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Convergent stereospecific synthesis of C292 (or LL-Z1640-2), and hypothemycin. Part 1

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Abstract—The stereospecific synthesis of the precursors required for the 14-membered ring formation either via an intramolecular Suzuki coupling or via an intermolecular Suzuki coupling followed by a macrolactonisation is herein reported. One-pot Suzuki couplings were here achieved with vinyldisiamylboranes which were generated in situ from the related chiral precursor. The present convergent approach of C292 (or LL-Z1640-2) and hypothemycin gives a flexible access to related macrolides.

Due to our interest in radicicol **1**,[1,2] we were quite intrigued by a Sandoz patent[3] which appeared in 1994 concerning the biological properties of the macrolide 87-250904-F1 **2** and later on, in 1996, by patents on LL-Z1640-2 (Takeda)[4] or C292 (Cor Therapeutics)[5] **3**. Those patents showed that these molecules were inhibitors of the release of some cytokines (IL-1β, IL-1α, IL-6, TNFα) and thus had properties which appeared quite similar to those of radicicol. The mechanism of action of all these molecules was then unknown. Moreover, identity of LL-Z1640-2 (first discovered at Lederle Laboratories[6]) and C292 was not discussed. Quite remarkably, C292 was shown to be a specific inhibitor of PTK, not inhibiting PKA or PKC, and moreover a highly selective inhibitor among some tyrosine kinases (receptor or non receptor).[5] Since 1992, radicicol was known to be a specific inhibitor of some tyrosine kinases such as $p60^{v\text{-}src}$.[7] Later on, radicicol[8] and 87-250904-F1[9] were also shown to be specific inhibitors of the expression of COX-2 (not of COX-1) and of some cytokines (via an accelerated degradation of their mRNA). Indeed, these apparent similarities were puzzling since radicicol and the other macrolides differed by the chiral center at 10′ and by the functionalities, these compounds being necessarily in quite different conformations. On the other hand, the structure of hypothemycin had just been corrected in 1993 by an X-ray structure[10] and appeared thus to be the epoxide of **3**. Therefore we were interested in achieving a flexible convergent stereospecific synthesis of these resorcylic macrolides which appeared then to be important tools for biochemistry, especially for the study of signal transduction, and could be considered as new leads.

The total synthesis of LL-Z1640-2 **3** from D-ribose has been reported in 2001 by Tatsuta and co-workers.[11] We wish now to disclose our stereospecific convergent synthesis.[12] Macrolides **2**–**4** are related to zearalenone which is produced very efficiently industrially by fermentation. Therefore, in a preliminary work, we first studied a hemisynthesis of **3** starting from zearalenone, but were unable to obtain the required intermediates.[12] Concerning the synthesis of **2**–**4**, one difficult problem is to preserve the *Z* enone in the intermediates and the final macrolide, due to previous results showing that these 14-membered macrolides having the $Z_{7',8'}$ keto-6′ enone are highly disfavoured energetically and give the corresponding $E_{7',8'}$ enone as the only product under basic or acidic conditions.[3,5,12] According to our preliminary work on epoxidation of zearalenone derivatives, we chose to introduce the highly sensitive 1′,2′-epoxide in the last steps, even if we were aware that the $E_{1',2'}$ double bond was unexpectedly unreactive towards many epoxidation reagents,[12] as already pointed out in the early work of the Merck group on zearalenone derivatives.[13] However, based on the X-ray structure of hypothemycin **4**, we expected the highly stereoselective formation of the desired epoxide for steric reasons, assuming that the precursor might have such an analogous conformation.

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

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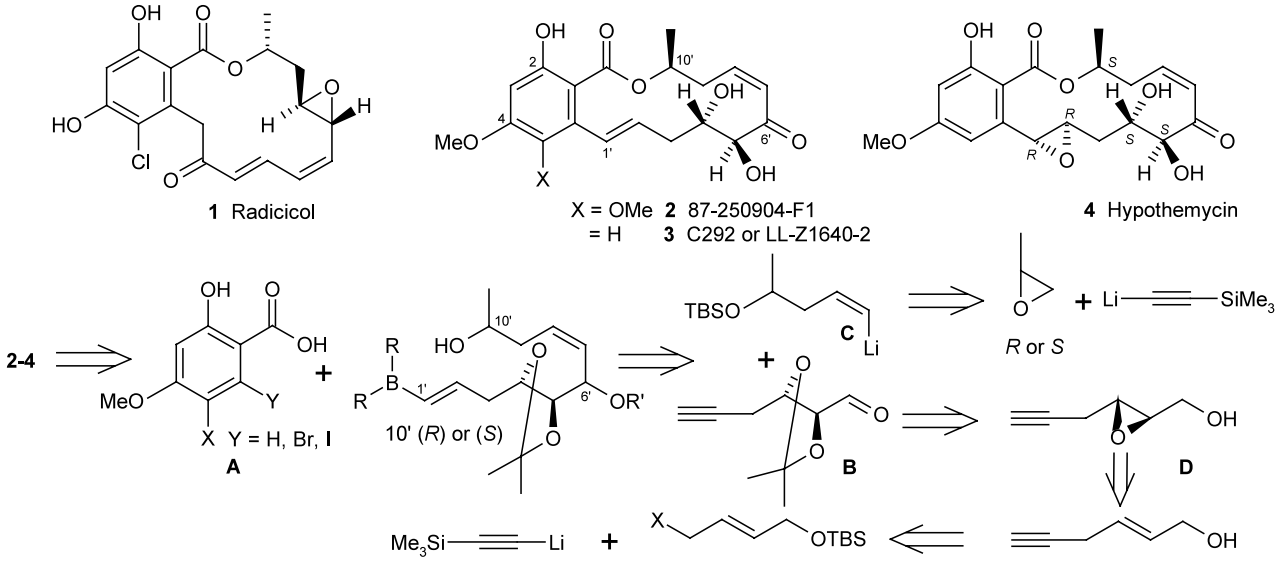
Our synthesis is based on the retrosynthetic analysis described in Scheme 1, which leads to three subunits: the aromatic part **A**, the C_1–$C_{6'}$ and $C_{7'}$–$C_{10'}$ enantiopure subunits **B** and **C**. This approach is quite flexible and allows examination of the formation of the 14-membered macrocycle either via an intramolecular Suzuki coupling or via a macrolactonisation (via an acyl activation or a Mitsunobu reaction). Hence, the enantiopure subunits **B** and **C** derive from easily available starting materials. We decided to generate the required 4′,5′-diol by the regio- and stereospecific opening of the epoxide by a carbamate derived from **D** in the presence of $BF_3{\cdot}Et_2O$:[14] this route has also some flexibility since the same carbamate can also set up an amino alcohol[15] in a regio- and stereospecific reaction under different conditions, and moreover, an epoxy alcohol such as **D** can generally be obtained in high yield and enantiomeric purity by a Sharpless asymmetric epoxidation of a *trans*-disubstituted allylic alcohol. We preferred such a route to a Sharpless asymmetric dihydroxylation of a *Z* disubstituted olefin.

1. Synthesis of the aromatic part (Scheme 2)

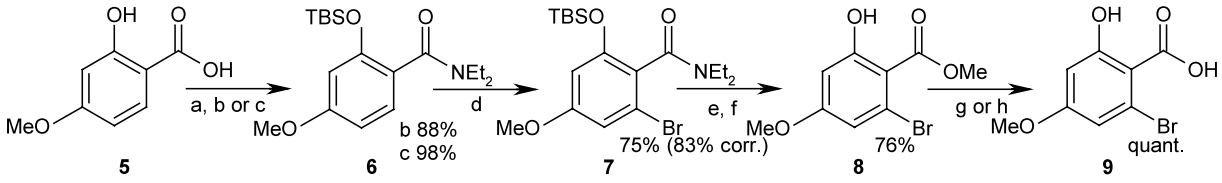
The methyl ester **8** was obtained in 48% overall yield from 4-methoxysalicylic acid **5**. It is worth pointing out that the OTBS protective group here allows avoidance of *o*-metalation at position 3 of **6** by its steric effect. The 2-OTBS group also allows conversion of the amide **7** into the methyl ester **8** in good yield, this is probably because the preliminary easy cleavage of the phenol OTBS group leads to a conformation of the intermediate imidate salt favouring the desired cleavage of the tetrahedral intermediate; when the same phenol was protected as a methyl ether, the initial amide was the only product after hydrolysis of the corresponding imidate salt. The acid **9** was finally obtained in a quasi-quantitative yield, under conditions avoiding the decarboxylation which occurs at higher temperatures or with longer heating, or also very easily at the reacidification when the *o*-phenol is deprotected.[16]

2. Enantiopure $C_{7'}$–$C_{10'}$ subunit synthesis (Scheme 3)

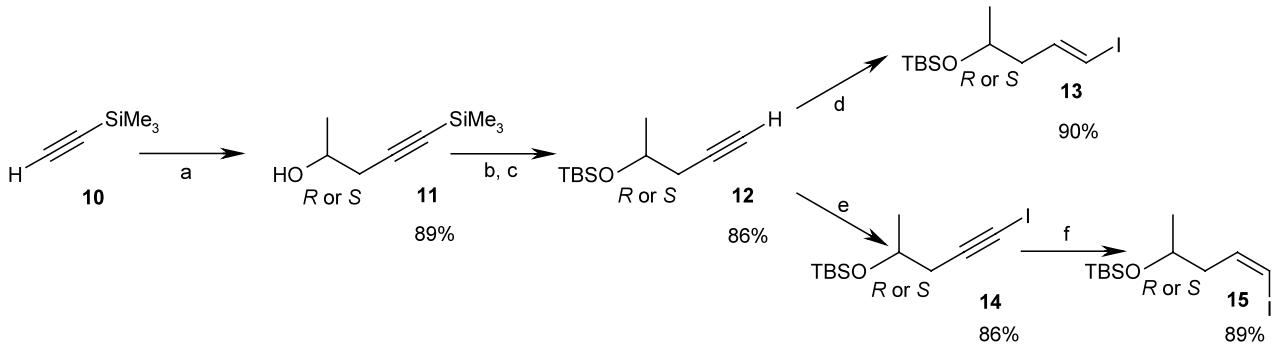
The alkyne **11** was obtained via the opening of enantiopure (*R*) or (*S*) propylene oxide by the lithio derivative of **10** at −78°C, in the presence of $BF_3{\cdot}Et_2O$, under stoichiometric conditions. Further protection of the alcohol as a TBS ether and specific deprotection of the TMS-alkyne under mild conditions gave **12** in 76% overall yield (three steps). The enantiopure, (*R*) or (*S*), *E* and *Z* vinyl iodides **13** and **15** were obtained from **12**,



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) TBSCl (2.5 equiv.), iPr$_2$NEt (3.6 equiv.), DMF, rt, 2 h; (b) oxalyl chloride (1.1 equiv.), DMF cat., CH_2Cl_2, −10°C→rt, overnight, then Et_2NH (2.0 equiv.), 1 h, rt; (c) Et_2NAlMe_2 from Me_3Al (4 equiv.) and Et_2NH (4 equiv.), toluene, −6°C→rt, 45 min, then bis-OTBS from **5**, reflux, overnight; (d) tBuLi/pentane (1.08 equiv.), Et_2O, −78°C, 10 min, then Br_2 (1.06 equiv.); (e) Me_3O^+, BF_4^- (1.3 equiv.), CH_2Cl_2, rt, overnight, then evaporation; (f) aq. satd Na_2CO_3/MeOH (1/1), rt, 6 h; (g) conc. NaOH/DME (1/1), reflux, overnight; (h) TMSOK (2 equiv.), DME, reflux, overnight.



Scheme 3. *Reagents and conditions*: (a) **10** (1.05 equiv.), Et_2O, −78°C, *n*BuLi (1.05 equiv.), 30 min, then (*R*) or (*S*) propylene oxide (1.0 equiv.), and further addition of $BF_3{\cdot}Et_2O$ (1.0 equiv.) in 50 min, −78°C; (b) TBSCl/imidazole/DMF, rt; (c) K_2CO_3 (1.1 equiv.)/MeOH, rt, 5 h; (d) Cp_2ZrCl_2 (2 equiv.), $LiBHEt_3$ (2 equiv.), THF, rt, then **12**, rt, 15 min and I_2 (1.1 equiv.) in THF; (e) *n*BuLi (1.1 equiv.), THF/hexane, −78°C, 15 min, then I_2 (1.1 equiv.) in THF; (f) Sia_2BH (2 equiv.), THF, −20→0°C, 3 h and then AcOH, 65°C, 3 h.

respectively, by hydrozirconation with Schwartz' reagent[17a] (generated in situ under Lipshutz conditions[17b]), or by hydroboration of the derived iodoalkyne **14** with Sia_2BH and further protonolysis by acetic acid.[18]

3. Enantiopure $C_{1'}$–$C_{6'}$ subunit synthesis (Scheme 4)

Compound **20** was obtained in 34% overall yield from 2-butyne-1,4-diol **16** (six steps). The highly selective deprotection of the TBS ether of **19** was best achieved with DDQ (5 mol%) in CH_3CN/H_2O (9/1)[19] at rt, thus affording **20** in 74% yield and reisolated **19** (17%) after chromatography; other deprotection conditions (AcOH/THF/H_2O/rt or TBAF/AcOH/THF/rt) led to competitive deprotection of the TMS-alkyne. Sharpless asymmetric epoxidation of **20** with (+)-DET gave the epoxyalcohol **21** in 85% yield and high enantiomeric excess since no trace of the other enantiomer could be detected by careful ^1H NMR analysis (300 MHz) of the corresponding (+)- and (−)-MTPA esters.[20] The carbamate assisted epoxide opening of **22**, in the presence of $BF_3{\cdot}Et_2O$,[14] was regio- and stereospecific to afford **23** in 91% yield. Simultaneous hydrolysis of the carbonate and TMS deprotection of the alkyne was achieved under mild conditions (MeONa/MeOH, rt) and the triol **24** was isolated in 93% yield after purification over a Dowex-H^+ column. Specific protection of the primary alcohol and further acetonide formation gave **25** (73% overall). The terminal alkyne had to be reprotected as a TMS derivative in order to avoid proton abstraction in the presence of the more basic vinyllithio reagent to be used for the condensation with the $C_{1'}$–$C_{6'}$ aldehyde.

The highly selective deprotection of the TBS ether was again best achieved with DDQ (8 mol%) in CH_3CN/H_2O (9/1), at rt, in order to minimize the cleavage of the acetonide and that of the TMS–alkyne, and thus afford **26** (73%) and recovered TMS–alkyne derivative of **25** (15%) after chromatography. Swern oxidation of **26** gave the pure aldehyde **27** in quantitative yield after chromatography.

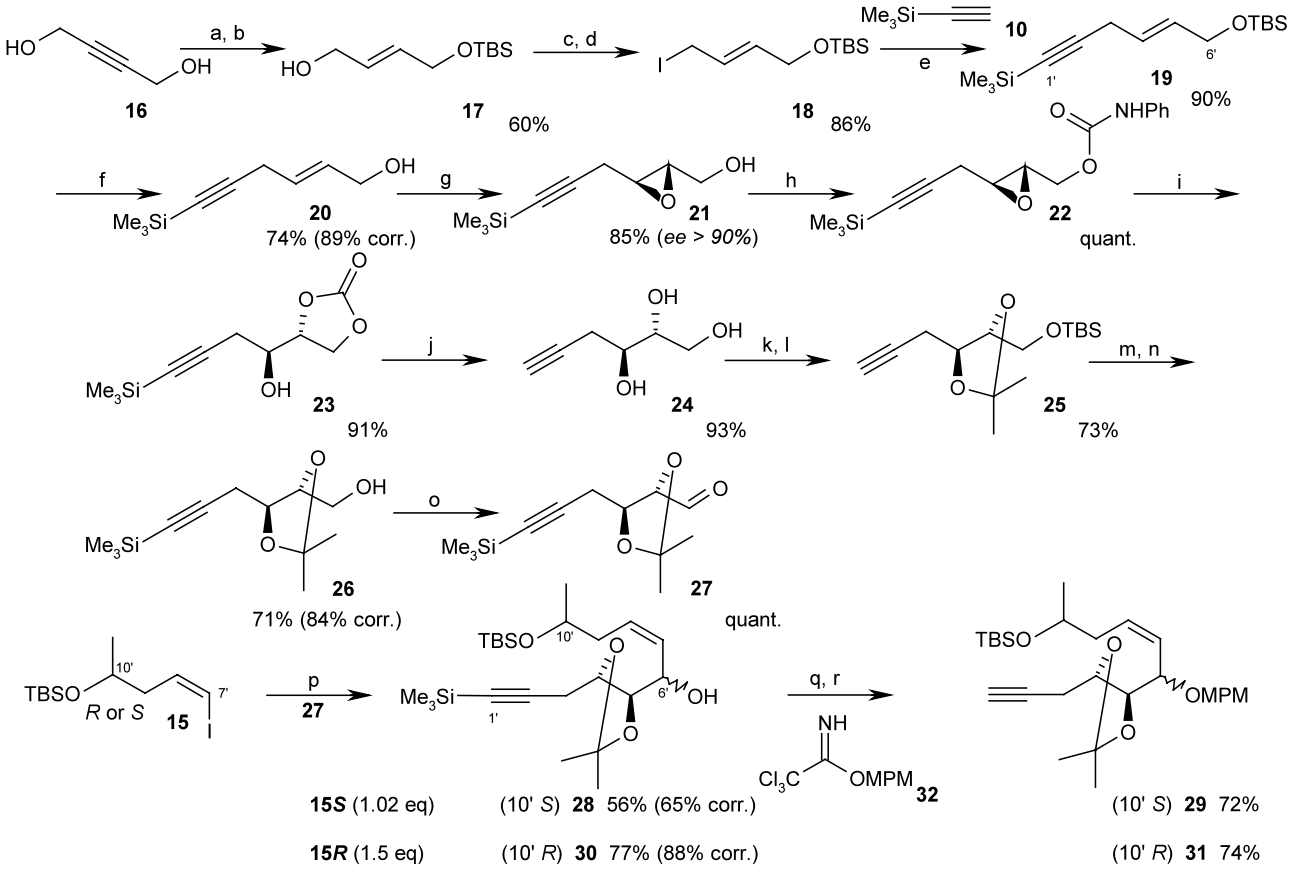
4. $C_{1'}$–$C_{10'}$ fragment (Scheme 4)

The condensation of the two enantiopure fragments was optimized with 1.5 equiv. of **15** to afford a 60/40 mixture of the two diastereoisomers **28** (10′*S*) or **30** (10′*R*), epimeric at 6′, in 77% yield and recovered unreacted aldehyde **27** (13%) after chromatography. After deprotection of the TMS–alkyne, the 6′-OH was protected as an OMPM ether by reaction of the mixture of the two diastereoisomers with the trichloroacetimidate **32** and triflic acid catalysis[21] to afford a 60/40 mixture of the corresponding 6′-OMPM ethers. At this level, we decided to complete the synthesis with this 60/40 mixture of 6′ epimers, since the two diastereoisomers were not easily separable either as 6′-OH (**28** or **30**) or as 6′-OMPM (**29** or **31**); we were also confident in that strategy, due to our previous work in which the synthesis of radicicol could be completed with the two epimers at 6′ in comparable yields throughout all the steps of the sequence.[2]

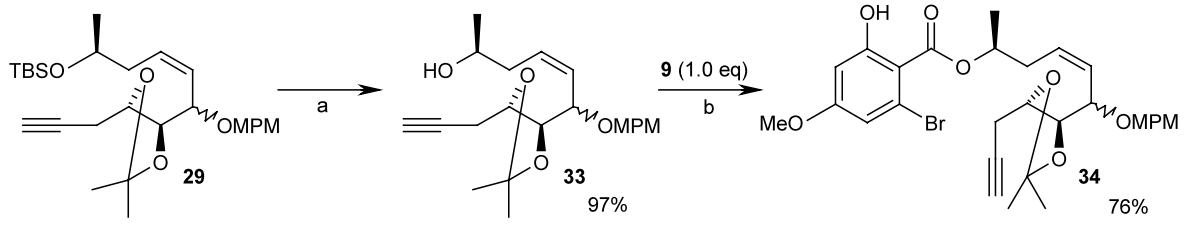
5. Macrocyclisation precursors (Schemes 5 and 6)

The precursor **34** (10′*S*) required for an intramolecular Suzuki coupling was obtained in 74% overall yield from **29**. The ester was prepared under stoichiometric conditions via an acyl activation (DCC/DMAP, rt) of the acid **9** (1 equiv.) (Scheme 5). The other precursor **36** (10′*R*) required for a macrolactonisation via a Mitsunobu reaction was obtained in 47% overall yield from **31**, via an intermolecular Suzuki coupling of the vinyldisiamylborane prepared in situ[2] (Scheme 6). This coupling was optimized with **8** (1.2 equiv.), and results were less satisfactory with the corresponding 2-phenol TBS or methyl ethers. The best results were obtained under the conditions described in Scheme 6, with tri-2-furylphosphine.[12] Cleavage of the methyl ester of **35** here was quite difficult, but nevertheless afforded the acid **36** under optimized conditions in 65–70% yield.

The completion of our synthesis of C292 (or LL-Z1640-2) and hypothemycin is described in the accompanying note.[22]



Scheme 4. *Reagents and conditions*: (a) Red-Al^{R} (1.5 equiv.)/toluene, THF, 0°C→rt, overnight, 81%; (b) NaH (1.03 equiv.), THF, rt, 1 h, then −78°C, TBSCl (1.03 equiv.), 36 h, 74%; (c) MsCl (1.1 equiv.), NEt_3 (1.1 equiv.), CH_2Cl_2, −10°C→rt, 30 min; (d) NaI (1.5 equiv.), acetone, rt, 1 h; (e) **10** (1.5 equiv.), THF, *n*BuLi (1.5 equiv.), −78°C, 30 min, then **18** and HMPA (THF/HMPA = 10/1), rt, 4 h; (f) DDQ (5 mol%), MeCN/H_2O (9/1), rt, 2 h; (g) Ti(O*i*Pr)$_4$ (1 equiv.), (+)-DET (1.24 equiv.), anhydr. CH_2Cl_2, *t*BuOOH (~3 M in isooctane) (2.1 equiv.), −25°C, overnight; (h) PhNCO (2.5 equiv.), CH_2Cl_2/pyridine, rt, 1 h; (i) $BF_3{\cdot}Et_2O$ (1.1 equiv.), Et_2O, −20°C, 2 h, then 1N H_2SO_4, rt, overnight; (j) MeONa (0.35 equiv.), MeOH, rt, 8 h, then Dowex 50 WX8 column eluted by MeOH; (k) TBSCl (1.05 equiv.), imidazole (1.05 equiv.), DMF, rt, 1 h; (l) 2-methoxypropene (2 equiv.), TsOH cat., CH_2Cl_2, rt, 1 h; (m) *n*BuLi/hexane (1.1 equiv.), Et_2O, −30°C, 30 min, then TMSCl (1.1 equiv.), −30→−10°C, 98%; (n) DDQ (8 mol%), MeCN/H_2O (9/1), rt, 2 h, 73%; (o) oxalyl chloride (1.1 equiv.), DMSO (2.2 equiv.), CH_2Cl_2, −78°C, 30 min, then **26**, 30 min and NEt_3 (5.0 equiv.), −78→0°C; (p) **15** (*n* equiv.), Et_2O, −78°C, then *t*BuLi/pentane (2*n* equiv.), 15 min, and further addition of **27** in pentane, −78→0°C; (q) K_2CO_3 (1.4 equiv.), MeOH, rt, 5 h; (r) **32** (2 equiv.), Et_2O, CF_3SO_3H (0.004 equiv.), rt, 4 h.



Scheme 5. *Reagents and conditions*: (a) TBAF 1 M/THF (1.1 equiv.), rt, 10 h; (b) DCC (2.2 equiv.), DMAP (1.2 equiv.), CH_2Cl_2, rt, 5 h.

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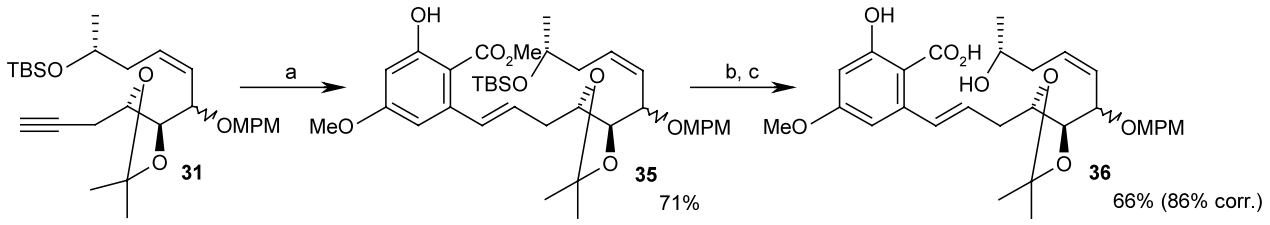

Scheme 6. *Reagents and conditions*: (a) Sia_2BH (2 equiv.), THF, −25°C→rt, 2 h and then aq. 2 M K_3PO_4 (2 equiv.), further addition of that mixture via cannula at rt to a solution of **8** (1.2 equiv.) and 15 mol% [$Pd(OAc)_2$+4TFP] in DME; DME/H_2O ~7/1, reflux, 8 h; (b) TBAF 1 M/THF (3.5 equiv.), rt, 6 h, 93%; (c) 2N aq. NaOH (13 equiv.)/MeOH (1/3), reflux, overnight, 71%.

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