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Communication

Towards the Total Synthesis of Stawamycin. Synthesis of C11-C21 Fragment.

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A porção carbocíclica (C11-C21) da Estavamicina foi preparada através de uma sequência envolvendo 11 etapas (10% de rendimento global) a partir do (R)-(-)-3-hidróxi-2-metilpropionato de metila. As etapas chave envolvem um acoplamento de Stille entre uma vinilestanana e um iodeto vinílico, catalisado por complexo de paládio seguido de uma cicloadição de Diels-Alder intramolecular conduzindo ao isômero desejado como produto majoritário juntamente com outros 3 isômeros em 78% de rendimento.

The carbocyclic (C11-C21) 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 Pd-catalyzed Stille coupling reaction between a vinyl iodide and a vinylstannane followed by an intramolecular Diels-Alder cycloaddition reaction to afford the desired adduct as the major isomer together with three other possible adducts in 78% overall yield.

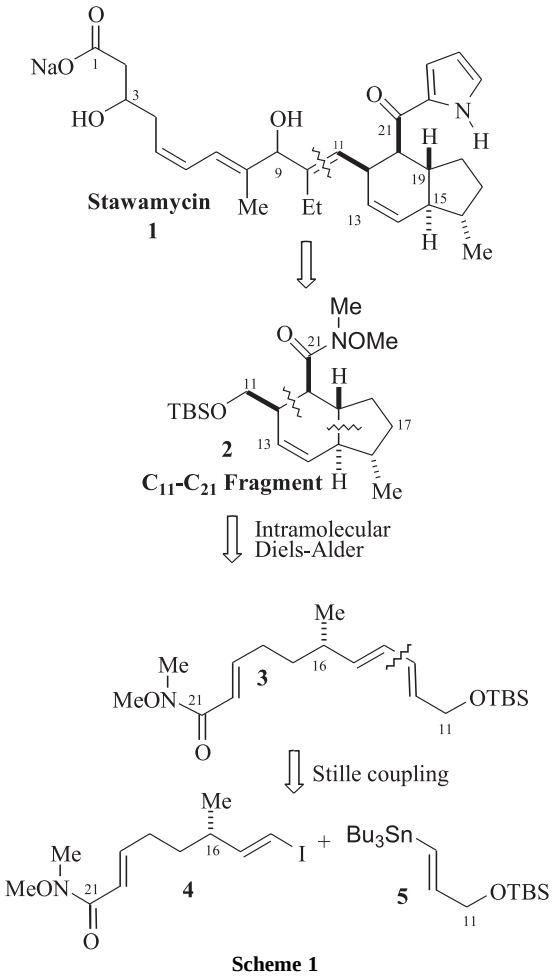
Keywords: intramolecular Diels-Alder reaction, Stille coupling, herpes virus inhibitor

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)**, a new natural product from the pyrroloketoindane family was isolated from the 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 μM (Scheme 1)[2]. Stawamycin has a carbocyclic ring containing five asymmetric centers and a side chain that contains two asymmetric centers at C3 and C9 (relative configuration not determined), a doubly allylic alcohol and a sodium carboxylate residue (Scheme 1). To determine the relative configuration between C3 and C9, to establish the absolute configuration of Stawamycin, and to provide material for further biological studies, we initiated a study towards its total synthesis. We wish to describe here our initial efforts towards the preparation of the C11-C21 fragment.

Results and Discussion

Our first disconnection, summarized in Scheme 1, involved cleavage of the C10-C11 double bond to give



Scheme 1

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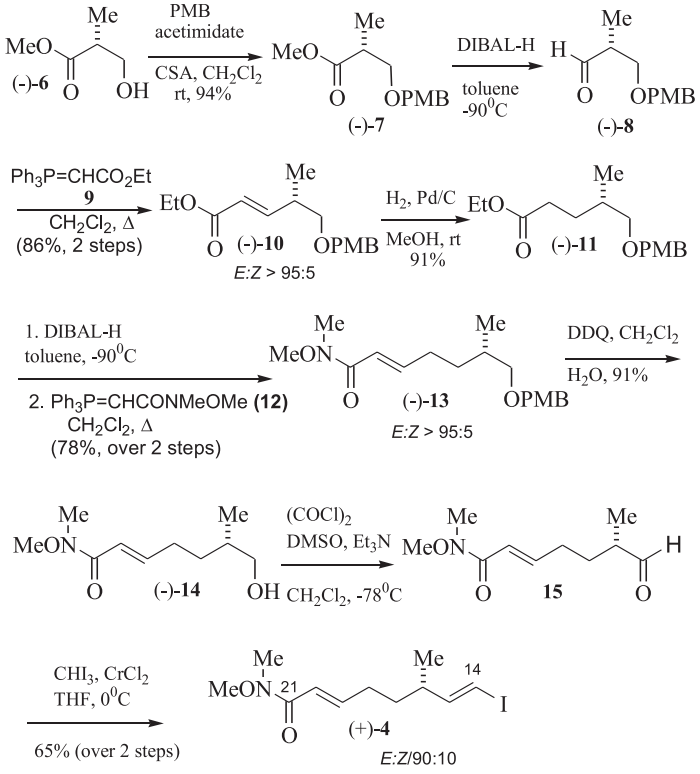
fragment **2**. Cleavage of the C12-C20 and C15-C19 bonds in **2** afforded the α,β-unsaturated Weinreb amide **3**. Further synthetic analysis involved the cleavage of C13-C14 to give vinyl iodide **4** (C14-C21 segment) and vinyl stannane **5** (C11-C13 segment). Key steps in this approach are a Pd-catalyzed Stille coupling reaction between a vinyl iodide and a vinyl stannane followed by an intramolecular Diels-Alder cycloaddition to set up the remaining 4 stereogenic centers of the cyclic fragment.

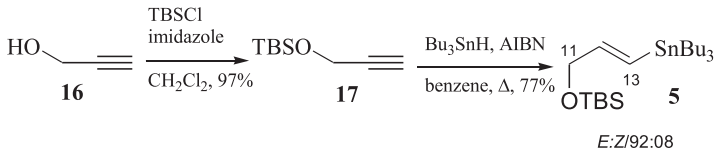
Synthesis of the C14-C21 segment began with the known *p*-methoxybenzyl ether (-)-**7**, which was most conveniently prepared from commercially available methyl-(R)-(-)-3-hydroxy-2-methylpropionate (-)-**6** by treatment with *p*-methoxybenzyltrichloroacetimidate under acid catalysis (CSA, CH_2Cl_2, 94%) (Scheme 2)[3]. Ester (-)-**7** was smoothly reduced to aldehyde (-)-**8** on treatment with diisobutylaluminum hydride in toluene at low temperature. This unpurified aldehyde was directly subjected to a Wittig homologation with the requisite stabilized ylide reagent **9** to afford α,β-unsaturated ester (-)-**10** in 86% yield over two steps (*E:Z*/>95:5 diastereoselectivity). Selective hydrogenation of the double bond in the α,β-unsaturated ester (-)-**10** under very mild conditions (H_2/Pd/C, 25°C, 1 atm, 40 min, 91%) afforded ester (-)-**11** leaving the PMB group intact[4]. Careful reduction of (-)-**11** with diisobutylaluminum hydride in toluene at -90 °C afforded the desired aldehyde that was directly submitted to a Wittig reaction with phosphorane **12** to afford the corresponding α,β-unsaturated Weinreb amide (-)-**13** (*E:Z*/ > 95:5) in 78% overall yield for the two-step sequence[5].

The next step in the synthesis involved DDQ-mediated oxidative deprotection of *p*-methoxybenzyl ether in aqueous CH_2Cl_2 to provide the corresponding primary alcohol (-)-**14** corresponding to the C15-C21 segment, in 91% isolated yield[6]. Swern oxidation under the standard conditions afforded the intermediate aldehyde that was directly submitted to the Takai olefination reaction conditions (CHI_3, $CrCl_2$, THF) to produce a 90:10 ratio of *E* and *Z* olefin isomers in 65% yield for the two-step sequence (vinyl iodide (+)-**4**, 9 steps from ester (-)-**6**, in 34% overall yield) [7].

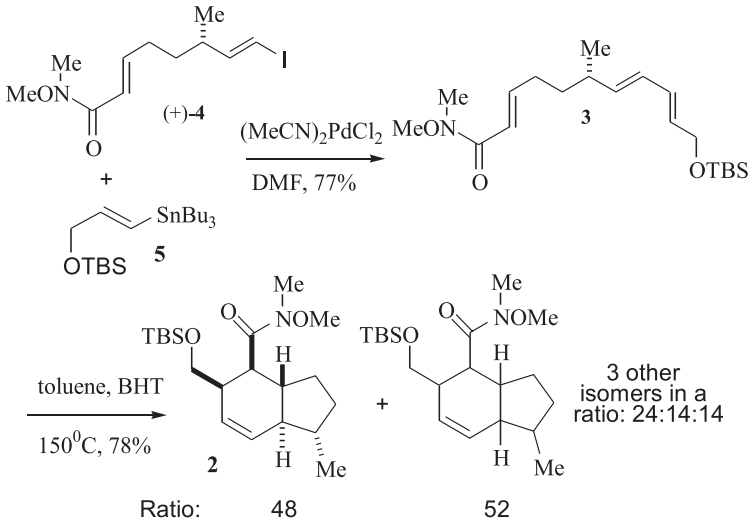
The *E*-vinylstannane **5** was smoothly prepared using a two-step protocol from commercially available propargyl alcohol **16**[8]. Protection of the primary OH-functionality in **16** as its TBS ether (TBSCl, imidazole, 97%) followed by tributylstannylation with Bu_3SnH and AIBN under reflux



Scheme 2



Scheme 3

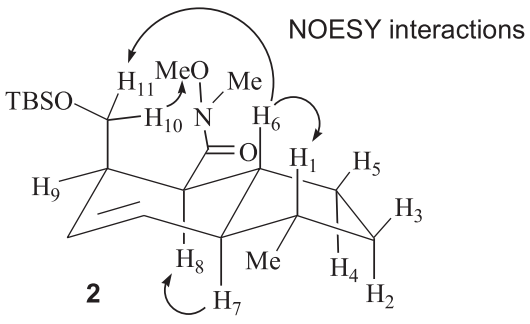


Scheme 4

in benzene afforded pure vinyl stannane **5**, corresponding to the C11-C13 segment (*E:Z*/ 92:08) in 77% yield after purification by flash chromatography.

With synthesis of the requisite C11-C13 and C14-C21 fragments in hand, their coupling was undertaken. This was done by using Stille coupling conditions in the presence of palladium dichloride *bis*-acetonitrile complex to give the desired *E,E,E* triene **3** in 77% yield (Scheme 4)[9]. With triene **3** in hand, the critical Diels-Alder reaction assembling the carbocyclic fragment of Stawamycin was attempted[10-12]. Thermal cycloaddition reaction (toluene, BHT, 150 °C) afforded the desired cycloadduct **2** as the major isomer along with three other diastereomers. The major isomer **2** was isolated together with a minor one (60% yield, 48:14 mixture) after flash chromatography. A second fraction containing a 24:14 mixture of two other Diels-Alder adducts was also isolated in 18% yield. An analytical sample of cycloadduct **2** was obtained by preparative TLC in order to determine the relative stereochemistry.

The observed relative stereochemistry of the major isomer **2** was proved by analysis of coupling constants in its ^{1}H NMR spectrum as well as by NOESY experiments. The illustrated NOESY interactions between H7/H8, H1/H6, H6/H11 and between H10/OMe together with the large vicinal coupling constant between H7 with both H6 and H1 (t, 11,0 Hz, after selective irradiation of H8) confirmed the *trans*-diaxial relationship between H7, H1 and H6 and unambiguously established the relative stereochemistry of the major isomer as being that desired for the synthesis of Stawamycin. In these stereochemical assignments, the C16 stereocenter configuration served as an important reference point.



Scheme 5

Conclusions

The synthesis required 11 steps (longest linear sequence) and produced the desired carbocyclic fragment **2** in 10% overall yield. As a result, the route to the carbocyclic fragment of Stawamycin presented here is, in principle, readily applicable to its total synthesis. Further detailed studies are still needed in order to improve the selectivity in the Diels-Alder cycloaddition step and the results will be reported in due course[13,14].

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