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Synthetic studies towards the group A streptogramin antibiotics. Synthesis of the C9–C23 fragment

Chris J. Brennan and Jean-Marc Campagne*

Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France

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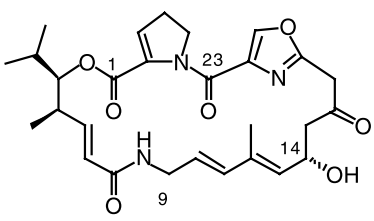
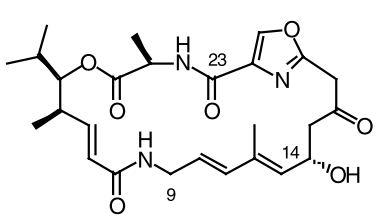
Abstract—A synthesis of the C9–C23 subunit of the group A streptogramin antibiotics is described. The synthesis incorporates a palladium-catalysed *sp–sp* coupling and a catalytic asymmetric vinylogous Mukaiyama aldol reaction to induce the stereogenic centre at C14. © 2001 Elsevier Science Ltd. All rights reserved.

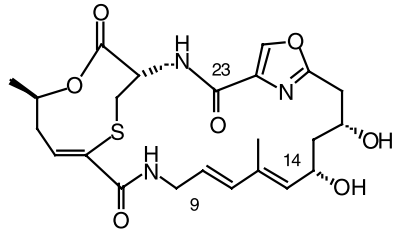
The streptogramin antibiotics are a family of natural products which have been isolated from strains of *Streptomyces* found in soil organisms. The streptogramin antibiotics can be divided into two groups; Group A and Group B. Group A consists of a series of 23-membered macrolactones each incorporating a 2,4-disubstituted oxazole, an (*E*,*E*)-dienylamine and 1,3 dioxygenation such as in virginiamycin **1**,[1,2] madumycin **2**[3] and griseoviridin **3**.[4,5] Group B[6] streptogramins antibiotics, such as etamycin, usually contain a series of amino acids in cyclic array. Group A and B streptogramin antibiotics used together exhibit a potent synergistic effect against Gram-positive bacteria and a combination of two semisynthetic group A and B streptogramin antibiotics, marketed under the name Synercid (Aventis), was recently approved by the F. D. A. for the treatment of vancomycin-resistant bacteria.[7]



1 Virginiamycin M2



2 Madumycin I



3 Griseoviridin

The structural similarities between group A natural products, specifically the C9–C23 subunit, are obvious. However, the structural differences throughout the rest of the macrocycle are also apparent, for example, the unusual tetrahydro-[1,5]-oxathionin-2-one core of griseoviridin **3**, the first total synthesis of which has only recently been described by Meyers.[4] Herein we report our investigations towards the synthesis of the C9–C23 subunit of the group A streptogramin antibiotics. In connection with ongoing projects[8] towards the development and application of vinylogous Mukaiyama-aldol reactions,[9] our approach was to exploit the vinylogous aldol reactions in the construction of C9–C23 compound **E** (Scheme 1).

We initially planned to elaborate aldehyde **C** by utilising a racemic vinylogous reaction between aldehyde **A** and silyl dienolate **B**, followed by dehydration of the resulting alcohol (Scheme 1). Submitting aldehyde **C** to a second catalytic asymmetric vinylogous aldol reaction would ultimately lead to alcohol **D**. However, despite exhaustive approaches,[10] we were unable to persuade the initial aldol reaction. Thus, we turned our attention to a Trost yne–yne palladium-catalysed coupling[11] between *N*-Boc propargylamine and methyl 2-butynoate. Using $Pd(OAc)_2$ and triphenylphosphine as the catalytic system in THF at room temperature, the yne–eneoate compound **4** was isolated in 83% yield (Scheme 2). After an in-depth investigation, we found it

* Corresponding author. E-mail: jean-marc.campagne@icsn.cnrs-gif.fr

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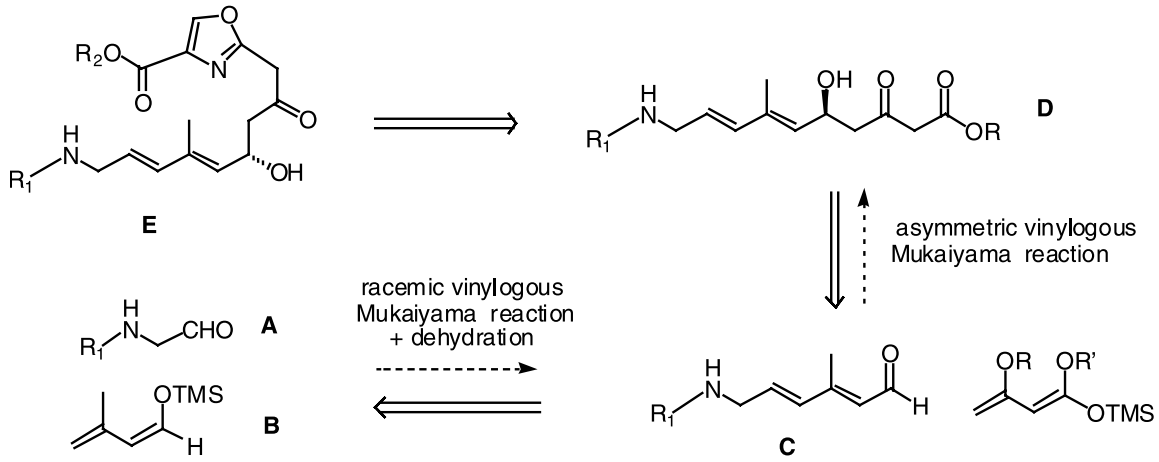
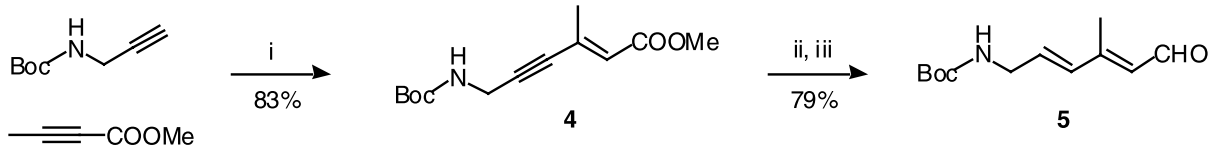


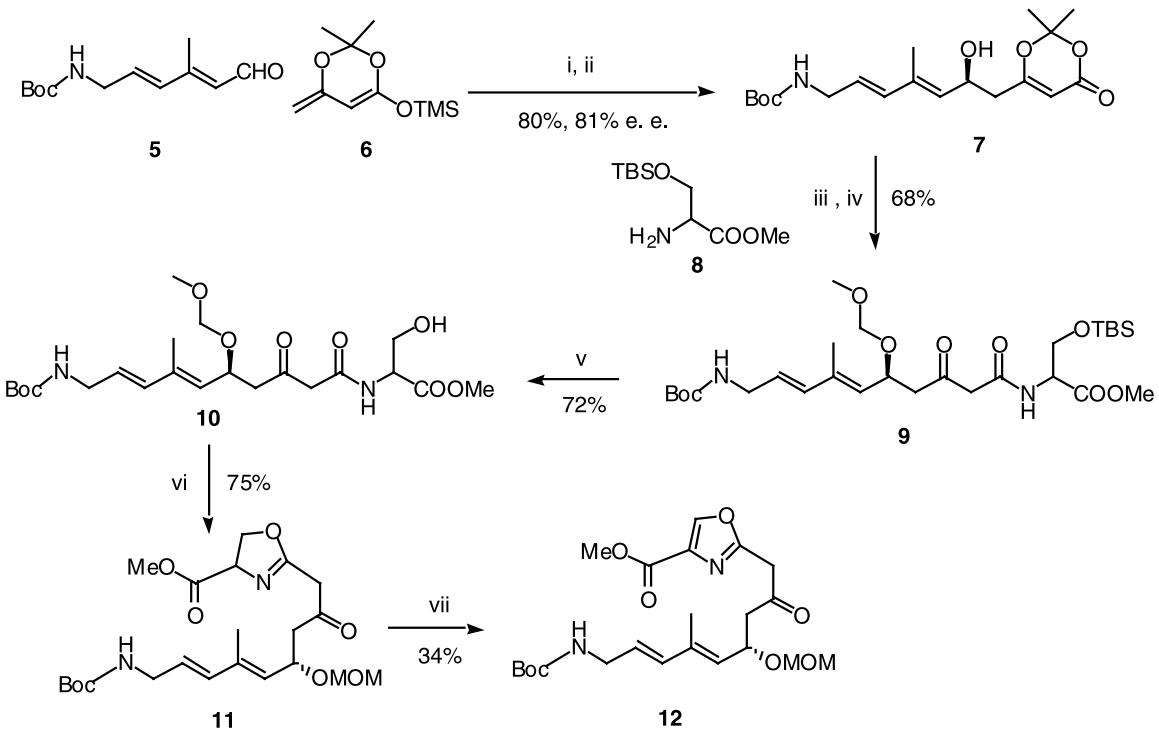
Scheme 1.



Scheme 2. *Reagents and conditions*: (i) $Pd(OAc)_2$, PPh_3, THF, rt, 24 h; (ii) $LiAlH_4$, THF 0°C to rt, 22 h; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C, rt, 2 h.

was possible to reduce both the alkyne and the methyl ester in one step. Thus, dropwise addition of 1 M solution of $LiAlH_4$ in THF over 30 min to the yne–enoate **4** at 0°C and stirring at room temperature for 24 hours gave the desired (*E,E*) alcohol in 86% yield. Subsequent treatment of the alcohol to the Swern oxidation conditions gave the previously described[2a] aldehyde **5** in 92% yield.

With the key aldehyde **5** in hand, we attempted the asymmetric aceto-acetate vinylogous Mukaiyama-aldol reaction.[12] Hence, treatment of aldehyde **5** in the pres-



Scheme 3. *Reagents and conditions*: (i) CuF(*R*)-tolBinap, THF, −78°C, 8 h; (ii) PPTS, MeOH, rt, 6 h; (iii) MOM-Cl, CH_2Cl_2, 0°C to rt, 48 h; (iv) H-Ser(OTBS)-OMe **8**, toluene, 110°C, 1 h; (v) HF–pyridine, THF, 0°C to rt, 4 h; (vi) DAST, K_2CO_3, DCM, −78°C; (vii) NiO_2, PhH, 8 h.

ence of dienolate **6**[13] and 10% of the precatalyst CuF.(*R*)-tolBinap, under the conditions developed by Carreira,[12e,f] and sequential deprotection of the TMS group with PPTS in methanol, provided the alcohol **7** in a gratifying 80% yield and 81% e.e. (Scheme 3).[14] Further protection of the alcohol as a MOM ether and subsequent opening of the dioxinone ring in the presence of H-Ser(OTBS)-OMe **8** afforded the corresponding amide **9** in 68% yield. At this stage, we anticipated that the deprotection of the TBS group and the subsequent oxazole formation in the presence of the unprotected ketone at C16 could be problematic. Nevertheless, the successful deprotection of the TBS–ether using HF–pyridine under standard conditions followed by a DAST[15]-promoted cyclodehydratation of the resulting amido-alcohol **10** provided the oxazoline **11** in a respectable 75% yield. The final step of our synthesis proved to be rather difficult and adopting the standard procedures[15–17] for this type of oxidation lead only to a plethora of by-products of which the elimination of the OMOM moiety appeared to be a dominant event. The oxidation was finally effected using nickel peroxide[18] to give the oxazole **12** albeit in an unoptimised yield of 34% (Scheme 3).

In conclusion, we have developed a straightforward access (nine steps) to the C9–C23 subunit of the group A streptogramin antibiotics incorporating a Trost palladium-catalysed yne–yne coupling and a Carreira catalytic asymmetric vinylogous aldol reaction. Further optimisation and the complete construction of some streptogramin antibiotics are currently underway.

Acknowledgements

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