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Total Synthesis of Aquayamycin

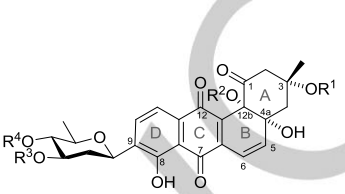
Shunichi Kusumi, Harunobu Nakayama, Takumi Kobayashi, Hajime Kuriki, Yuka Matsumoto, Daisuke Takahashi and Kazunobu Toshima*

Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday

Abstract: An efficient and practical total synthesis of aquayamycin has been accomplished. The highly oxidized and stereochemically complex tetracyclic ring system was constructed using three key reactions: 1) highly diastereoselective 1,2-addition of *C*-glycosyl naphthyllithium to a cyclic ketone, 2) indium-mediated site-selective allylation-rearrangement sequence of naphthoquinone, and 3) diastereoselective intramolecular pinacol coupling. This synthetic strategy offers a novel and efficient pathway to prepare aquayamycin-type angucycline antibiotics.

In the past 50 years, more than 100 types of angucycline antibiotics have been reported and represent an important class of microbial antibiotics.[1] They exhibit a broad spectrum of biological activity, such as antifungal, antitumor, and enzyme inhibitory activity, and their unique angular tetracyclic core skeleton (benz[*a*]anthraquinone) have attracted many synthetic organic chemists. Some angucyclines, including landomycin A[2] and vineomycin B_2,[3] have been synthesized in a regio- and stereoselective manner by several different methods,[1,4] such as Diels-Alder reaction, Friedel-Crafts reaction, nucleophilic addition, Hauser annulation, and free-radical annulation. Despite the synthetic strategies developed, there are still remaining challenges with regard to the synthesis of aquayamycin-type angucyclines.

Among angucycline antibiotics, aquayamycin (**1**) and aquayamycin-type angucyclines constitute the largest class; more than 30 types of compounds, such as vineomycin A_1,[5] PI-080,[6] urdamycins,[7] and saquayamycins,[8] have been isolated (Figure 1). The most structurally basic compound **1** was isolated in 1967 by Umezawa *et al*. from culture broth of *Streptomyces misawanensis*. It is active against Gram-positive bacteria, Ehrlich ascites carcinoma, and Yoshida rat sarcoma cells.[9] Structurally, its features include a *C*-glycosylated benz[*a*]anthraquinone skeleton and two hydroxyl groups at the ring junction (C-4a and C-12b positions).[10] Compared with other angucycline antibiotics, the main difficulty in the synthesis of aquayamycin-type angucycline antibiotics is construction of the highly oxidized and stereochemically complex AB-ring system, which possesses an angular *cis*-diol. In addition, this system decomposes easily under acidic, basic, and photo-irradiation conditions.[10] Therefore, although it possesses important biological activities and an interesting chemical structure, only two groups have achieved the total synthesis of **1** and related compounds.[11-13]



Compounds	R^1	R^2	R^3	R^4
aquayamycin (**1**)	H	H	H	H
vineomycin A_1	**S**$_3$	H	H	**S**$_3$
PI-080	**S**$_4$	H	H	**S**$_3$
saquayamycin A	**S**$_3$	H	H	**S**$_2$
urdamycin A	H	**S**$_1$	**S**$_5$	H
derhodinosyl-urdamycin A	H	H	**S**$_5$	H

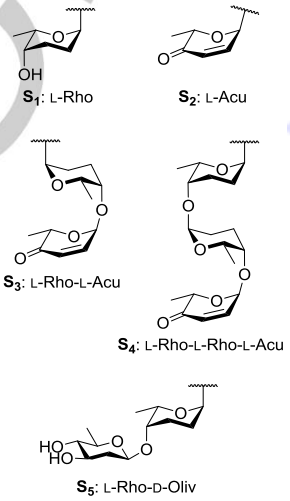


Figure 1. Chemical structures of representative aquayamycin-type angucycline antibiotics. L-Rho = L-rhodinose, L-Acu = L-aculose, D-Oliv = D-olivose.

Suzuki *et al.* achieved the total synthesis of **1** in 2000.[11] Their strategy involves Hauser annulation of *C*-glycosylphthalide **3** and cyclohexanone **4** to construct the BCD-ring system, and intramolecular pinacol coupling reaction of ketoaldehyde **2** to form the A-ring with an angular *cis*-diol (Scheme 1A). The research group of Zhu reported the total synthesis of the related compound, derhodinosylurdamycin A, in 2015, using modified Suzuki's strategy to construct the aglycon moiety.[12] This strategy enabled construction of the unstable AB-ring system in a highly stereoselective manner during a late stage of the synthesis. However, preparation of the key intermediates **3** and **4** required 24 and 23 steps, respectively, from commercially available starting materials **5**-**7**. In addition, a total of 60 steps were required for the total synthesis of **1** (see Supporting Information for a summary). Thus, development of a new approach to the total synthesis of **1** that involves fewer steps is needed for investigations such as SAR study and drug discovery is highly desirable.

The present report describes a novel synthetic approach for **1** that has 16 fewer steps than the previously reported synthesis and has three major features: 1) highly diastereoselective 1,2-addition of easily prepared *C*-glycosyl naphthyllithium and a cyclic ketone to connect the CD-ring and A-ring, 2) indium-mediated site-selective allylation rearrangement of naphthoquinone, and 3) diastereoselective intramolecular pinacol coupling for constructing the B-ring.

A retrosynthetic analysis is shown in Scheme 1B. The B-ring moiety was constructed from the known intermediate **8**[11a] during a late stage by intramolecular diastereoselective pinacol

[*] S. Kusumi, H. Nakayama, T. Kobayashi, H. Kuriki, Y. Matsumoto, Prof. Dr. D. Takahashi, Prof. Dr. K. Toshima
Department of Applied Chemistry, Faculty of Science and Technology, Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522 (Japan)
E-mail: toshima@applc.keio.ac.jp

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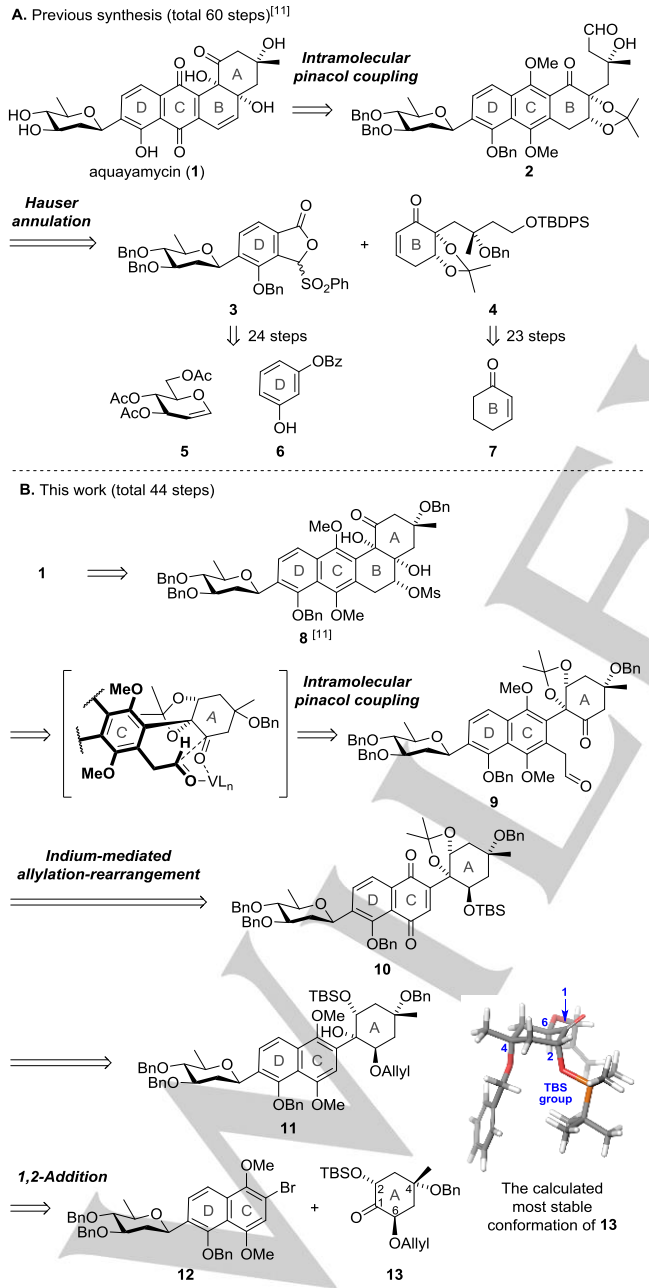
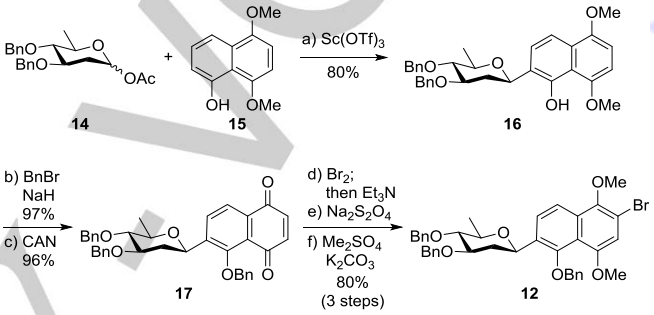
coupling of ketoaldehyde **9**. Diastereoselectivity was expected to be obtained by approach of the vanadium complex from the convex face of **9**. Compound **9** would be prepared by two-carbon elongation of the naphthalene **11** by indium-mediated allylation-rearrangement[14] of the corresponding naphthoquinone **10**. The connection of the CD-ring and A-ring would be achieved *via* diastereoselective 1,2-addition of naphthyllithium species, derived from bromonaphthalene **12**, to an appropriately functionalized cyclic ketone **13**. Calculations indicated that the α-face of **13** was more crowded than the β-face, due to the bulkiness of the TBS group on the adjacent axial hydroxyl group (the most stable conformation of **13** was calculated using B3LYP/6-31G*; see Supporting Information).



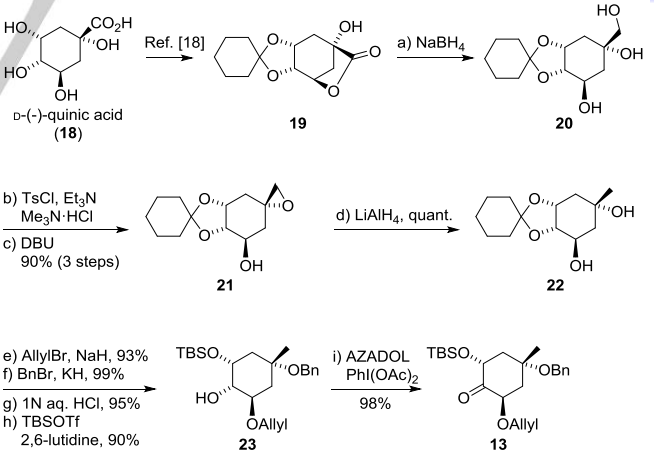
Scheme 1. Comparison of retrosynthetic analyses of aquayamycin (**1**).

Highly functionalized **13** would be prepared from commercially available D-(-)-quinic acid as a chiral source.

The synthesis of bromonaphthyl *C*-glycoside **12** is outlined in Scheme 2. After optimizing conditions for *C*-glycosylation, $Sc(OTf)_3$-catalyzed *C*-glycosylation[15] of D-olivosyl acetate **14** and naphthol **15**[16] proceeded smoothly to produce *C*-glycoside **16** in high yield with excellent β-stereoselectivity (80% yield, α:β = 1:>99). The phenolic hydroxyl group of **16** was benzylated, and the resulting naphthalene was oxidized using CAN to give naphthoquinone **17** in high yield. Regioselective bromination, followed by sodium dithionite reduction and subsequent methylation using Me_2SO_4 and K_2CO_3,[17] afforded **12** in good yield.



Scheme 2. Synthesis of bromonaphthyl *C*-glycoside **12**. Reagents and conditions: a) $Sc(OTf)_3$, Drierite®, DCE, -30 to -10 ºC, 80%; b) BnBr, NaH, DMF, 0 ºC, 97%; c) CAN, MeCN-H_2O, 0 ºC, 96%; d) Br_2, $CHCl_3$, -60 ºC; then Et_3N, -60 ºC, e) aq. $Na_2S_2O_4$, $NaHCO_3$, CH_2Cl_2-Et_2O, RT; f) Me_2SO_4, K_2CO_3, acetone, reflux, 80% (3 steps). CAN = cerium(IV) ammonium nitrate, DCE = 1,2-dichloroethane, DMF = *N,N*-dimethylformamide.



Scheme 3. Synthesis of cyclic ketone **13**. Reagents and conditions: a) $NaBH_4$, EtOH, RT; b) TsCl, Et_3N, Me_3N·HCl, MeCN, 0 ºC; c) DBU, benzene, RT, 90% (3 steps); d) $LiAlH_4$, THF, RT, quant.; e) AllylBr, NaH, DMF, 0 ºC, 93%; f) BnBr, KH, DMF, 0 ºC, 99%; g) 1 N aq. HCl, dioxane, 50 ºC, 95%; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC, 90%; i) AZADOL®, $PhI(OAc)_2$, CH_2Cl_2-phosphate buffer (pH 7), RT, 98%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran, AZADOL® = 2-hydroxy-2-azaadamantane.

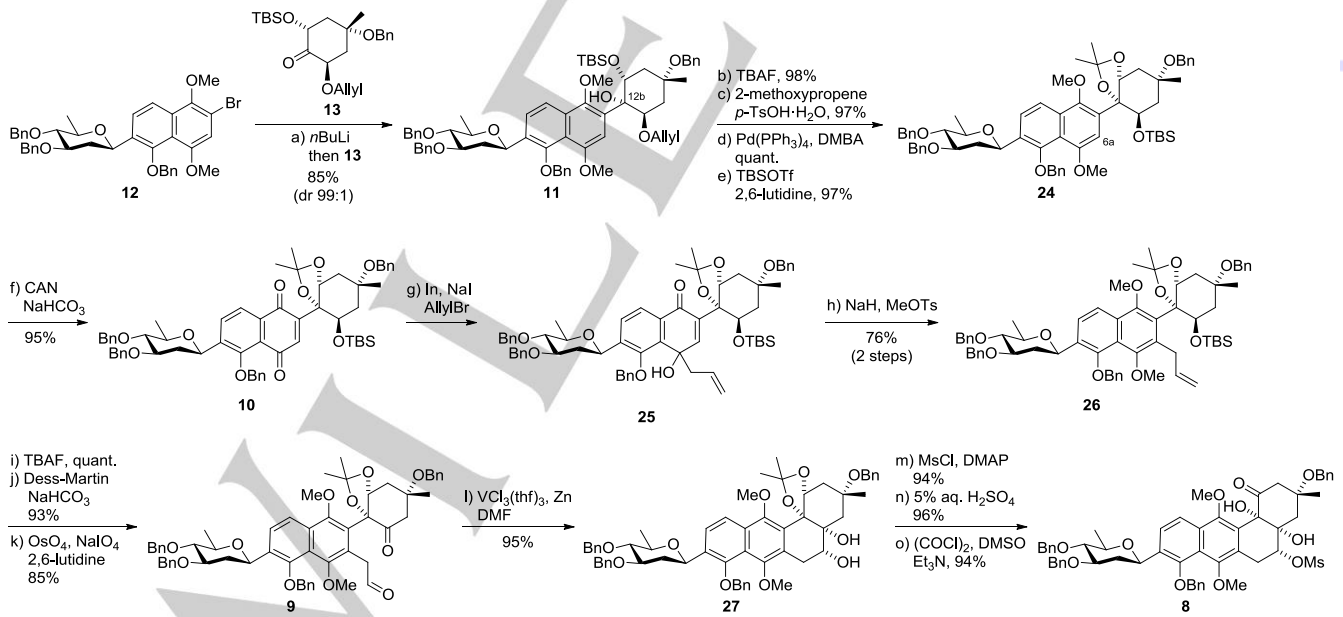
Next, the highly functionalized cyclic ketone **13** was synthesized (Scheme 3). The lactone **19**,[18] derived from D-(-)-

quinic acid (**18**), was reduced by $NaBH_4$ to afford triol **20**. Tosylation of the primary alcohol, followed by intramolecular substitution using DBU as base and reduction of the resulting epoxide **21** using $LiAlH_4$, gave diol **22**. Protecting group manipulations of **22** (1. allylation of the secondary alcohol; 2. benzylation of the tertiary alcohol; 3. deprotection of the cyclohexylidene acetal; 4. selective silylation of the secondary alcohol) and AZADO-mediated oxidation[19] of the remaining secondary alcohol gave cyclic ketone **13** in high yield.

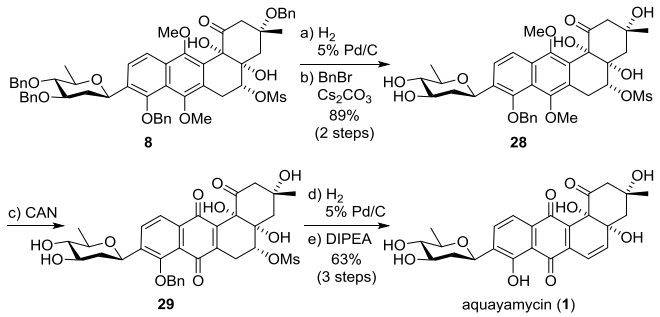
With the key fragments prepared, connecting the A-ring and CD-ring was investigated (Scheme 4). Bromonaphthalene **12** was lithiated with *n*BuLi, followed by addition of the cyclic ketone **13** to the resulting naphthyllithium. Reaction proceeded smoothly to afford **11** in good yield with excellent diastereoselectivity (99:1). Efforts to determine the stereochemistry of **11** at this stage failed, therefore, stereochemistry of the tertiary alcohol at C-12b position (aquayamycin-based numbering) was confirmed after the pinacol coupling reaction (*vide infra*), and the desired diastereomer was found to be obtained as expected. Next, **11** was converted into **24** by 4-step protecting group manipulations (1. desilylation; 2. acetonide protection; 3. deallylation;[20] 4. silylation) in each nearly quantitative yield.

The next challenge was construction of the B-ring moiety. Initially, introduction of an allyl group at the C-6a position (aquayamycin-based numbering) in **24** was examined by halogenation or metalation, but these attempts failed. However, after extensive effort, introduction of allyl group was achieved *via* the naphthoquinone **10**. Thus, after treatment of **24** with CAN, the resulting naphthoquinone **10** was added to a solution of allylindium species, which was prepared *in situ* from indium, sodium iodide, and allylbromide,[14] to form the allylated quinone **25**. Then, one-pot rearrangement-methylation of **25** was conducted using NaH and MeOTs to afford **26** in 76% yield in 2 steps.[21,22] Next, allylnaphthalene **26** was converted into ketoaldehyde **9** by removal of the TBS group, followed by Dess-Martin oxidation and mild oxidative cleavage using OsO_4, $NaIO_4$, and 2,6-lutidine.[23] Next, intramolecular pinacol coupling of ketoaldehyde **9** was examined utilizing a Pedersen modified procedure.[24] Results showed that the desired diol **27** was obtained successfully in high yield as a single diastereomer. Compound **27** was converted into the known bis-acetonide to confirm the stereochemistry.[25,26] The high stereoselectivity observed in this reaction was due to reaction of the aldehyde from the convex face of **9**, along with the expected chelation of the 1,2-diol with a vanadium(II) complex.[24] Finally, mesylation of the secondary alcohol of **27**, followed by removal of the acetonide group and Swern oxidation, afforded the known intermediate **8** in high yield.

Intermediate **8** was converted into aquayamycin (**1**) by a modified procedure (Scheme 5).[11a] Deprotection of all benzyl ethers of **8** over 5% Pd/C catalyst,[27,28] and the resulting hexa-ol was mono-benzylated using Cs_2CO_3 to afford **28**. Compound **28** was oxidized with CAN to afford the naphthoquinone **29**. Finally, hydrogenolysis of **29** and subsequent elimination of the mesylate under mild conditions afforded aquayamycin (**1**) in 63% yield over three steps. Synthetic **1** was identical in all respects with the natural product (see Supporting Information).



Scheme 4. Synthesis of the known intermediate **8**. Reagents and conditions: a) *n*BuLi, THF, -78 ºC; then **13** (2.0 eq.), -78 ºC to RT, 85% (dr 99:1); b) TBAF, THF, RT, 98%; c) 2-methoxypropene, *p*-TsOH·H_2O, benzene, RT, 97%; d) $Pd(PPh_3)_4$, DMBA, dioxane-H_2O (3:1), 50 ºC, quant.; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC, 97%; f) CAN, $NaHCO_3$, MeCN-H_2O, 0 ºC, 95%; g) In, NaI, AllylBr, DMF, -40 to 0 ºC; h) NaH, MeOTs, DMF, 0 ºC to RT, 76% (2 steps), i) TBAF, THF, RT, quant.; j) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 93%; k) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane-H_2O (4:1), RT, 85%; l) $VCl_3(thf)_3$, Zn, DMF, CH_2Cl_2, RT, 95%; m) MsCl, DMAP, CH_2Cl_2-pyridine (2:5), RT, 94%; n) 5% aq. H_2SO_4-dioxane (1:4), 80 ºC, 96%; o) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -50 to 0 ºC, 94%. TBAF = tetrabutylammonium fluoride, DMBA = dimethylbarbituric acid, DMAP = *N,N*-dimethyl-4-amino pyridine, DMSO = dimethylsulfoxide.



Scheme 5. Completion of total synthesis of **1**. Reagents and conditions: a) H_2, 5% Pd/C, EtOAc-MeOH (1:1), RT; b) BnBr, Cs_2CO_3, DMF, 0 ºC to RT, 89% (2 steps); c) CAN, MeCN-H_2O, 0 ºC; d) H_2, 5% Pd/C, EtOAc-MeOH (1:1), RT; e) DIPEA, dioxane, RT, 63% (3 steps). DIPEA = *N,N*-diisopropylethylamine.

In summary, a highly efficient and practical synthetic route of aquayamycin (**1**) was developed. This novel synthesis features construction of the complex AB-ring system in a highly stereoselective and step-economical manner, utilizing diastereoselective 1,2-addition of *C*-glycosyl naphthyllithium to a cyclic ketone, indium-mediated site-selective allylation-rearrangement, and diastereoselective intramolecular pinacol coupling. This synthetic strategy offers an efficient path to aquayamycin-type angucycline antibiotics. Synthetic studies of other aquayamycin-type angucycline antibiotics, such as vineomycin A_1, are now in progress.

Acknowledgements

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Keywords: natural products • total synthesis • antitumor antibiotics • angucycline antibiotics • aquayamycin

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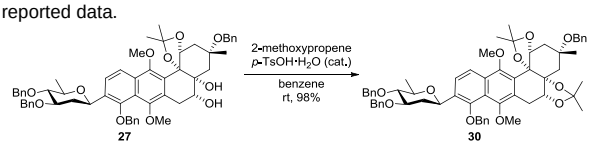
[25] The diol of **27** was protected by acetonide group to afford known bis-acetonide **30**.[26] The structure of **30** was found to be identical with the reported data.



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[27] Since the overreduction at the anomeric position of **8** was observed when the debenzylation of **8** was conducted according to the original procedure using excess amount of 10% Pd/C catalyst, we used catalytic amount of 5% Pd/C in this reaction. This difference may arise from the supplier and type of Pd/C catalyst (see Supporting Information).

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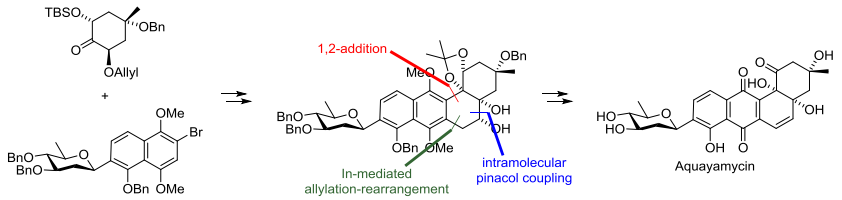

Efficient and practical total synthesis of aquayamycin has been accomplished. The complex tetracyclic ring system was constructed by highly diastereoselective 1,2-addition, indium-mediated site-selective allylation-rearrangement, and diastereoselective intramolecular pinacol coupling.

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