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Convergent stereospecific synthesis of LL-Z1640-2 (or C292), hypothemycin and related macrolides. Part 2

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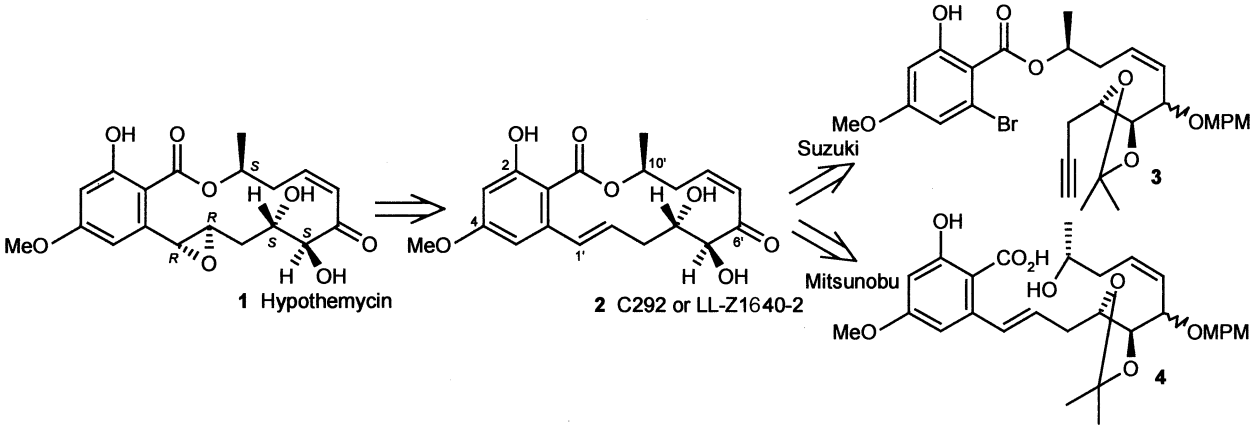
Abstract—The total synthesis of C292 (or LL-Z1640-2) and hypothemycin has been achieved. The 14-membered ring formation was achieved either via an intramolecular Suzuki coupling or much more efficiently via a Mitsunobu macrolactonisation. Reaction conditions were found to preserve the *Z* enone; selective epoxidation of C292 afforded hypothemycin.

We herein report the completion of a total synthesis of hypothemycin **1** and C292 (or LL-Z1640-2) **2**.[1] In the preceding communication,[2] we described the stereospecific convergent synthesis of the precursors **3** and **4** which are required for achieving the formation of the 14-membered ring, either via an intramolecular Suzuki coupling or via a Mitsunobu macrolactonisation (Scheme 1). Another total synthesis of **2**, starting from D-ribose, has been disclosed in 2001 by Tatsuta and coworkers.[3] In our work, it is worth pointing out that all the synthesis described here has been achieved with the 60/40 mixture of the two diastereoisomers, epimeric at C-6′, starting either from **3** or from **4**. We were confident in that strategy, due to our previous work showing that the synthesis of radicicol could be completed with the two epimers at C-6′ in quite comparable yields throughout all the steps of the sequence.[4] Noteworthy in the present work, unless otherwise specified, we observed no significant variation (i.e. less than 5%) of the 60/40 ratio of the two diastereoisomers, epimeric at C-6′, in the reactions described further.

1. Intramolecular Suzuki couplings (Scheme 2)

In a previous synthesis of (*S*)-zearalenone, Hegedus and coworkers could achieve the intramolecular coupling of an aryliodide and a vinylstannane, in 30–54%



Scheme 1.

Keywords: macrolides; antitumour compounds; coupling reactions; boron and compounds; Suzuki reactions; Mitsunobu reactions.

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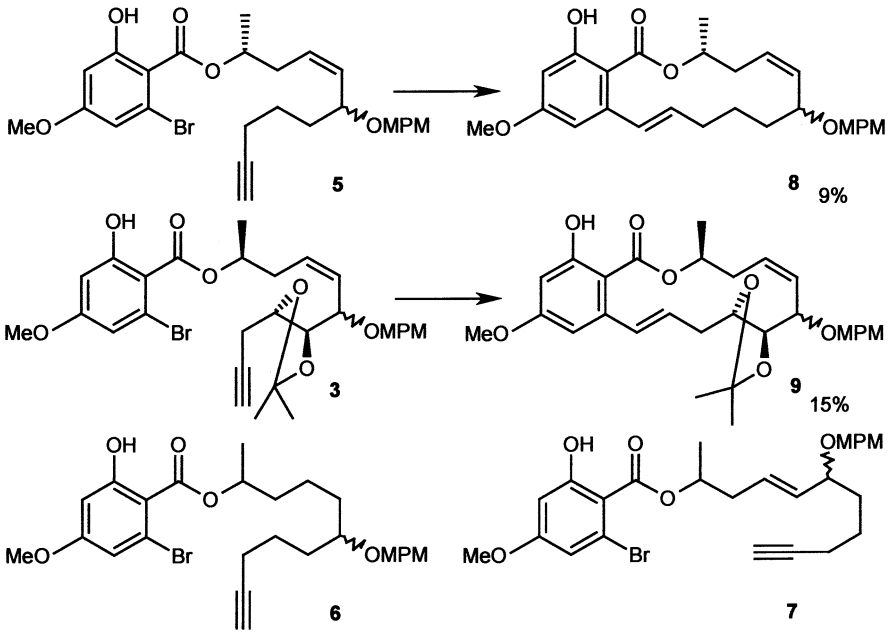
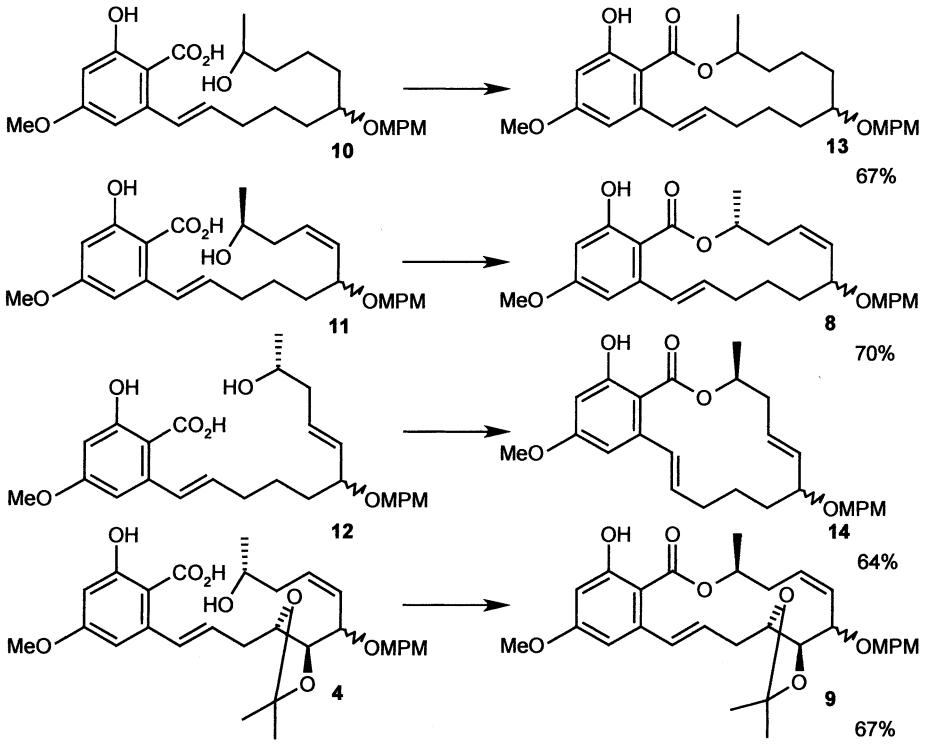


Scheme 2. *Reagents and conditions*: Sia_2BH (3.9 equiv.), THF, −20°C→rt, 2 h, then addition of acetone (3 equiv.) and afterwards 2 M aq. K_3PO_4 (2 equiv.) at −10°C→rt, further addition of that mixture via cannula to a solution of 4 mol% [$Pd(OAc)_2$+4TFP] in DME, i.e. substrate 0.034 M in DME/H_2O (~30/1), reflux, 6 h.

yield depending on the conditions, thus showing for the first time that the 14-membered macrolide could be formed via a palladamacrocycle.[5] We first examined the intramolecular Suzuki couplings of vinyldisiamylboranes, generated in situ, derived from the alkyne **3** and related compounds **5**–**7**. Hydroboration conditions were determined on the model compound **5**, by following the disappearance of the starting material by TLC and further protonolysis (AcOH, 70°C) to yield the corresponding terminal olefin in a quantitative yield, and were thus optimised when using 3.9 equiv. Sia_2BH (THF, −20°C). Preliminary studies for the coupling were done in the case of **5** and showed that they were at best achieved with no protection of the phenol, like in the parent previous intermolecular couplings (such as the one affording **4**) and model studies.[1,2] Best results were obtained when, after hydroboration completion, excess Sia_2BH was destroyed in situ by addition of anhydrous acetone (3 equiv.) before achieving the Suzuki coupling. Thus, in the conditions described in Scheme 2, the desired macrolides **8** and **9** were isolated in only 9% and 15% yields, respectively. Noteworthy, the same reaction conditions applied to **6** and **7** gave no trace of the corresponding 14-membered macrolides, although these should be energetically more favoured by less ring strain and steric interactions than in **8** and **9**. All those couplings showed quite complex reactions and only some by-products could be characterized. One major difficulty here was to get a good turn-over of the catalyst, at the minimal dilution (0.03–0.04 M) required for minimising intermolecular reactions and kinetically compatible with the time scale required for finding the conformations allowing the formation of the palladamacrocycle. Quite significantly, the most flexible substrates **6** and **7** having a *trans*-7′,8′ double bond gave no cyclisation at all, moreover **7** affording alone a significant amount of the product of homocoupling of the derived vinyldisiamylborane (6%). In all the reactions, even in the described conditions, we isolated the terminal olefin corresponding to the reduction of the alkyne in **3** (~3%), **5** (10%), **5**-OTBS (12%), and **7** (8%). It is worth pointing out that, for the macrolides **8** and **9**, the ratio of the C-6′ epimers was still 60/40, thus showing that the relative configuration of this centre had no effect in these cyclisations.

2. Macrolactonisation via Mitsunobu reaction (Scheme 3)

All the macrolactonisations were achieved in toluene, at rt, at a concentration of the precursor of 0.007–0.01 M, affording the desired macrolides in quite comparable yields (64–70%), and quite remarkably whatever the privileged conformation, ring strain or steric interactions in the final macrolide, thus showing that these macrolactonisations do not have a late transition state. Here again, it is also worth pointing out that there was no incidence of the configuration at C-6′ (60/40 ratio) and that no significant amount of diolide was formed in those reactions which were not run in high dilution conditions, as we already observed in our previous work concerning radicicol.[4,6] The complete inversion of configuration at C-10′ was shown with no ambiguity by the transformation of **4** (10′*R*) into **9** (10′*S*), which was further converted into hypothemycin (by the comparison with the published data); it was also clearly demonstrated for the conversion of **11** (10′*S*) into **8** (10′*R*) which could be compared with the product of the intramolecular Suzuki coupling (Scheme 2) by ^1H NMR.



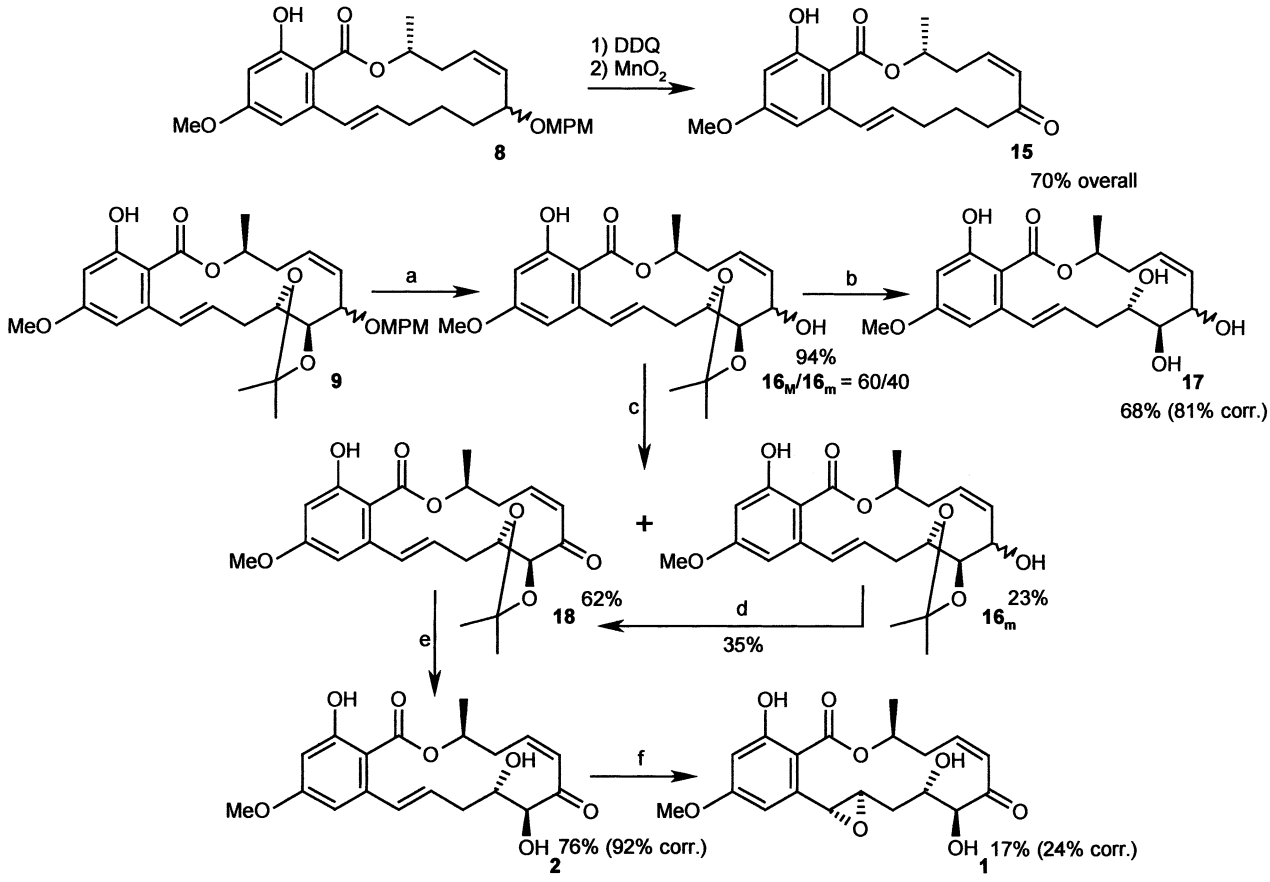
Scheme 3. *Reagents and conditions*: hydroxy-acid 0.007 M in anhydr. toluene, PPh_3 (2 equiv.), DEAD (2 equiv.), rt, 15 min.

3. Conversion of macrolide 9 into C292 (LL-Z1640-2) and hypothemycin (Schemes 4 and 5)

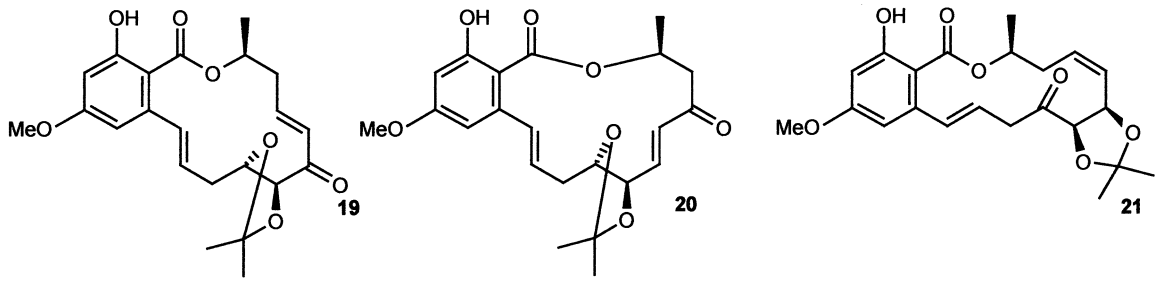
In a preliminary study, the $Z_{7',8'}$-enone **15** could be isolated in 70% overall yield from **8**, after cleavage of the MPM ether by DDQ[7] in buffered conditions (pH 7) and further oxidation of the mixture of allylic alcohols ($C_{6'}$-epimers ~60/40) by active MnO_2. No difference of reactivity of the $C_{6'}$-epimers and no isomerisation of the enone were observed in that sequence. The 6′-OMPM ether of **9** was deprotected by DDQ in buffered conditions to afford the alcohols $\mathbf{16_M}$ and $\mathbf{16_m}$ (60/40 ratio, not separable by chromatography) in 94% yield. However, in contrast with the easy and univoque formation of **15**, the mixture of the two 6′-OH epimers $\mathbf{16_M}$ and $\mathbf{16_m}$ could not be oxidised into the enone either with a large excess of active MnO_2 (commercial sources, Attenburrow, Sondheimer, Fatiadi)[8] or by DDQ[9] (1–5 equiv., toluene, 60°C, 48 h) and only starting material was recovered. With DDQ, higher temperatures led to complex mixtures. In order to change the conformation of the macrolide and modify steric interactions, the triol **17** was prepared but also gave complex mixtures with active MnO_2 at rt. On the other hand, reaction of the mixture of 6′-OH epimers **16** with PCC in the presence of 2,5-dimethylpyrazole[10] showed now a clear difference of reactivity between the two diastereoisomers, for the first time at this level of the sequence: the major epimer $\mathbf{16_M}$ was converted quantitatively into the desired *Z*-enone **18**, isolated in 62% yield in the specified conditions, while the minor one $\mathbf{16_m}$ was recovered unchanged, pure after chromatography (23%). The pure minor diastereoisomer $\mathbf{16_m}$, thus obtained, reacted very slowly in the same Parish conditions[10] and, after 24 h, afforded only the $E_{7',8'}$-enone **19** in 50% yield and recovered $\mathbf{16_m}$. However, quite fortunately, fast Jones oxidation of $\mathbf{16_m}$ (acetone, 0°C, 10 min) gave the desired *Z*-enone **18** (35%) and quite surprisingly the transposed enone **20** (Dauben-like rearrangement,[11] but here unusually on a secondary alcohol) (Scheme 5). Thus, with this procedure applied to a millimolar scale of **16** (60/40 mixture), we isolated the desired *Z*-enone in 74% yield, the rearranged enone **20** (10%) and still recovered $\mathbf{16_m}$ (7%).

Noteworthy, oxidation of the triol **17** with PCC/2,5-dimethylpyrazole was unsatisfactory and gave complex mixtures. It is worth also mentioning that Swern oxidation of $\mathbf{16_M}$ (DMSO 2.2 equiv./oxalyl chloride 1.1 equiv./*i*-Pr_2NEt 5 equiv., CH_2Cl_2, −78°C to rt, and pH 7 work-up) afforded the desired *Z*-enone **18** in only 30% yield and recovered $\mathbf{16_M}$ (58%) after chromatography; Swern oxidation of $\mathbf{16_m}$, in the same conditions, unexpectedly gave **21** in 50% yield (Scheme 5) and unreacted $\mathbf{16_m}$ (50%).

Acetonide cleavage of **18** could be achieved in carefully established conditions (0.5 equiv. pTsOH, CH_2Cl_2/MeOH 1/1, rt, 3 h 30 min) to afford **2** (C292[12] or LL-Z1640-2[13]) in 76% yield and 20% of recovered **18** after chromatography. These conditions gave us the best compromise in order to avoid the isomerisation into the $E_{7',8'}$-enone and also the 4′-OH intramolecular 1,4-addition on the enone (adduct stereochemistry not determined) which occur competitively on longer reaction times. Selective epoxidation of **2** was quite difficult, due to an unusually unreactive 1′,2′-double bond and lability of the products, and was at best achieved in buffered conditions (MCPBA/$NaHCO_3$ (3 equiv.), CH_2Cl_2, −20 to 0°C, 4 h) to afford hypothemycin **1** and



Scheme 4. *Reagents and conditions*: (a) DDQ (1 equiv.), CH_2Cl_2/pH 7 buffer (9/1) rt, 30 min; (b) *p*TsOH (0.2 equiv.), MeOH, rt, 4 h; (c) PCC (3 equiv.), 2,5-DMP (10 equiv.), CH_2Cl_2, 0°C, 6 h; (d) Jones' reagent, acetone, 0°C, 10 min; (e) *p*TsOH (0.5 equiv.), CH_2Cl_2/MeOH (1/1), rt, 3 h 30 min; (f) MCPBA/$NaHCO_3$ (3 equiv.), −20°C→0°C, 4 h, then pH 7 work-up.



Scheme 5.

unreacted **2** in, respectively, 17 and 30% yield after chromatography and no other epoxide was isolated. Noteworthy, dimethyldioxirane (acetone, −20°C), or Mn(TPP)Cl in the presence of imidazole with 30% H_2O_2 ($MeCN/CH_2Cl_2$, rt), which were successful in model studies led only to complex mixtures with **2**.[1] The epoxide thus obtained with MCPBA was unambiguously identified with hypothemycin by comparison of all the data (particularly by comparison of their ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra in $CDCl_3$ with those of the natural product.[14]

The synthesis described herein and in the accompanying note is stereospecific, convergent and highly flexible, allowing modification of the aromatic part. Our syntheses give an access to a whole group of resorcylic macrolides, related either to zearalenone in the present work or to radicicol[4,6], which are very important tools for the study of signal transduction.[15] Recently, hypothemycin has also been shown to be a highly selective inhibitor of some MEK or MAPK kinases,[15] and to be a new lead as an inhibitor of T cell activation with a novel mode of action and a unique modulatory activity on cytokine production.[16]

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