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A short approach to the bicyclo[4.3.0]nonane fragment of stawamycin

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Abstract—The bicyclo[4.3.0]nonane (C_{11}–C_{21}) fragment of stawamycin has been prepared by a sequence involving 11 steps (10% overall yield) from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate. Key steps are a Pd-catalysed Stille coupling reaction between a vinyl iodide and a vinyl stannane followed by an intramolecular Diels–Alder cycloaddition reaction to give the desired adduct as the major isomer in 21% overall yield.

1. Introduction

Epstein-Barr virus (EBV) is a human herpes virus that infects lymphocytes and epithelial cells. It has been estimated that this virus infects a large part of the world's population.[1] In 1995, stawamycin (**1**),[2] a new natural product from the pyrroloketoindane family was isolated by Miao et al. from a liquid culture of *Streptomyces* sp. and displayed moderate inhibitory activity against the binding of the EBV BZLF1 transcription factor to DNA with $IC_{50} = 50\ \mu M$ in a DNA binding assay (Fig. 1).[2] Stawamycin has a trisubstituted *trans*-fused *endo*-bicyclo[4.3.0]nonane substructure containing five stereogenic centres and a side chain that contains two stereogenic centres at C_3 and C_9 (absolute configuration not determined), a doubly allylic alcohol and a sodium carboxylate residue.[3,4]

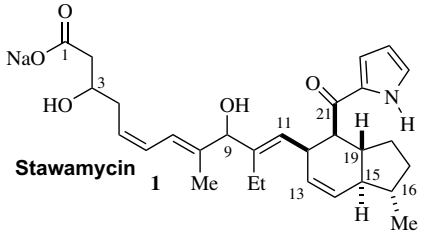

Figure 1. Stawamycin.

It has been speculated that stawamycin and the other members of its family arise biosynthetically by a Diels–Alder cycloaddition reaction.[5] To determine the relative configurations between C_3 and C_9, to establish the absolute configuration of stawamycin, and to provide material for further biological studies as well as access to novel analogues, we initiated a study towards the synthesis of this very interesting compound.[6] We wish to describe here our successful efforts towards the preparation of the C_{11}–C_{21} carbocyclic fragment of stawamycin.

Our disconnection strategy summarised in Scheme 1, involved cleavage of the C_{12}–C_{20} and the C_{15}–C_{19} bonds in **2** to give the α,β-unsaturated oxazolidinone **3**. Further synthetic analysis involved the cleavage of the C_{13}–C_{14} bond in **3** to give vinyl iodide **4** (C_{14}–C_{21} fragment) and vinyl stannane **5** (C_{11}–C_{13} fragment). Key steps in this approach are a Pd-catalysed Stille coupling reaction between a vinyl iodide and a vinyl stannane followed by an intramolecular Diels–Alder cycloaddition reaction (IMDA) to set up the remaining four stereogenic centres of the bicyclo[4.3.0]nonane fragment.[7]

We decided to investigate the use of chiral and achiral oxazolidinones attached to the dienophile part of the triene, since the presence of two carbonyl groups would offer a two-point binding with the Lewis acid, probably increasing the *endo* selectivity under mild conditions.

Keywords: Pyrroloketoindane family; Intramolecular Diels–Alder reaction; Stille coupling; Lactone.
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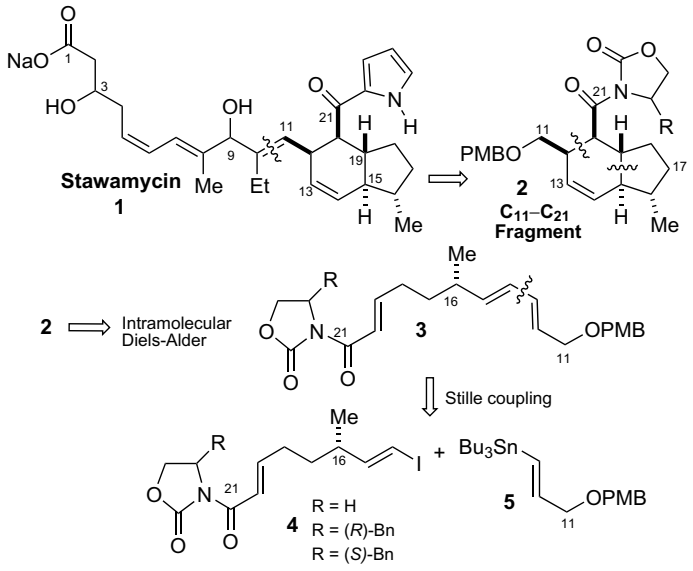


Scheme 1. Retrosynthetic analysis.

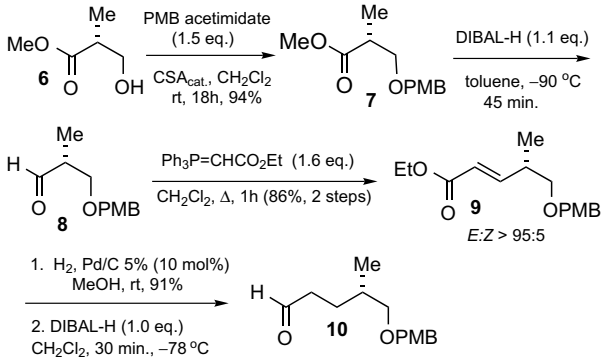
2. Results and discussion

Synthesis of the C_{14}–C_{21} fragment began with the known *p*-methoxybenzyl ether **7** (Scheme 2), which was most conveniently prepared from commercially available methyl-(*R*)-(−)-3-hydroxy-2-methylpropionate **6** by treatment with *p*-methoxybenzyltrichloroacetimidate under acid catalysis (CSA, CH_2Cl_2, 94%).

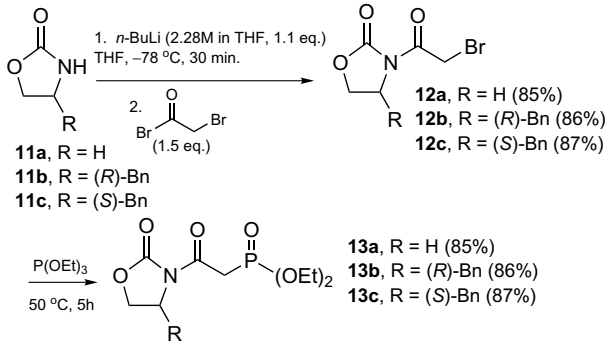
Ester **7** was smoothly reduced to aldehyde **8** on treatment with diisobutylaluminium hydride in toluene at low temperature.[8,9] The unpurified aldehyde was directly subjected to a Wittig homologation with the requisite stabilised ylide reagent to give the (*E*)-α,β-unsaturated ester **9** in 86% yield over two steps (*E*:*Z* >95:5 diastereoselectivity). Selective hydrogenation of the double bond in the α,β-unsaturated ester **9** under very mild conditions (H_2/Pd/C, 25 °C, 1 atm, 40 min, 91%) gave an intermediate ester leaving the PMB group intact.[10] Careful reduction of this ester with diisobutylaluminium hydride at −78 °C gave the desired aldehyde **10**.

At this point, we carried out the preparation of achiral phosphonate **13a** and chiral phosphonates (*R*)-**13b** and (*S*)-**13c**.[11] These were easily prepared in very good yields by acylation of the corresponding oxazolidinones **11a**–**c** with *n*-BuLi and bromoacetyl bromide followed by reaction with triethyl phosphite, as described in Scheme 3.

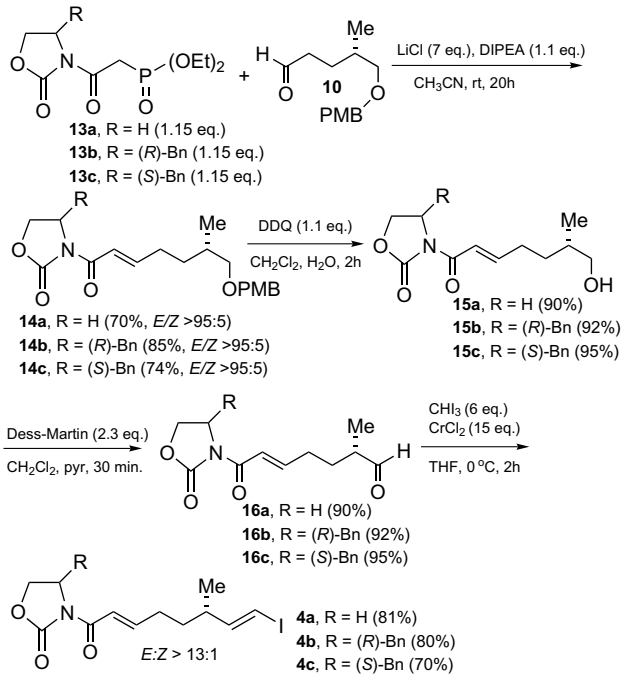
Aldehyde **10** was directly submitted to Horner–Emmons coupling reactions with phosphonates **13a**–**c** to give the corresponding (*E*)-α,β-unsaturated oxazolidinones **14a**–**c** with great *E*:*Z* selectivities (*E*:*Z* >95:5) and in good overall yields (Scheme 4). The next step involved DDQ-mediated oxidative deprotection of *p*-methoxybenzyl ethers **14a**–**c** in aqueous CH_2Cl_2 to provide the corresponding primary alcohols **15a**–**c** (corresponding to the C_{15}–C_{21} segment), in excellent yields.[12] Oxidation[13] of the primary alcohol functionality in **15a**–**c** using the Dess–Martin periodinane reagent under the standard conditions gave the intermediate aldehydes **16** that were directly submitted to Takai et al.[14] olefination reaction conditions (CHI_3, $CrCl_2$, THF) to produce *E*-vinyl iodides **4a**–**c** in good yields and high selectivities (**4a**, 13:1 *E*/*Z*; **4b**, 13:1 *E*/*Z* and **4c**, 13:1 *E*/*Z*).



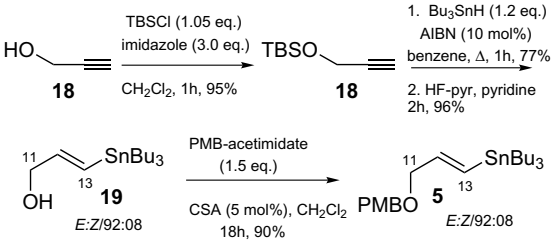
Scheme 2. Preparation of aldehyde **10**.



Scheme 3. Preparation of phosphonates **13a**–**c**.



Scheme 4. Synthesis of vinyl iodides **4a**–**c**.

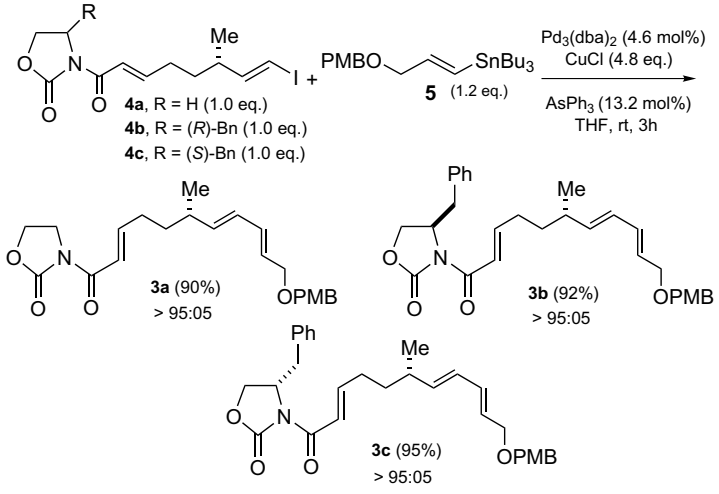


Scheme 5. Preparation of vinyl stannane **5**.

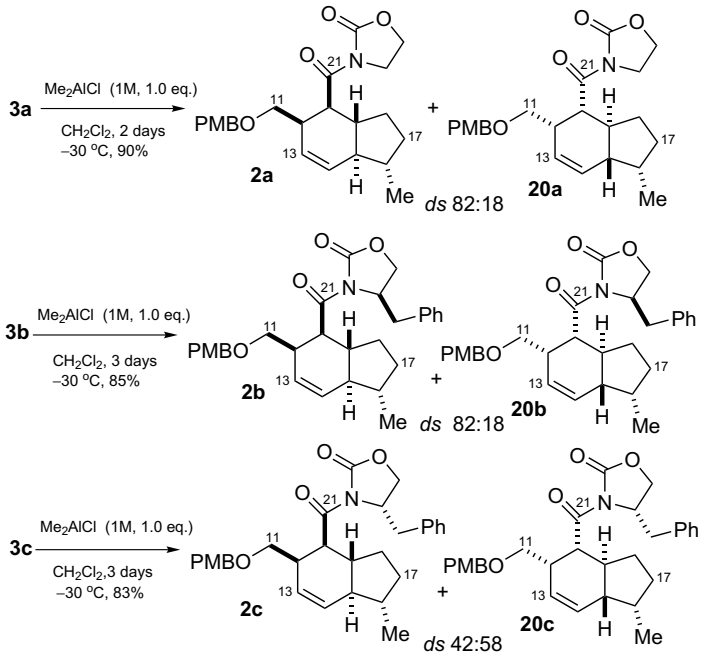
The (*E*)-vinylstannane **5**, corresponding to the C_9–C_{11} fragment, was smoothly prepared using a four-step protocol from commercially available propargylic alcohol **17** (Scheme 5).[15] Protection of the primary OH-functionality in **17** with TBSCl gave **18** in 95% yield. Tributylstannylation of **18** with Bu_3SnH and AIBN under reflux in benzene followed by TBS removal with HF–pyr in pyridine gave pure vinyl stannane **19**. Protection of the OH-function in **19** as its PMB ether (PMB-acetimidate, CH_2Cl_2, catalytic CSA) gave the corresponding C_{11}–C_{13} segment **5** (*E*:*Z* 92:08) in 77% yield after purification by flash chromatography.[15]

With the requisite C_{11}–C_{13} and C_{14}–C_{21} fragments in hand, their coupling was undertaken. This was done by using Stille coupling conditions in the presence of the palladium dichloride bis-dibenzylideneacetone complex to give the desired *E*,*E*,*E* trienes **3a**–**c** in excellent yields (Scheme 6).[16]

We next investigated the critical Diels–Alder reactions for assembling the carbocyclic fragment of stawamycin.[6,17] Unfortunately, thermal IMDA cycloaddition of triene **3a** resulted in low diastereoselectivity (48:52, *endo*(**2a**):*others*). The desired *endo*-cycloadduct **2a** was obtained as a mixture with three other cycloadducts after flash chromatographic purification in 60% yield. After extensive experimental work, we observed that Et_2AlCl as Lewis acid provided the best result in terms of yields. Lewis acid induced cycloaddition reactions of trienes **3a**–**c** (Et_2AlCl (1.0 equiv), CH_2Cl_2, −30 °C, 2–3 days) gave the desired *endo*-cycloadducts **2a**–**c** as the major isomers along with only a second *endo*-isomer **20a**–**c** after flash column chromatography (Scheme 7). It is noteworthy that the IMDA reaction with diene **3a**, bearing an achiral oxazolidinone auxiliary, gave the best results both in terms of yields and selectivities, favouring the desired cycloadduct **2a** (*endo*-**2a**/*endo*-**20a** = 82:18, 90% yield). The use of dienes **3b** and **3c** led to disappointing results in terms of selectivities (*endo*-**2b**/*endo*-**20b** = 82:18, 85% yield; *endo*-**2c**/*endo*-**20c** = 42:58, 83% yield). The observed result with triene **3b** was really surprising, since we were expecting much better levels of diastereoselectivity in a *matched* case. The best result with triene **3a** shows that we are probably having a competition between the two possible *endo* transition states.



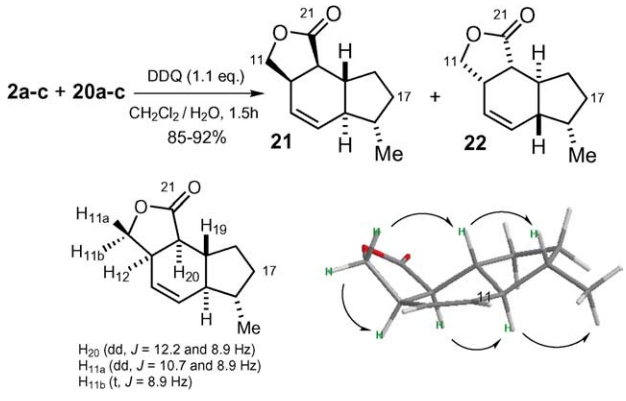
Scheme 6. Stille coupling: preparation of **3a**–**c**.



Scheme 7. Intramolecular Diels–Alder reactions.

Although we have not determined the relative stereochemistry at the cycloadduct stage, we have observed that, after treatment with DDQ/H_2O, all cycloadducts led to exactly the same mixture of two lactones (Scheme 8). Treatment of cycloadducts with DDQ/H_2O led to deprotection of the PMB ether followed by lactonisation to give lactones **21** and **22** in excellent yields. We later found that the use of 5 equiv of Et_2AlCl with **3a–c** to promote the IMDA cycloaddition led to lactones **21** and **22** directly, avoiding the use of the extra step with DDQ. An analytical sample of lactone **21** was obtained in order to determine the relative stereochemistry.

The observed relative stereochemistry of the major isomer **21** was proved by analysis of coupling constants in its ^1H NMR spectrum as well as by NOESY experiments. The illustrated NOESY interactions between H_{11a}/H_{19}, H_{11b}/H_{12}, H_{15}/H_{20}, H_{16}/H_{19} and between H_{15}/Me together with the large vicinal coupling constant between H_{20} with both H_{12} and H_{19} (dd, 12.2 and 8.9 Hz) confirmed the *trans*-diaxial relationship between H_{19} and H_{20} as well as the *cis* relationship between H_{12} and H_{20} and unambiguously established the relative stereochemistry of the major isomer as being that desired for the synthesis of stawamycin. In these stereochemical assignments, the methyl stereocentre configuration served as an important reference point.[4]



Scheme 8. Lactone formation coupling constants and NOESY interactions for lactone **21**.

3. Conclusions

This approach to the bicyclo[4.3.0]nonane fragment of stawamycin requires 11 steps (longest linear sequence) and produced the desired carbocyclic fragment **2a** in 27% overall yield. The best result was obtained with the use of a triene bearing an achiral oxazolidinone in the presence of Et_2AlCl to promote the IMDA cycloaddition reaction. As a result, the route to the carbocyclic fragment of stawamycin presented here is, in principle, readily applicable for the preparation of stawamycin as well as to additional analogues. Extension of this work to the synthesis of stawamycin and analogues is underway and the results will be described in due course.[18]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.004.

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4. The numbering of **1** as well as of each intermediate follows that suggested in Ref. 2.
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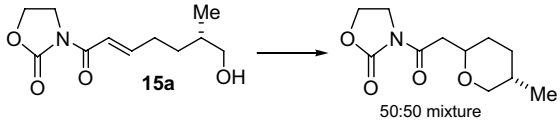
13. For alcohol **15a**, oxidation must be done immediately after deprotection in order to avoid formation of the product from intramolecular Michael addition reaction.



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18. New compounds and the additional isolated intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.