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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5601–5604

Improved synthesis of the polyhydroxylated central part of phoslactomycin B

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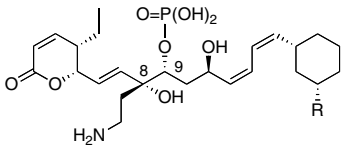
Received 28 May 2007; revised 11 June 2007; accepted 15 June 2007
Available online 17 June 2007

Dedicated to the late Professor Yoshihiko Ito, Kyoto University

Abstract—A new approach to the C(7)–C(13) intermediate for the synthesis of phoslactomycin B was investigated. Asymmetric dihydroxylation of the β,γ-unsaturated ester proceeded cleanly to afford the β-hydroxyl-γ-lactone with 97.6% ee, which upon protection as the PMB ether followed by hydride reduction furnished a diol. After selective protection of the *prim*-OH, oxidation of the *sec*-OH and chelation-controlled addition of CH_2=CHMgBr afforded the C(7)–C(11) segment. Later on, the C(11) stereocentre was constructed by the asymmetric transfer hydrogenation using the Noyori catalyst.

Phoslactomycin B (**1**) is one of the phoslactomycin family that shows a selective PP2A inhibitory activity.[1] The common structure of **1** and the other members is drawn in Figure 1, while each member of the family possesses a specific substituent on the cyclohexane ring. The same structural unit is also seen in leustroducsins.[2] To study the biological profile at molecular level with structural analogues and compounds possessing a specific function, synthesis of these compounds should be established. Synthesis of leustroducsin B (R = 6-methyloctanoic acid moiety) has been published first by Fukuyama and co-workers[3] and quite recently by Imanishi and co-workers.[4] Although the syntheses are elegant, the long sequences of reactions and the low-yielding steps seem to be improved in order to apply the methods to synthesis of analogues for the biological study.



R = H, Phoslactomycin B (**1**)
R = $OC(O)C_nH_{2n+1}$, Phoslactomycins, Leustroducsins

Figure 1. Phoslactomycins and leustroducsins.

On the other hand, we reported a synthesis of **1**.[5] The synthesis features the chelation-controlled addition of CH_2=CHMgBr to the α-PMB-oxy ketone **5** to produce the key intermediate **6** that covers the most congested part of the molecule (Scheme 1). The addition was highly stereoselective (**5**→**6**), and the strategy will be applicable to synthesis of other phoslactomycins. However, the method suffers from that the Sharpless asymmetric epoxidation[6] (Sharpless AE) does not exceed 50% yield in theory.

Herein, taking advantage of the chelation-controlled addition in mind, we retrosynthesized the key intermediate **6** to a keto aldehyde **7** as delineated in Scheme 2. The first approach to a real compound **8** of type **7** involves asymmetric dihydroxylation[7] (AD reaction) of olefin **9** to hydroxyl lactone **8** through lactonization of the initially formed diol.[8] Alternatively, we conceived stereoselective addition of an acetate anion (MCH_2CO_2R) to an aldehyde derivative **10** of L-malic acid.

Olefin **9**, the substrate for the AD reaction in the first approach (Scheme 3), was prepared from butane-1,4-diol (**11**) in 77% yield with a modification[9] of the method of Lee and co-workers,[10] who submitted the olefin to

Keywords: Phoslactomycin B; Chelation-controlled addition; Asymmetric dihydroxylation; Asymmetric transfer hydrogenation.
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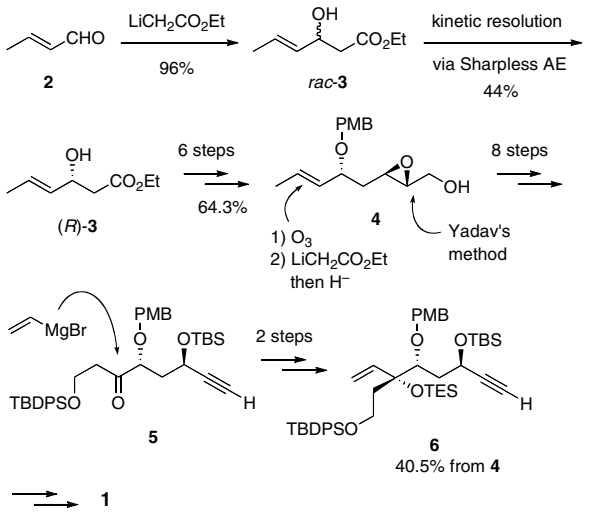
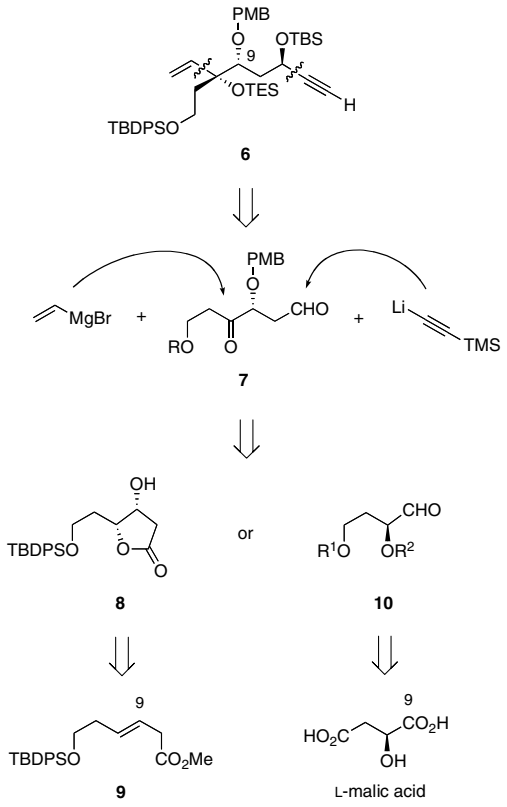
doi:10.1016/j.tetlet.2007.06.058



Scheme 1. Summary of the previous synthesis of phoslactomycin B (**1**) through **6**. PMB: *p*-$MeOC_6H_4CH_2$, TBS: $SiMe_2Bu$-*t*, TBDPS: $SiPh_2Bu$-*t*, TES: $SiEt_3$.



Scheme 2. Retrosynthesis of the key intermediate **6**.

AD reaction with AD-mix-α to afford the hydroxyl lactone (enantiomer of **8**) with somewhat low 86% ee. Instead, we used AD-mix-β, which provided **8** with 97.6% ee (determined by chiral HPLC analysis of the derived benzoate). Although a reason for the difference in the observed enantiomeric purities was not clear, the high level in our side was reproducibly attained. The hydroxyl group of **8** was protected to PMB ether **14** with *p*-methoxybenzyl trichloroacetimidate (PMB-Im) in the presence of $BF_3{\cdot}OEt_2$ (3 mol %), while CSA (10 mol %), one of the standard acids for PMB protection,[11] assisted the reaction incompletely.

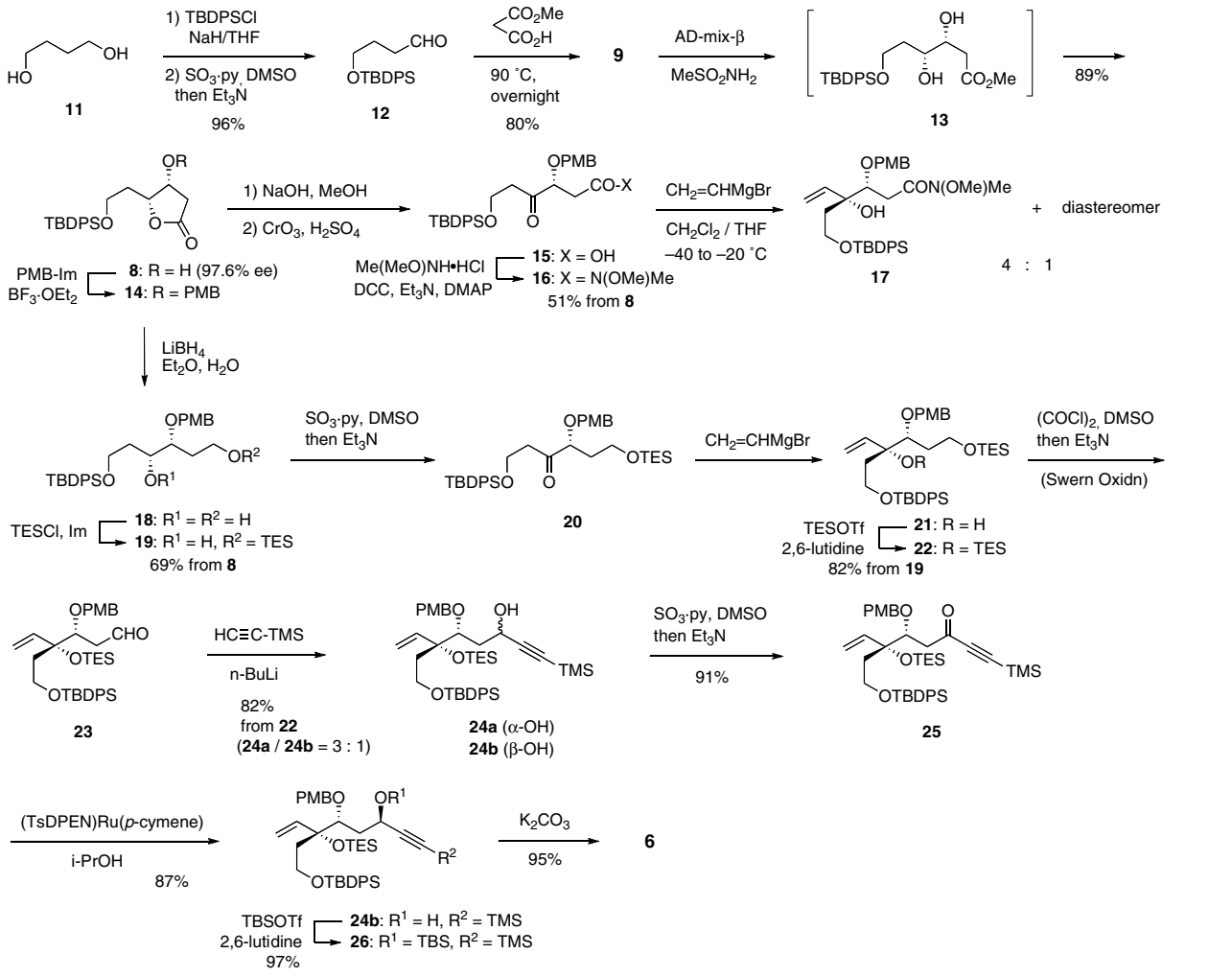
Addition of $CH_2{=}CHMgBr$ was first attempted with a ketone **16**, which was prepared in 51% yield from **8** through hydrolysis of the lactone **14**, Jones oxidation, and condensation with Me(MeO)NH·HCl/DCC.[12] While the addition in THF at −78 °C produced a mixture of products, that in CH_2Cl_2/THF (12:1) gave **17**, but as a diastereomeric mixture in a 4:1 ratio. Thus, conversion of the amide to the corresponding ketone with $TMSC{\equiv}CLi$ was not investigated.

A synthetic route we investigated next was hydride reduction of **14** to diol **18**. Although $LiAlH_4$, $LiB(H)Et_3$ and DIBAL each in THF produced a mixture of **18** and unidentified less polar product(s), $LiBH_4$ in aqueous Et_2O[13] produced diol **18**, which was converted to TES ether **19** in 69% yield from **8** (three steps). Oxidation of the secondary hydroxyl group of **19** gave ketone **20**, which was submitted to reaction with $CH_2{=}CHMgBr$ at −78 °C in THF to furnish alcohol **21** exclusively.[14] Protection of the newly formed hydroxyl group as a TES group gave **22** in 82% yield, which upon Swern oxidation[15] furnished aldehyde **23** as the sole product.

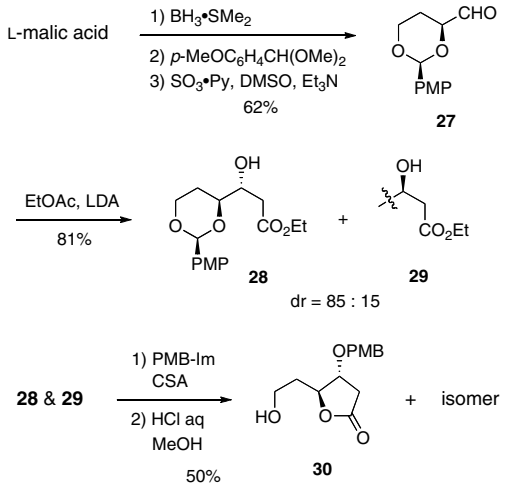
Addition of the lithium anion derived from $TMSC{\equiv}CH$ and *n*-BuLi produced a 3:1 diastereomeric mixture of **24a** and **24b** (desired product) by ^1H NMR spectroscopy.[16] Although the mixture was separable, oxidation with $SO_3{\cdot}py$ and DMSO was carried out without separation to afford ketone **25** cleanly. Subsequently, asymmetric transfer hydrogenation[17] using the Noyori catalyst furnished **24a** and **24b** in a 1:17 ratio, which was separated easily by chromatography on silica gel. Finally, protection of the newly formed hydroxyl group with TBSOTf and subsequent removal of the TMS group at the acetylenic carbon produced the intermediate **6** in good yield. The total yield of **6** from diol **11** was 23.1% in 16 steps, while that in the original method[5] was 11.0% from crotonaldehyde (**2**) in 18 steps. In addition to the improved yield and steps, the present synthesis has another advantage of easy operation of the reactions involved in the synthesis.

We also examined the chiral pool strategy using L-malic acid, which was converted efficiently to aldehyde **27** of type **10** (in Scheme 2) by the literature method (Scheme 4).[18] Addition of an anion derived from EtOAc and LDA at −78 °C in THF produced a 85:15 mixture of **28** and **29** in 81% yield.[19,20] Although **28** is the none-chelation product, addition of HMPA as a co-solvent did not improve the selectivity (82% dr). The mixture was transformed into **30** in two steps of PMB protection of the hydroxyl group and the PMP acetal cleavage. Unfortunately, mobility of **30** and the diastereomer on TLC was close, and we did not investigate this approach.

In summary, we developed an alternative approach to the key intermediate **6** for synthesis of phoslactomycin



Scheme 3. Synthesis of the key intermediate **6**.



Scheme 4. Synthesis of **30**. PMP: *p*-$MeOC_6H_4$.

B. The overall yield was 23.1%, which is almost twice of that reported previously, and the procedure has several synthetic advantages.

Acknowledgement

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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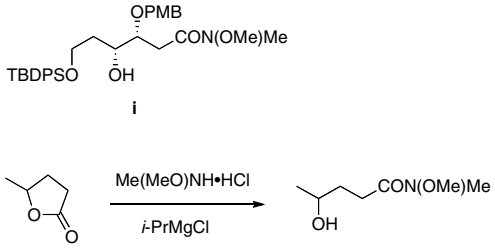

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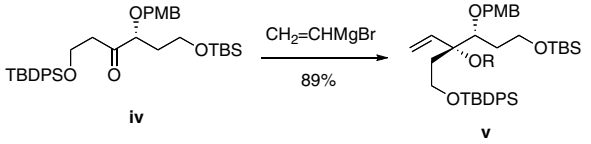

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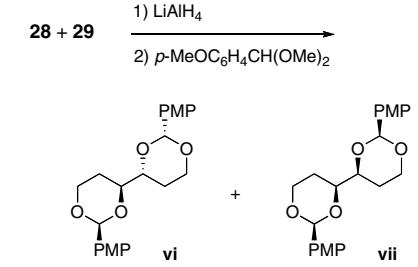

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