produce a 94 : 6 mixture of diastereomers from which the desired adduct **5** was isolated in 84% yield. Having completed the backbone of the northern C1–C7 fragment, we envisaged that the removal of the TBS protecting group could trigger the simultaneous protection of the ketone and the resultant primary alcohol, which would facilitate further transformations.[8] As planned, deprotection of **5** produced the dihydroxy ketone **6** with an excellent yield; but the carbonyl group turned out to be completely unreactive and the desired pyran **7** (Scheme 2) was never observed in the reaction mixtures. This lack of reactivity is probably due to *syn*-pentane interactions developed by the geminal dimethyl group in the cyclic form. Other attempts to protect the carbonyl group as a ketal also failed, which forced us to revise our approach.



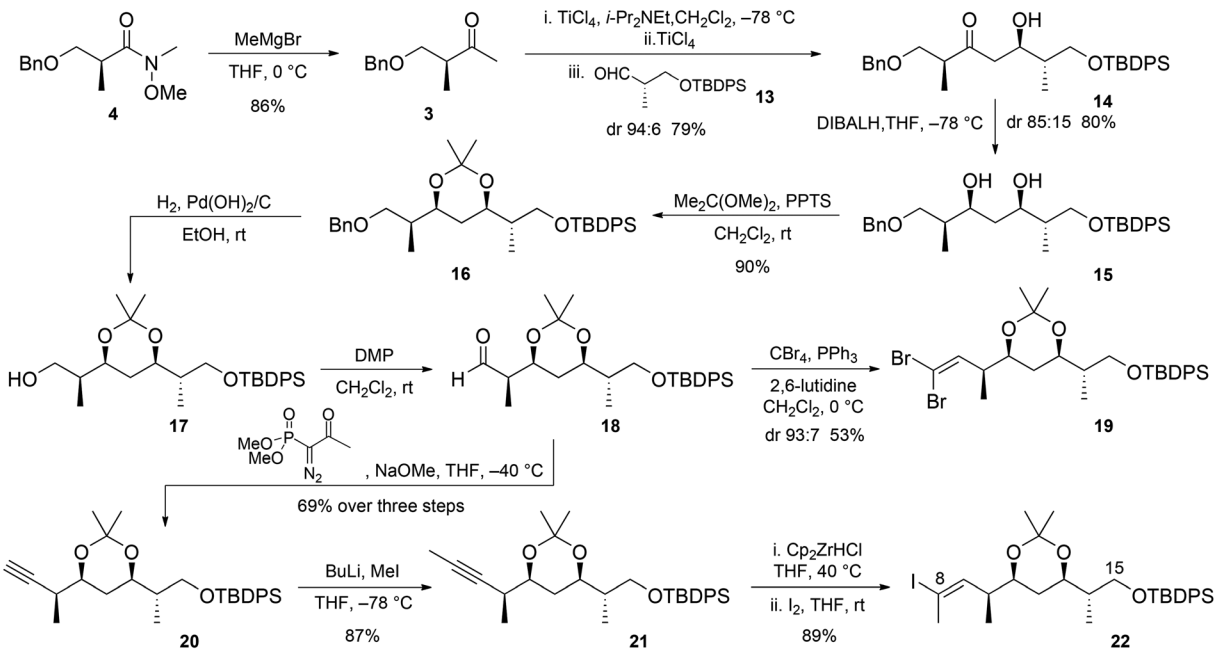
Scheme 2 First approach to the synthesis of the northern fragment.

Since the protection of the ketone proved to be difficult, it was necessary to reduce it to install the required aldehyde at C7 securely. Indeed, protection of the C3 alcohol and removal of the benzyl protecting group produced pure hydroxy ketone **9** in a straightforward manner (Scheme 3). The subsequent substrate-controlled reduction[9] of the carbonyl proceeded with excellent stereocontrol to provide diol **10** as a 92 : 8 mixture of diastereomers and in 93% combined yield, whose treatment with TESOTf gave fully protected polyol **11** in 89% yield. Finally, the selective oxidation of the TES-protected primary alcohol[10] furnished the desired aldehyde, **12**, in 83% yield. Therefore, the northern fragment was synthesized in six steps and with 45% overall yield from isopropyl ketone **2**.

Once the aldehyde **12** was prepared, we focused our attention on the southern fragment. The starting chiral methyl ketone **3** was readily available from Weinreb amide **4**, previously prepared for the synthesis of isopropyl ketone **2** (Scheme 4). So, double differentiating aldol addition of **3** to the chiral aldehyde **13** led to the *anti*-Felkin aldol adduct **14** in 79% yield and 94 : 6 diastereomeric ratio. This was a remarkable result since the *anti*-Felkin relationship corresponds to a putative mismatched pair.[7] Next, we assessed the stereo-



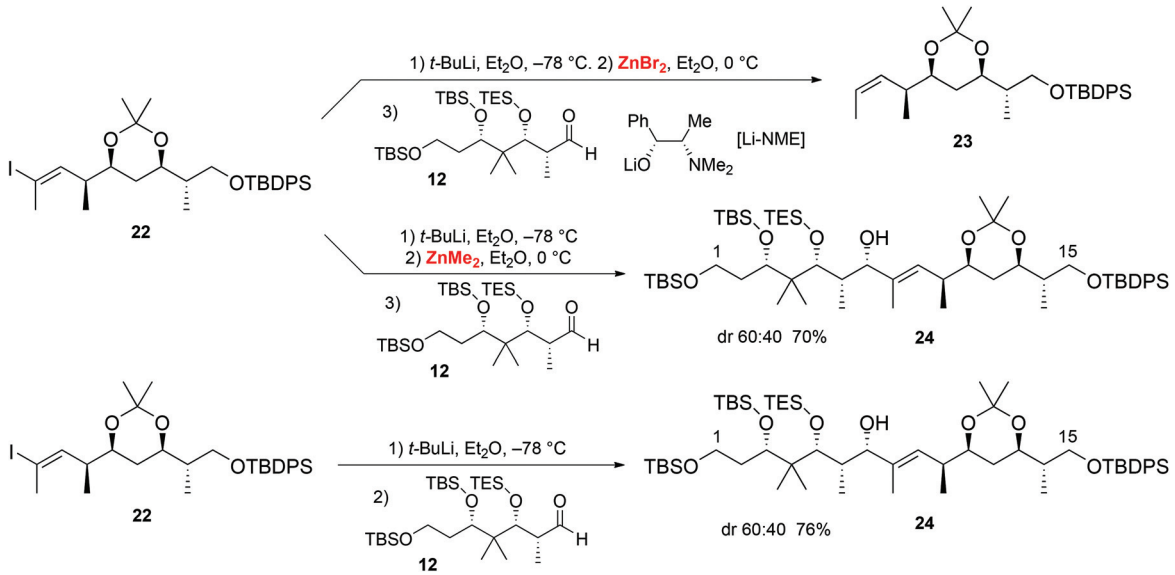
Scheme 3 Synthesis of the C1–C7 northern fragment.



Scheme 4 Synthesis of the C8–C15 southern fragment.

selective reduction of the carbonyl group. Preliminary attempts based on Narasaka–Prasad conditions[11] were disappointing and *syn* diol **15** was obtained with a modest combined yield (60%) and a low diastereomeric ratio (dr 70 : 30). Thus, we were pleased to observe that the use of DIBALH under Kiyooka conditions[12] led to an 85 : 15 mixture, from which enantiomerically pure *syn* diol **15** was isolated with 80% yield. The protection of the resulting diol and the accurate hydrogenolysis of the benzyl ether **16** produced the primary alcohol **17**, which was immediately oxidized without further purification with Dess–Martin periodinane[13] to give aldehyde **18**. Then, the conversion of the carbonyl into a terminal alkyne was evaluated. Application of the Corey–Fuchs conditions[14] to **18** produced the dibromoalkene **19** with a certain epimerization (dr 93 : 7) and in modest yield (53%). The Ohira–Bestmann method[15] turned out to be much more effective provided that mild experimental conditions were employed to avoid the epimerization of the sensitive aldehyde **18**. Indeed, treatment of **18** with dimethyl (acetyldiazomethyl)phosphonate and NaOMe at −40 °C[16] gave enantiomerically pure terminal alkyne **20** in 69% overall yield over the three steps. Finally, methylation of **20** and hydrozirconation of the resultant alkyne **21** with Cp_2ZrHCl, followed by treatment of the vinylzirconium intermediate with iodine, provided the desired iodoalkene **22** with 89% combined yield. Thus, the southern fragment **22** had been synthesized in eight steps and 30% yield from methyl ketone **3**.

With both fragments **12** and **22** in hand, we next tackled their assembly. Surprisingly and in spite of the synthetic importance of the metal-mediated asymmetric additions of halo alkenes to aldehydes, there is still a lack of models to predict their stereochemical outcome. This limitation probably



Scheme 5 Coupling of northern and southern fragments: synthesis of the C13-*epi* C1–C15 fragment.

stems from the large number of variables that determine the configuration of the new stereocentre, which involves the geometry of the olefin, the metal, the structure of both partners, and the influence of other chiral additives.[17]

Facing such a daunting task, we initially examined the conversion of iodo olefin **22** into a vinylzinc compound and the subsequent addition to aldehyde **12**. Marshall reported that the addition of vinyl zinc bromide intermediates to α-chiral aldehydes in the presence of lithiated (+)- or (–)-*N*-methylephedrine under non-chelation conditions proceeded stereoselectively to afford the corresponding *anti* or *syn* adducts with predominant reagent control.[18–20] Thus, we considered that the appropriate choice of the enantiomer of the easily available *N*-methylephedrine might permit the stereocontrolled coupling of the northern and southern fragments. Unfortunately and despite intensive efforts, such a transformation did not produce the desired C1–C15 fragment. Instead, we always recovered the starting aldehyde **12** and dehalo derivative **23** (Scheme 5), which suggests that the chiral NME complex is not efficiently formed or turns out to be too bulky to attack the carbonyl.

Interestingly, related vinylzincates, prepared by transmetalation of vinyllithium intermediates with $ZnMe_2$, can also participate in highly diastereoselective substrate-controlled reactions of halo alkenes and aldehydes and have already been employed in the total syntheses of natural products.[21] Particularly, comprehensive studies by Gennari have established that double asymmetric additions of chiral lithium vinylzincates to chiral aldehydes usually proceed in high yields, although the stereocontrol depends heavily on the structure of the nucleophile and is difficult to rationalize.[17,22] With this conceptual framework in mind, we next assessed its application to the synthesis of the C1–C15 fragment. Thus, we were pleased to observe that treatment of iodo olefin **22** with *t*-BuLi and transmetalation of the resultant intermediate with $ZnMe_2$ produced a vinylzincate that, added to aldehyde **12**, gave the desired C13-*epi* C1–C15 fragment **24**‡ as a 60 : 40 mixture of two diastereomers in 70% combined yield (Scheme 5).§

Aiming to simplify the overall procedure, we then focused our attention on the addition of trisubstituted alkenyl lithium intermediates to aldehydes. The stereocontrol of such reactions is usually poor, but occasionally they proceed with moderate to high diastereoselectivity.[23] Indeed, some examples reported by Smith were encouraging since they involved aldehydes and iodo olefins that are structurally close to our northern and southern fragments respectively.[24] These Smith conditions proved to be highly effective and produced the C13-*epi* C1–C15 fragment **24** in 76% yield and 60 : 40 diastereomeric ratio (Scheme 5).

In summary, we have achieved the stereocontrolled syntheses of aldehyde **12** and iodo olefin **22**, two fragments of similar size and complexity on route towards the synthesis of tedanolide C. Both approaches are based on highly efficient substrate-controlled titanium-mediated aldol reactions from chiral ketones derived from the (*S*)-Roche ester. Addition of the alkenyl lithium intermediate from **22** to aldehyde **12** provides alcohol **24**, an advanced C13-*epi* C1–C15 fragment of tedanolide C, in high yield but modest stereocontrol. Further studies on such a coupling and other improvements are currently underway in our group and will be reported in due course.

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‡The configuration of C7 of the major diastereomer was established through comprehensive NMR studies on a bis acetonide derivative. Particularly, diagnostic peaks in ^{13}C NMR were crucial to assign the 7*S* configuration. See ref. 25 and the ESI.†

§Considering such a high overall yield, we tried to increase the diastereoselectivity of the mixture putting into practice a common tactic based on its oxidation and the subsequent asymmetric reduction of the resultant enone. Treatment of the mixture with DMP smoothly afforded the desired enone in excellent yield but our efforts to reduce stereoselectively the carbonyl bond with CBS or other achiral agents were unsuccessful.

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