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Good Timing in Total Synthesis: The Case of Phoslactomycin A

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Abstract: The importance for the right order of functional group introduction and manipulation (good timing) was demonstrated in the course of a total synthesis of phoslactomycin A. The synthetic strategy comprised a Cu^{I}–thiophene carboxylate (CuTC, Liebeskind's reagent)-mediated coupling to introduce the *Z*,*Z*-diene at the final stage of the synthesis in the presence of a protected phosphate. Key features for the assembly of the C1–C13 fragment were an asymmetric dihydroxylation, an Evans-aldol reaction and an advanced protective group strategy. The C14–C21 fragment was accessible via an asymmetric 1,2-addition to cyclohexenone and a subsequent diastereoselective ketone reduction. One crucial task was the dihydroxylation of the C8–C9 alkene, the introduction of the C6–C7 double bond and the generation of the C25-nitrogen functionality. A second example consisted of the best sequence for the generation of the functional groups in the core part (first phosphorylation, second iodo-olefination, third azide/carbamate conversion). The synthetic solutions from this approach are compared with the already existing contributions in the phoslactomycin area.

Keywords: cross-coupling · natural products · phoslactomycin · total synthesis

Introduction

The total synthesis of natural products forms a main challenge for synthetic chemistry. A good synthetic strategy is one key factor for a successful synthesis.[1] Of equal importance are timing and tactics.[2] A target structure with a multitude of functional groups can be assembled by different sequences of functional group introduction. It is important to choose the right timing for the introduction of functional groups. The right order of functional group manipulations including protective operations often determines success or failure. The phoslactomycins bear a large number of different functional groups. Efforts towards the total synthesis of this class of natural products are a valuable case study for timing in total synthesis. The phoslactomycins, leustroducsins form together with fostriecin, cytostatin and sultriecin a class of structurally similar natural products with comparable biological activities (Figure 1). Phoslactomycins A–F were isolated from *Streptomyces nigrescens*.[3] Phoslactomycin B (phospholine) was also found in *Streptomyces hydroscopicus*.[4] Leustroducsins A–H, which differ from the phoslactomycins in the C16 side chain of the cyclohexyl fragment were isolated from *Streptomyces platensis*.[5] Fostriecin was the first compound of this class of isolated natural products[6] and therefore most intensively studied.[7] Cytostatin[8] and sultriecin[9] have a similar structure and biological profile.

The biological activities of the phoslactomycines and the related compounds are of pharmaceutical interest (antitumor, antibacterial and antifungal) and have been connected with a selective human protein phosphatase 2A (PP2A) inhibition.[10] SAR studies showed the importance of the unsaturated lactone.[11]

Two total syntheses of leustroducsin B by Fukuyama[12] and by Iminashi[13] as well as two successful routes to phoslactomycin B by Kobayashi[14] and by Hatakeyama[15] have been reported. Cossy has achieved formal total synthesis of leustroducsin B[16] and phoslactomycin B.[17] Kobayashi et al. has published an improved synthesis of the C7–C13 fragment of phoslactomycin B.[18] All phoslactomycin syntheses reported thus far gained benefit from the numerous syntheses of fostriecin.[19] Here, we focus in a comparative way on the problems of timing in the synthesis for phoslactomycins

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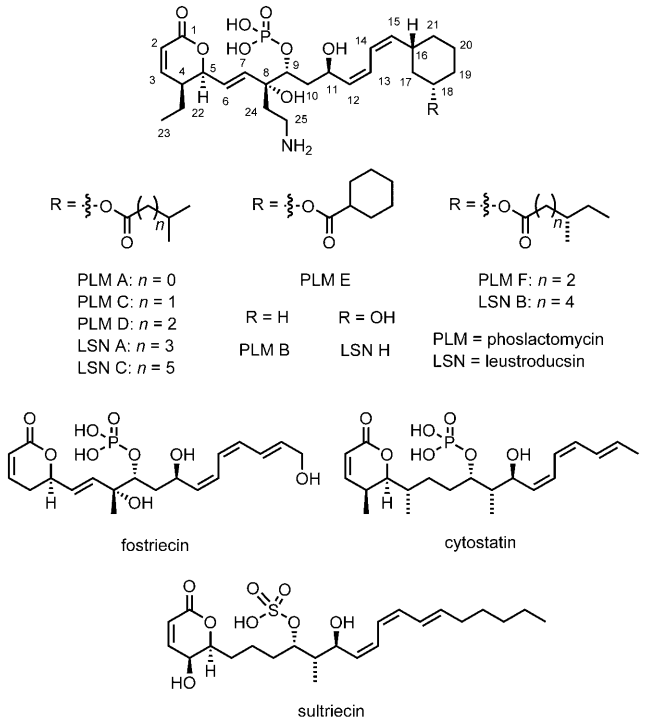
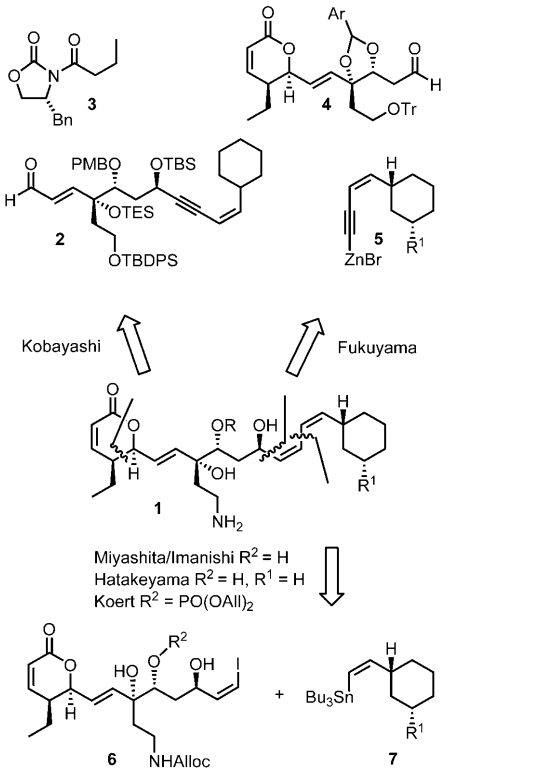


Figure 1. Structures of phoslactomycins and related natural products.



Scheme 1. Comparison of the synthetic strategies to phoslactomycins.

and report the details of our total synthesis of phoslactomycin A.[20]

Results and Discussion

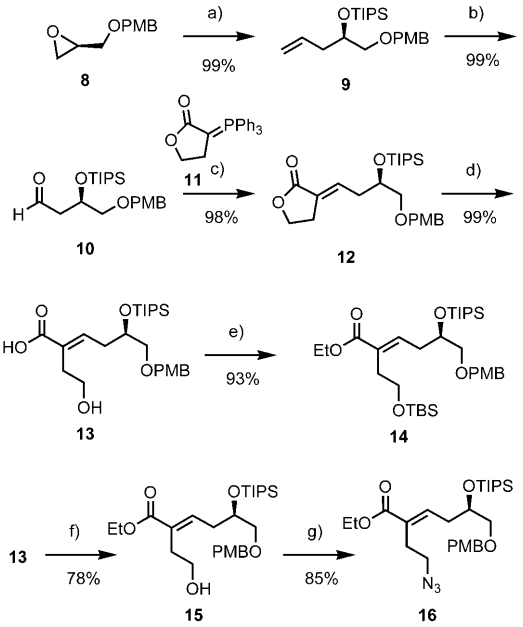
A comparative retrosynthetic consideration of the five published routes to phoslactomycins exhibits two conceptionally different approaches (Scheme 1).

The first route chosen by Kobayashi and Fukuyama connects both fragments with simultaneous generation of stereocenters. Both groups achieve an excellent degree of stereocontrol for these steps. Kobayashi uses an Evans-aldol reaction (**2** + **3**) while Fukuyama adds alkynyl zinc bromide **5** to aldehyde **4**. The introduction of the amino group and the phosphate is postponed in both approaches past the convergent skeleton construction step.

The second approach relies on a cross-coupling reaction to prepare the *Z*,*Z*-diene. An alkenyl iodide **6** and a stannane **7** were used by three groups (Miyashita/Imanishi, Hatakeyama, Koert). Here all stereocenters are introduced separately in earlier steps. The disadvantage of these additional steps is paid off by a higher convergency. Miyashita/Imanishi and Hatakeyama install the amino group before the coupling step. We achieved a maximum of convergency with the amino group and the phosphate already present in the coupling step.

In the present case the synthesis of the C7–C12 phoslactomycin core structure with the three stereocenters C8, C9 and C11 was investigated first. With a chiral pool solution for C11, a stereoselective dihydroxylation of a trisubstituted alkene was selected for the C8–C9 diol function. Three different alkenes **12**, **14**, and **16** were synthesized (Scheme 2) and evaluated (Scheme 3). *S*-glycidol-PMB ether **8**[21] was transformed via a Cu^{I}-mediated epoxide opening and a subsequent TIPS-protection into the alkene **9**. Oxidative cleavage of the double bond gave aldehyde **10** which led with ylide **11**[22] in an *E*-selective Wittig reaction to alkene **12**. Opening of the γ-lactone via the hydroxy carboxylic acid **13** gave ethyl ester **14**. Compound **13** could also be transformed into hydroxyl ester **15**, which delivered azide **16** under Mitsunobu conditions.[23]

The Sharpless dihydroxylation[24] of trisubstituted alkenes **12**, **14** and **16** proceeded with remarkable different diastereoselectivities (Scheme 3). A low diastereoselectivity of 2:1 was observed for the lactone case (**12**→**17**), while a 9:1 selectivity could be achieved with the ethyl ester (**14**→**19**). The major stereoisomers could be obtained in pure form at the stage of acetals **18** and **20**. An excellent stereoselectivity (17:1) was observed for the dihydroxylation of the azide-substituted alkene **16**. Diol **21** was accessible in pure form by chromatography and could be converted into acetal **22**. Compound **22** is due to the presence of the nitrogen functionality a more advanced synthetic intermediate than TBS ether **20**. However, problems during the subsequent introduction of the C6/7 double bound (triazoline formation, see below) disfavored further use of **22**. In terms of timing, it was advantageous to position the dihydroxylation step prior to the introduction of the C6–C7 double bond and the nitro-

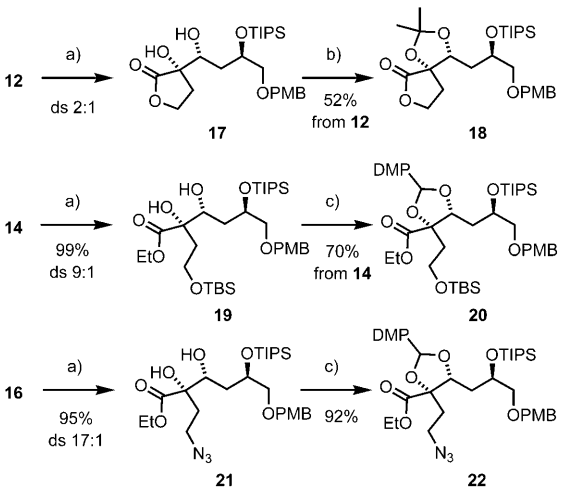


Scheme 2. Synthesis of the alkenes **12**, **14**,and **16**. a) i) $H_2C{=}CHMgBr$, CuI, THF, ii) TIPSOTf, 2,6-lutidine, CH_2Cl_2; b) i) $K_2OsO_2(OH)_4$, NMO, acetone/H_2O, ii) $NaIO_4$, THF/H_2O; c) THF, 50 °C; d) LiOH, THF/H_2O; e) i) TBSCl, imidazole, CH_2Cl_2, ii) EtI, K_2CO_3, actone/H_2O; f) EtI, K_2CO_3, actone/H_2O; g) $Zn(N_3)_2{\cdot}2py$, PPh_3, DIAD, toluene.

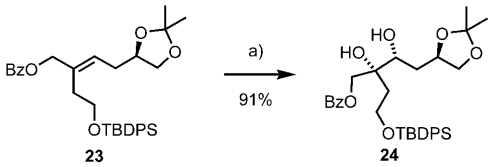
gen functionality. TBS ether **20** proved to be the most suitable synthetic intermediate.

Miyashita and Imanishi used in their synthesis the dihydroxylation of alkene **23** with a different oxidation state at C7 and obtained diol **24** as a single stereoisomer (Scheme 4).[13]

The next chapter of our synthesis focused on the elaboration of the C1–C6 substructure. An *E*-selective Wittig olefination was selected to introduce the C6–C7 double bond



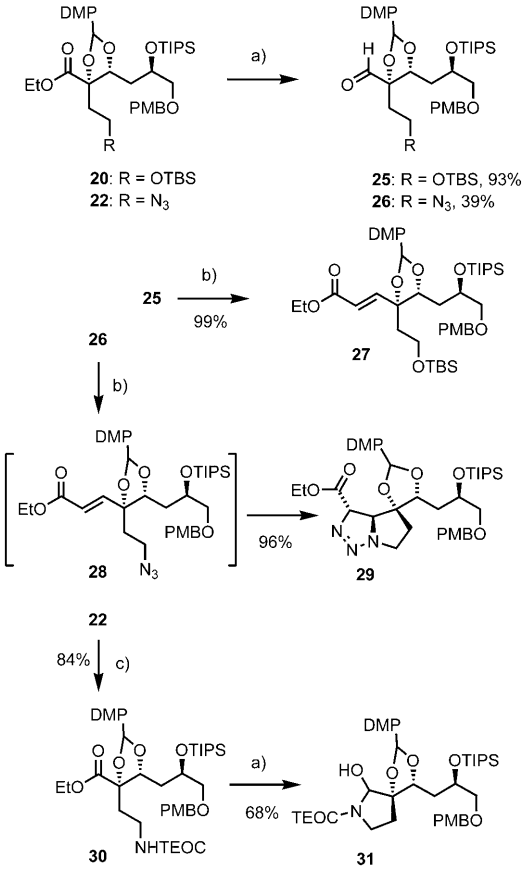
Scheme 3. Synthesis of the alkenes **12**, **14**,and **16**. a) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$ for **12**, $(DHQD)_2PYR$ for **14** and **16**, *t*BuOH/H_2O; b) dimethoxypropane, CSA, CH_3CN; c) $DMPCH(OMe)_2$, CSA, CH_3CN.



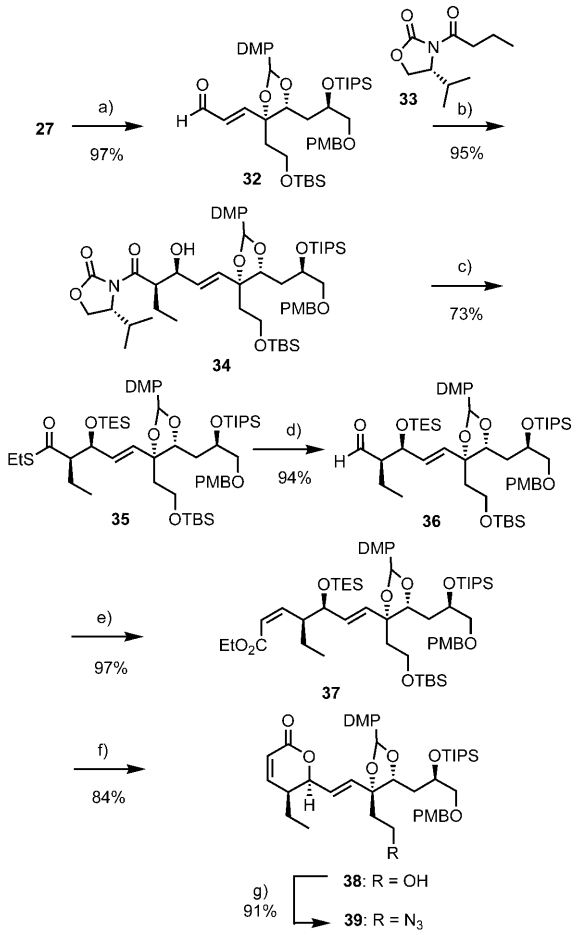
Scheme 4. Miyashiata/Imanishi dihydroxylation. a) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, *t*BuOH/H_2O.

(Scheme 5). The conversion of the C6 ester into the corresponding aldehyde via $LiBH_4$ reduction and Dess–Martin was applied to compounds **20** and **22**. The ethyl ester **20** led smoothly to aldehyde **25**, which delivered alkene **27** in very good yield. The same sequence applied to azido ethyl ester **22** led to a dead end. The conversion into the aldehyde **26** proceeded with a lower yield. More important, the Wittig product **28** could not been isolated, because a subsequent intramolecular 1,3-dipolar cycloaddition gave triazoline **29**. The electron-deficient double bond in **28** exhibits a high dipolarophile reactivity. Thus, if the nitrogen functionality shall be introduced via an azide, no electron-withdrawing group has to be present at the C6–C7 double bond. An attempt to reduce the azide into an amine led to a different problem. The Staudinger reduction of azide **22** gave compound **30** after TEOC protection. The latter was reduced to the alcohol and subsequently oxidized to the aldehyde stage. No free aldehyde was detected, but complete hemiaminal formation to **31** was observed. Attempts to use the hemiaminal for the following Wittig reaction were not successful.

With the identification of ester **27** as the most suitable intermediate, the completion of the C1–C6 substructure was addressed next (Scheme 6). DIBAH reduction to the alcohol and MnO_2 oxidation gave aldehyde **32**. Subsequent Evans-aldol reaction with oxazolidinone **33** to *syn*-aldol **34** proceeded with 95:5 diastereoselectivity and very good yield.[25] By this route the stereocenters C4 and C5 were introduced. A related aldol solution for both stereocenters was used by Kobayashi in his synthesis of phoslactomycin B.[14] The subsequent protection of the secondary hydroxyl group in **34** required a silyl ether, that could be selectively deprotected in the presence of the secondary TIPS group at HO-C11 to allow the ring closure to the six-ring lactone. TES should fulfill this criterion and therefore compound **34** was protected as a TES ether. The removal of the Evans auxiliary was planned at the aldehyde oxidation state. Towards this end the route via a thiol ester was chosen. Treatment of TES-protected **34** with lithium ethyl thiolate gave thiol ester **35**.[26] The high nucleophilicity of the sulfur allows removal of the auxiliary at 0 °C which prevents epimerization. Thiol ester **35** could be reduced to aldehyde **36** in 94 % yield. The Weinreb-amide alternative from **34** to **36** gave a considerable amount of epimerization and was therefore disfavored.[27] The following introduction of the C3–C4 double bond was achieved using $(PhO)_2POCH_2CO_2Et$ and NaHMDS.[28] A little excess of base to phosphonate and HMPA as a cosolvent prevented epimerization of the alde-



Scheme 5. Introduction of the C6–C7 double bond. a) i) $LiBH_4$, ii) Dess–Martin oxidation; b) $Ph_3PCH{=}CO_2Et$, toluene, 70 °C; c) PPh_3, THF/H_2O, TEOCOSu.



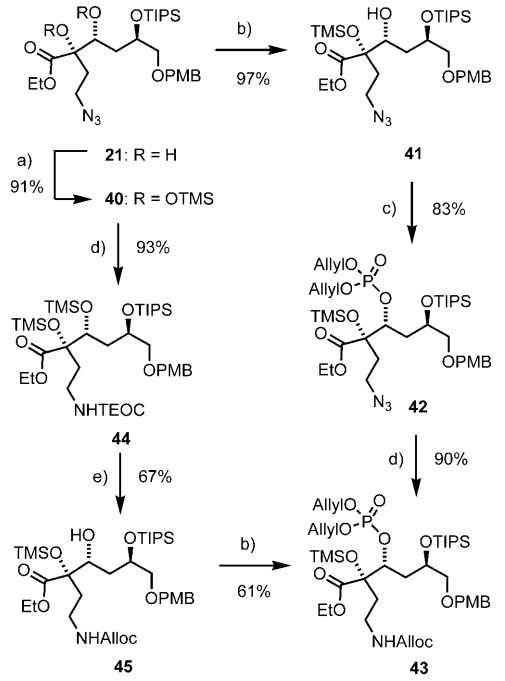
Scheme 6. Synthesis of the C1–C6 substructure. a) i) DIBAH, CH_2Cl_2, −78 °C, ii) MnO_2; b) nBu_2BOTf, CH_2Cl_2, NEt_3, −78 → −20 °C; c) i) TESOTf, 2,6-lutidine, ii) EtSH, *n*BuLi, THF, 0 °C; d) DIBAH, toluene, −78 °C; e) $(PhO)_2P(O)CH_2COOEt$, NaHMDS, THF/HMPA, −78 °C; f) i) $(HF)_3{\cdot}NEt_3$, ii) $Ti(O\mathit{i}Pr)_4$, benzene, 80 °C; g) $Zn(N_3)_2{\cdot}2py$, DIAD, PPh_3, toluene, 20 °C.

hyde and led to alkene **37** with complete *Z* selectivity. After selective deprotection of the TES and the TBS ether in the presence of the TIPS group with $[HF]_3{\cdot}Et_3N$, the resulting hydroxyl ester could be cyclized with titanium tetraisopropoxide in boiling benzene[14] to lactone **38**. At this stage of the synthesis the introduction of the nitrogen functionality via an azide-Mitsunobu reaction (**38**→**39**) could be achieved without the undesired dipolar cycloaddition encountered in the case **26**→**28**→**29** (Scheme 5).

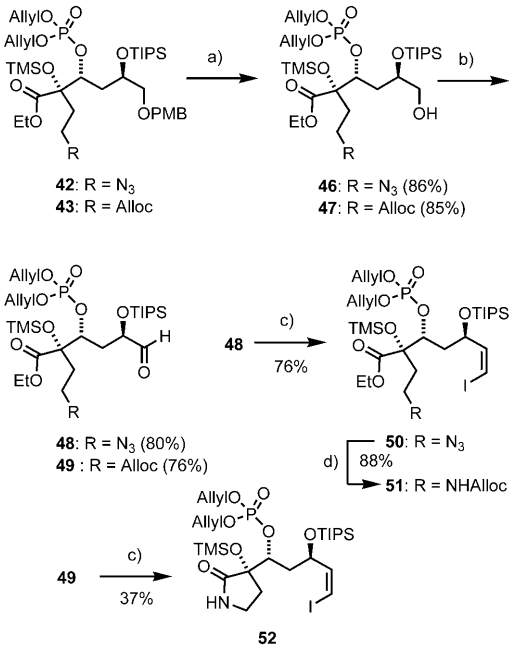
The remaining synthetic tasks left before the final cross-coupling were the introduction of the C9 phosphate, the azide/amine reduction and the generation of the C12–C13 alkenyl iodide. The right timing for the phosphate introduction/azide reduction was evaluated at the test system **21** which lacks the C1–C5 lactone (Scheme 7). TMS protection of diol **21** to bis-TMS ether **40** and subsequent selective deprotection of the C11 silyl ether using H_2SiF_6[29] at −30 °C gave alcohol **41** in excellent yield. Phosphorylation using diallyl phosphoroamidite followed by oxidation with *tert*-butyl hydroperoxide provided the bisallyl phosphate **42**.[30] After Staudinger reduction and Alloc protection carbamate **43** was obtained. The alternative sequence of first Staudinger reduction/Alloc protection (**40**→**44**) and subsequent phosphate introduction (**44**→**45**→**43**) gave a significant lower yield and was therefore disfavored.

The problem of timing for the alkenyl iodide introduction and azide reduction was investigated next (Scheme 8). Oxidative PMB deprotection worked well in the presence of the azide (**42**→**46**) and the corresponding carbamate (**43**→**47**). The subsequent Dess–Martin oxidation gave aldehydes **48** and **49** for both cases in good yields. The next step, the *Z* olefination[31] of the aldehyde to the alkenyl iodide gave a completely different outcome for the azide and the carbamate case. Azide-containing aldehyde **48** provided the desired product **50** in 76% yield, which could be converted smoothly into carbamate **51**. In contrast, the olefination of aldehyde **49** resulted in an undesired lactamization of the carbamate (**49**→**52**). The results from these model studies pointed to the optimal order of first phosphorylation, second iodo-olefination and third azide/carbamate conversion.

With the information obtained concerning the right timing for the introduction of the functional groups in the

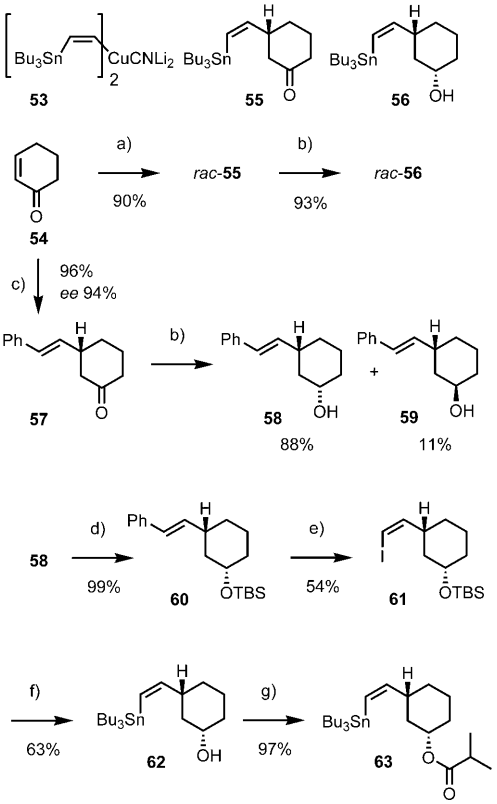


Scheme 7. Evaluation of the timing for phosphorylation and azide reduction: a) TMSCl, imidazole; b) H_2SiF_6, CH_3CN, −30 °C; c) $(iPr)_2NP(OAllyl)_2$, tetrazole, CH_3CN/CH_2Cl_2, then *t*BuOOH; d) PPh_3, THF/H_2O, then $NaHCO_3$, $Alloc_2O$; e) *p*TsOH, THF/H_2O, 20 °C.



Scheme 8. Evaluation of the timing for olefination and azide reduction: a) DDQ, CH_2Cl_2/H_2O; b) Dess–Martin periodinane, CH_2Cl_2, pyridine; c) ICH_2PPh_3I, NaHMDS, THF, −78→0 °C; d) PPh_3, THF/H_2O, then $NaHCO_3$, $Alloc_2O$.

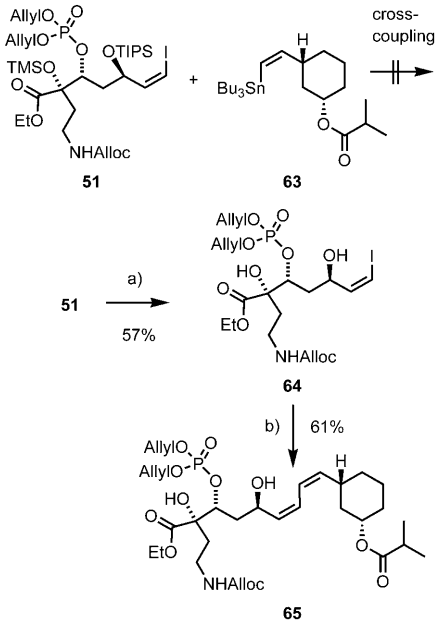
C1–C13 fragment we turned our attention to the C14–C21 fragment. Cyclohexenone **54** was chosen as starting material for the synthesis of the cyclohexyl substructure. The stannyl–cupration of acetylene according to the Pulido protocol[32] produced cuprate **53** which gave the 1,4-addition product *rac*-**55** in very good yields (Scheme 9). The $NaBH_4$ reduction of ketone *rac*-**55** delivered *cis*-cyclohexanol *rac*-**56** with an 18:1 diastereoselectivity. Although an asymmetric variant[33] of the cuprate addition was examined no significant enantioselectivity was achieved. However, the asymmetric Rh-mediated 1,4-addition of alkenyl boronic acids developed by Hayashi[34] could be applied successfully for the enantioselective synthesis of the cyclohexyl fragment. The asymmetric addition of (*E*)-styrylboronic acid to cyclohexenone **54** gave ketone **57** (*ee* 94%). The subsequent $NaBH_4$ reduction produced cyclohexanols **58** and **59** with a 7:1 diastereoselectivity in favor of the desired *cis*-disubstituted product **58**. Noticeably is the lower stereoselectivity for the reduction of ketone **57** bearing the *E*-alkene than for the ketone **55** with the *Z*-alkene. The TBS protection of **58** led to **60**, which upon ozonolysis of the double bond and a subsequent *Z*-selective Stork–Zhao olefination gave *Z*-alkenyl iodide **61**. The latter was transformed via iodine–lithium exchange into the corresponding *Z*-alkenyl stannane which was desilylated to produce alcohol **62**. Esterfication with isobutyric acid gave the desired cyclohexyl fragment **63**.



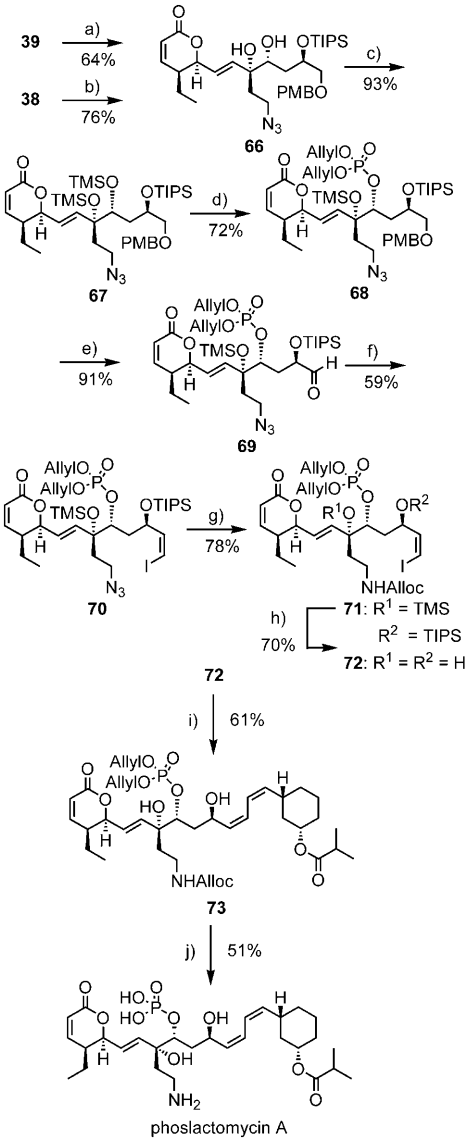
Scheme 9. Racemic und asymmetric synthesis of the cyclohexyl fragment **63**: a) $(Bu_3Sn)_2$, *n*BuLi, CuCN, HCCH, THF, −70 °C; b) $NaBH_4$, THF/H_2O, 0 °C; c) $[Rh(acac)(C_2H_4)_2]$, (*R*)-BINAP, (*E*)-$PhCHCHB(OH)_2$, dioxane/H_2O, reflux; d) TBSOTf, 2,6-lutidine, CH_2Cl_2; e) i) O_3, CH_2Cl_2, −78 °C; PPh_3, ii) ICH_2PPh_3I, NaHMDS, THF/HMPT, −78 °C; f) i) *t*BuLi, Et_2O, −78 °C, Bu_3SnCl; ii) TBAF, THF; g) $iPrCO_2H$, DCC, DMAP, CH_2Cl_2.

In order to find suitable conditions for the later final cross-coupling, the reaction of alkenyl iodide **51** with the alkenyl stannane **63** was investigated at this stage of the project. Miyashita/Imanishi applied in their leustroducsin B synthesis[13] a Stille reaction[35] ($[PdCl_2(MeCN)_2]$, RT, 1 h, 61%) in a related situation. Hatakeyama in his phoslactomycin B synthesis also chose Stille conditions ($[PdCl_2(MeCN)_2]$, RT, 1 h, 46%).[15] In both cases no protected phosphate was present at C9-OH. The easy cleavage of allyl phosphates with a Pd^0 catalyst[30] led us focus on an alternative to the Pd^0-mediatated cross-coupling. Although used not substoichiometrically such as a Pd catalyst, but in stoichiometric amounts, Cu^I–thiophene carboxylate (CuTC, Liebeskind's reagent)[36] is a valuable cross-coupling reagent which has passed the late-stage test in several total syntheses.[37] However, the CuTC-mediated cross-coupling of **51** with **63** was unsuccessful (Scheme 10). A possible explanation could be the steric shielding of the alkenyl iodide by the bulky TIPS group. Miyashita/Imanishi and Hatakeyama accomplished their Pd-mediated cross-coupling without a protective group at C11-OH.[13,15] Therefore in our case, the TIPS group in compound **61** was removed using 25% aqueous H_2SiF_6 in CH_3CN at 5°C, which led to simultaneous removal of the TMS ether at C8 and the formation of compound **64**. Now the CuTC-mediated cross-coupling with alkenyl stannane **63** gave the desired *Z*,*Z*-diene **65** in 61% yield.

The synthesis of the complete C1–C13 fragment applied the optimal order of first, phosphorylation, second, iodo-olefination and third, azide/carbamate conversion from the previous studies summarized in Schemes 7 and 8. Starting point for the introduction of the phosphate was diol **66** which was accessible from acetal **39** or in better overall yield from precursor **38** (Scheme 11). Double TMS protection delivered bis-TMS ether **67**. Selective deprotection of the C9-TMS group and subsequent phosphorylation led to protected phosphate **68**. Next, the olefination sequence was opened with an oxidative PMB-ether cleavage and a subsequent Dess–Martin oxidation to obtain the aldehyde **69**. A Stork–Zhao olefination gave (*Z*)-alkenyl iodide **70**. Finally, azide **70** was converted into Alloc-protected amine **71**. In order to remove the bulky C11-OTIPS group for the subsequent cross-coupling compound **71** was treated with H_2SiF_6 to obtain diol **72**. The CuTC-mediated cross-coupling of alkenyl iodide **72** and alkenyl stannane **63** proceeded successfully



Scheme 10. Cross-coupling studies: a) H_2SiF_6, CH_3CN/H_2O, 5°C; b) CuTC, NMP, 0°C, 1 h.



Scheme 11. Synthesis of the complete C1–C13 fragment: a) CSA, HCl, CH_2Cl_2/MeOH; b) i) $Zn(N_3)_2$·2py, DIAD, PPh_3, toluene, ii) TFA, MeOH; c) TMSCL, imidazole, CH_2Cl_2; d) i) CSA, THF/H_2O, 20°C, ii) $(iPr)_2NP(OAllyl)_2$, tetrazole, CH_3CN/CH_2Cl_2, then *t*BuOOH; e) i) DDQ, CH_2Cl_2/H_2O, ii) Dess–Martin periodinane, CH_2Cl_2, pyridine; f) ICH_2PPh_3I, NaHMDS, THF, −78→0°C; g) PPh_3, THF/H_2O, then $NaHCO_3$, $Alloc_2O$; h) H_2SiF_6, CH_3CN/H_2O; i) **63**, CuTC, NMP, 0°C, 1 h; j) $[Pd(PPh_3)_4]$, HCOOH, Et_3N, THF, 50°C.

in the presence of the protected phosphate to deliver the *Z*,*Z*-diene **73** in good yield. The final simultaneous deprotection at phosphorous and nitrogen required some optimization attempts. Pd^0 conditions gave a fast deprotection of the allyl phosphates but only a slow cleavage of the allyl carbamate. No Pd^0 attack at the C5–C7 allyl substructure was observed. Finally, using transfer hydrogenation conditions ($[Pd(PPh_3)_4]$, HCOOH, Et_3N)[12] at 50 °C for 3 h the target compound phoslactomycin A could be obtained. The purification of the target compound was achieved by reversed-phase HPLC. The spectra and analytical data of the synthetic sample corresponded to those reported for the natural material.[3]

Conclusion

The reported total synthesis of phoslactomycin A exemplifies several aspects of timing in synthesis. One is the optimal place for the stereoselective C8–C9 dihydroxylation (first), the introduction of the C6–C7 double bond (second) and the introduction of the C25 nitrogen function (third). The best sequence for the generation of the functional groups in the core part (first phosphorlyation, second iodo-olefination, third azide/carbamate conversion) was established in a test system prior to its application for the synthesis of the target molecule. The C13–C14 cross-coupling strategy used in the presence case is comparable to the work of Miyashita/Imanishi and Hatakeyama.[13,15] The strategic decision to accomplish the cross-coupling in the presence of the protected phosphate resulted in a higher convergence of our synthesis (**72**+**63**→**73**) and in a different optimal sequence for the partial solutions of the synthetic problem. A comparison of the approaches by Miyashita/Imanishi, Hatakeyama and the present one shows the high number of protective group transformations used in all three cases. Despite the request for a protective-group free synthesis,[38] a compound with the high density of different functional groups like phoslactomycin A needs (at the moment) also good timing with respect to the use of protective groups.

Experimental Section

Full experimental details with complete characterizations of all new compounds are given in the Supporting Information.

Acknowledgements

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