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Total Synthesis of (+)-Awajanomycin

Malte Wohlfahrt,[a] Klaus Harms,[a] and Ulrich Koert*[a]

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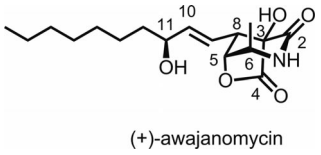
The total synthesis of (+)-awajanomycin has been achieved by asymmetric allylboration of a vicinal tricarbonyl compound as the key step. A substrate-controlled dihydroxylation and subsequent differentiation of diastereotopic ester groups were used to synthesize the γ-lactone substructure. After formation of the δ-lactam, the bicyclic core structure was established. The synthetic strategy and overall efficacy is compared with Huang's route to awajanomycin.

Introduction

The natural product (+)-awajanomycin (**1**; Figure 1) was first isolated in 2006 from the marine-derived fungus *Acremonium sp.* AWA16-1.[1] The name refers to its marine source, sea mud collected from around Awajishima Island (Japan).



(+)-awajanomycin

Figure 1. Structure of (+)-awajanomycin (**1**).

(+)-Awajanomycin (**1**) exhibits cytotoxic activity (IC_{50} for A549 cells 27.5 μg/mL). It possesses a unique bicyclic core structure consisting of a γ-lactone and a δ-lactam. A tertiary OH group is located at C-3 and a side-chain at C-8. The side-chain contains an allylic alcohol with the stereocenter at C-11.

Huang and co-workers achieved the total syntheses of (–)-awajanomycin (*ent*-**1**)[2] as well as (+)-awajanomycin (**1**)[3] and its C-11 epimer. Syntheses of the bicyclic core have been reported by Hiroya et al.[4] and Pritchard and Wilden.[5] We have communicated a total synthesis of (+)-awajanomycin (**1**) achieved by asymmetric allylboration of a *vic*-tricarbonyl compound as the key step.[6] Herein we present the development of our synthetic route in detail and compare this strategy with that of Huang and co-workers.

[a] Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse, 35043 Marburg, Germany
Fax: +49-6421-28-25677
E-mail: koert@chemie.uni-marburg.de

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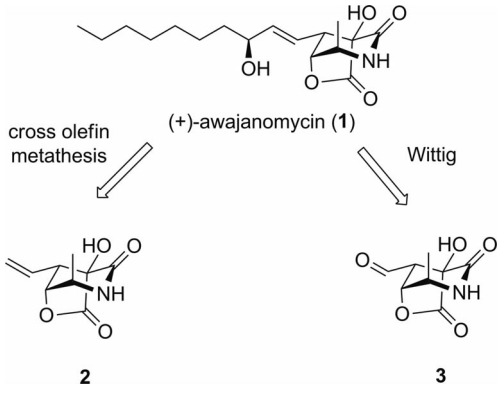
Results and Discussion

Comparative Retrosynthesis

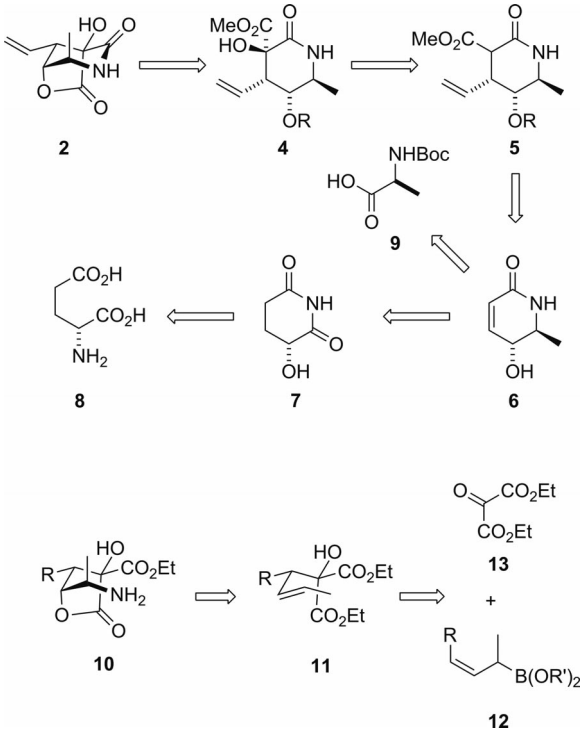
Both groups planned to introduce the C-8 side-chain at the end of the synthesis (Scheme 1). Huang and co-workers used a cross metathesis of the terminal olefin precursor **2**, which has the advantage of tolerating the presence of the unprotected C-11 hydroxy group. We planned to use an (*E*)-selective Wittig reaction of aldehyde **3** with subsequent stereoselective enone reduction.



Scheme 1. Different approaches to the introduction of the C-8 side-chain.

The strategy of Huang and co-workers for the synthesis of compound **2** relied on the early generation of the δ-lactam and the use of C-5 as directing stereocenter for the introduction of the remaining stereocenters (Scheme 2). The γ-lactone was generated late in the synthesis from the hydroxy ester **4**, which is accessible by hydroxylation of the malonic ester lactam **5**. This can be prepared from the α,β-unsaturated δ-lactam **6** by 1,4-addition of vinyl cuprate and trapping of the resulting enolate with $NCCO_2Me$. Two routes lead to lactam **6**: One begins with aspartate **8** and proceeds via imide **7**, the other has *N*-Boc-glycine **9** as the

starting point.[5] According to this plan, (+)-awajanomycin (**1**) was synthesized by Huang and co-workers for the first time in an overall yield of 3.8%.[3]

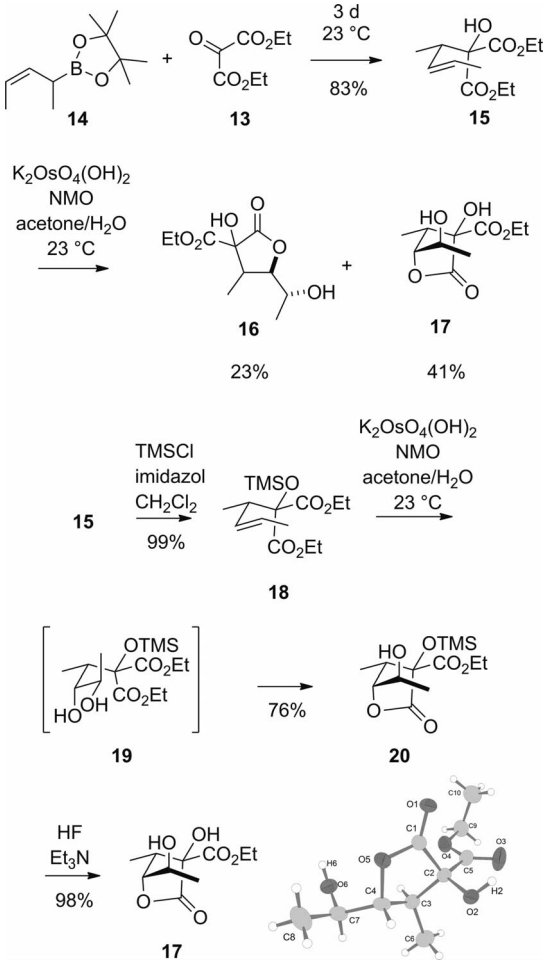


Scheme 2. Comparative retrosynthetic analyses for the bicyclic core structure of awajanomycin: alkene **2** (Huang's route), compound **10** (our approach).

The synthesis of aldehyde **3** or the more general compound **10** should be possible by stereocontrolled functionalization of alkene **11** and subsequent differentiation of the diastereotopic ester groups. The homoallylic alcohol **11** can be prepared from the substituted allylboronate **12** and diethyl mesoxalate **13**. The stereocontrolled allylboration of aldehydes and α-oxo esters is an established methodology.[7] Chiral (*Z*)-pentenylboronates are among the most efficient allylborating reagents for aldehydes,[8] and thus compounds of type **12** should be good candidates for the allylboration of *vic*-tricarbonyl compounds.

Racemic Synthesis of the Bicyclic Core

The synthesis of a racemic model system for the bicyclic core in which the C-8 side-chain is replaced by a methyl group was investigated first (Scheme 3). The allylboration of tricarbonyl compound **13** with racemic boronate **14**[9] gave, in a solvent-free reaction at room temperature, the homoallylic alcohol **15** in very good yield. Dihydroxylation of alkene **15** led to a mixture of products. Chromatographic separation gave a fraction containing stereoisomeric γ-lactone **16** and another of γ-lactone **17**, the unambiguous structural assignment of which was achieved by X-ray crystal structure analysis. Thus, the lack of differentiation of the diastereotopic ester groups in **15** resulted in a lactone mixture. This situation was completely avoided by TMS protection of the tertiary alcohol **15** (**15** → **18**). The resulting homoallylic TMS ether **18** exhibited a clear conformational bias that allowed substrate-controlled dihydroxylation of the (*E*)-alkene. The product of the dihydroxylation **19** underwent direct cyclization to the γ-lactone **20**. Only one of the diastereotopic ester groups in **19** was attacked by one hydroxy group of the diol to produce selectively lactone **20**. After removal of the TMS group, the lactone **17** obtained was identical to the previously prepared sample.

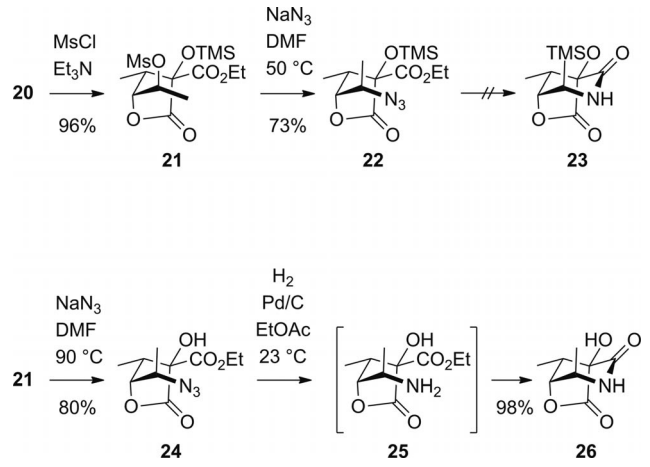


Scheme 3. Allylboration with boronate **14**, subsequent dihydroxylation, and differentiation of the diastereotopic ester groups. The crystal structure of **17** is provided.

Thus, in the case of osmylation of alkene **18**, introduction of the TMS group led to stereoselective dihydroxylation and subsequent differentiation of the diastereotopic ester groups. The TMS protecting group contributed actively through its conformative effect to the success of this reaction sequence.

The formation of the δ-lactam was examined next (Scheme 4). Conversion of the secondary alcohol **20** into the mesylate **21** then led to the azide **22**. Attempts to form the lactam ring by azide reduction (**22** → **23**) failed. The bulky TMS group inhibits lactam formation and had to be removed. This was possible if the reaction leading to the azide was conducted at higher temperatures. The resulting

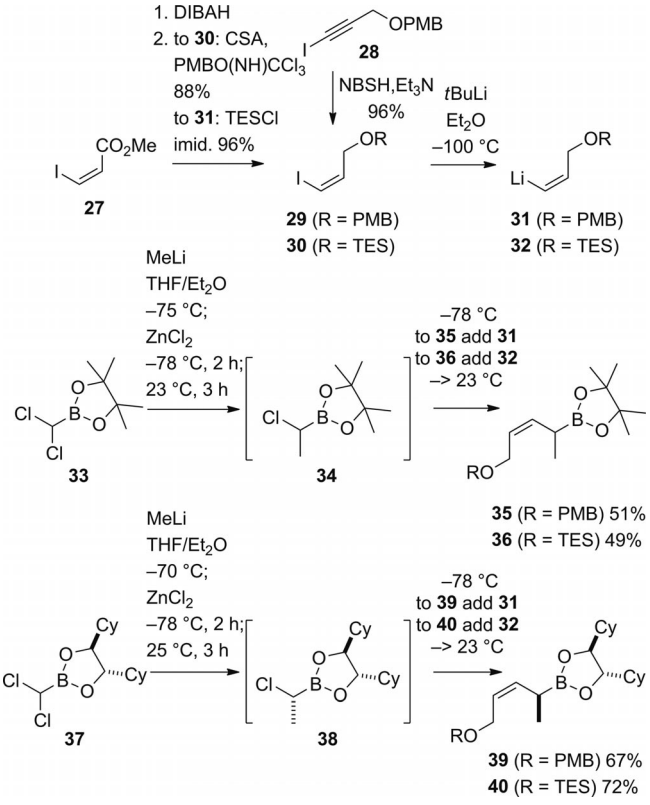
azido alcohol **24** could be cleanly reduced to the amino ester **25**, which spontaneously cyclized to the lactam **26**. Compound **26**, the model system for the bicyclic core with a methyl group as the C-8 side-chain, was accessible in six steps from the vicinal tricarbonyl compound **13** in 47% yield.



Scheme 4. Strategy for lactam formation.

Synthesis of the Bicyclic Core with a Protected C-8 Hydroxymethyl Group

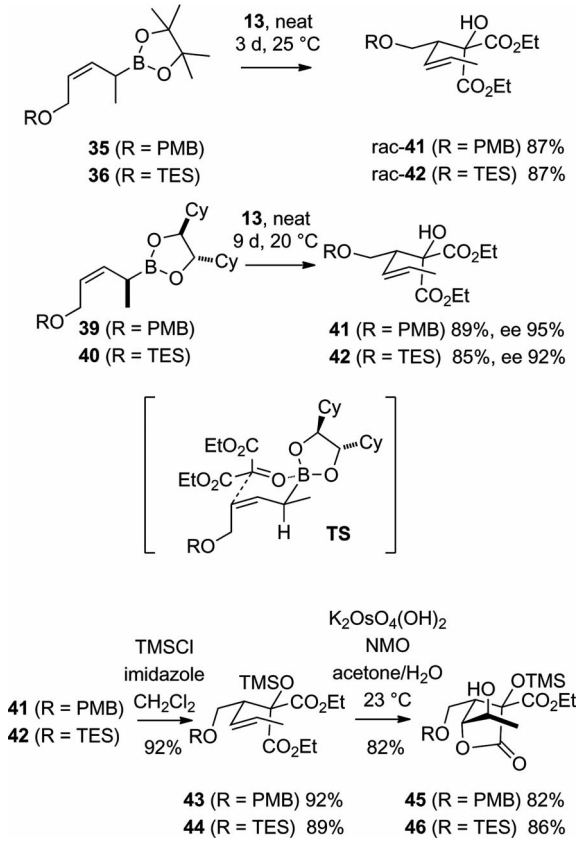
To synthesize aldehyde **3**, the corresponding alcohol with a hydroxymethyl group at C-8 is a suitable precursor. The allylboration strategy required for this task the preparation of an *O*-protected γ-(hydroxymethyl)allylboronate (Scheme 5). The racemic pinacol-derived substituted allylboronates **35** and **36** were prepared first. Then, the enantiomerically pure substituted allylboronates **39** and **40** were synthesized. 1,2-Dicyclohexylethane-1,2-diol was chosen as chiral director because of its known high stereoselectivity in reactions of α,γ-disubstituted allylboronates with aldehydes.[8,10] Methyl (*Z*)-β-iodoacrylate (**27**)[11] was converted into the (*Z*)-alkenyl iodides **29** and **30**. Compound **29** is also accessible from the iodoalkyne **28**[12] by diimide reduction using *o*-nitrobenzenesulfonyl hydrazide (NBSH).[13] The α,γ-disubstituted allylboronates were prepared by Matteson's method starting from (dichloromethyl)-boronates.[14] The required (*Z*)-alkenyllithium reagents **31** and **32** were prepared by iodine/lithium exchange in the corresponding (*Z*)-alkenyl iodides **29** and **30**, respectively, and used directly furthering the preparation of the allylboronates. Treatment of the (dichloromethyl)boronate **33**[15] with methyllithium gave the (1-chloroethyl)boronate **34**, which upon addition of the alkenyllithium reagent **31** led to the (racemic) α,γ-disubstituted allylboronate **35**, which could be purified by silica gel chromatography. The disubstituted allylboronate **36** was prepared by using the alkenyllithium reagent **32**. The enantiomerically pure (*S*,*S*)-(dichloromethyl)boronate **37** was prepared according to the method of Hoffmann et al.[8] by Sharpless asymmetric dihydroxylation of (*E*)-stilbene. Treatment of the (dichloromethyl)boronate **37** with methyllithium gave the (1-chloroethyl)boronate **38**, which upon addition of the alkenyllithium reagent **31** led to the chiral α,γ-disubstituted (2*S*)-allylboronate **39**. The disubstituted allylboronate **40** was prepared by using the alkenyllithium reagent **32**. The enantiomerically pure reagents **39** and **40** were purified by silica gel chromatography.



Scheme 5. Preparation of racemic allylboronates **35** and **36** and enantiomerically pure allylboronates **39** and **40**.

The allylboration of the *vic*-tricarbonyl compound **13** with the different racemic and enantiomerically pure α,γ-disubstituted allylboronates prepared as described above was the next task (Scheme 6). The reactions of the racemic allylboronates **35** and **36** proceeded smoothly to deliver the homoallylic alcohols *rac*-**41** and *rac*-**42**, respectively. The reactions with enantiomerically pure allylboronates **39** and **40** required longer reaction times to obtain the desired products **41** and **42** in more than 80% yield. The enantioselectivity of the allylboration reaction (95% *ee* for **41**, 92% *ee* for **42**) was determined by ^{19}F NMR analysis of the Mosher ester derived from the hydroxy lactones **45** and **46**. The stereochemical outcome of the asymmetric allylboration of the vicinal tricarbonyl compound **13** can be rationalized by a cyclic Zimmerman–Traxler-type transition state **TS**.[8] The α stereocenter of the allylboronate acts as director by placing the methyl group in an equatorial position, which leads, by avoidance of 1,3-allylic strain, to differentiation of the prochiral olefin sides and a backside attack of the carbonyl group. Thus, tricarbonyl compounds such as

13 behave in asymmetric allylboration reactions in a comparable way to aldehydes.

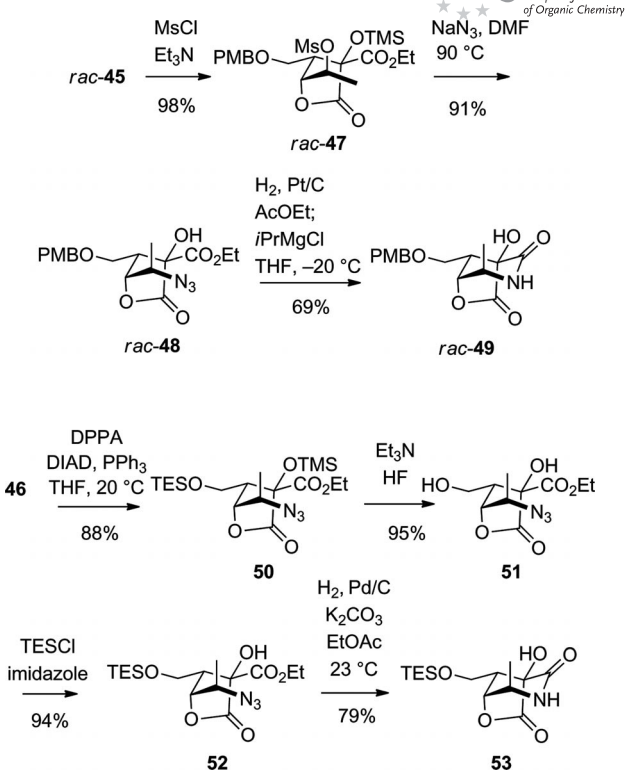


Scheme 6. Stereoselective allylboration reactions with racemic boronates **35** and **36** and enantiomerically pure boronates **39** and **40**, and subsequent dihydroxylation/lactonization.

Homoallylic alcohols **41** and **42** were both converted into the corresponding TMS ethers **43** and **44**. Stereoselective dihydroxylation and subsequent differentiation of the diastereotopic ester groups resulted in the formation of the hydroxy lactones **45** and **46**.

The conversion of hydroxy lactone **45** into the bicyclic lactam **49** was possible by the route developed for lactam **26**. This reaction sequence was performed on the racemic lactone **45** (Scheme 7) and proceeded via the mesylate *rac*-**47**. The azide *rac*-**48** was obtained, which led upon azide reduction to the corresponding amino ester. Cyclization to the lactam *rac*-**49** required activation by isopropylmagnesium chloride. The bicyclic structure of compound *rac*-**49** was unambiguously assigned by single-crystal X-ray analysis.[6]

The enantiomerically pure hydroxy lactone **46** was the starting point for the reaction sequence leading to lactam **53** (Scheme 7). Transformation of the secondary alcohol into the azide under Mitsunobu conditions[16] gave compound **50**. After deprotection of the tertiary alcohol (**50** → **51** → **52**), azide reduction resulted in the spontaneous formation of the bicyclic lactam **53**.

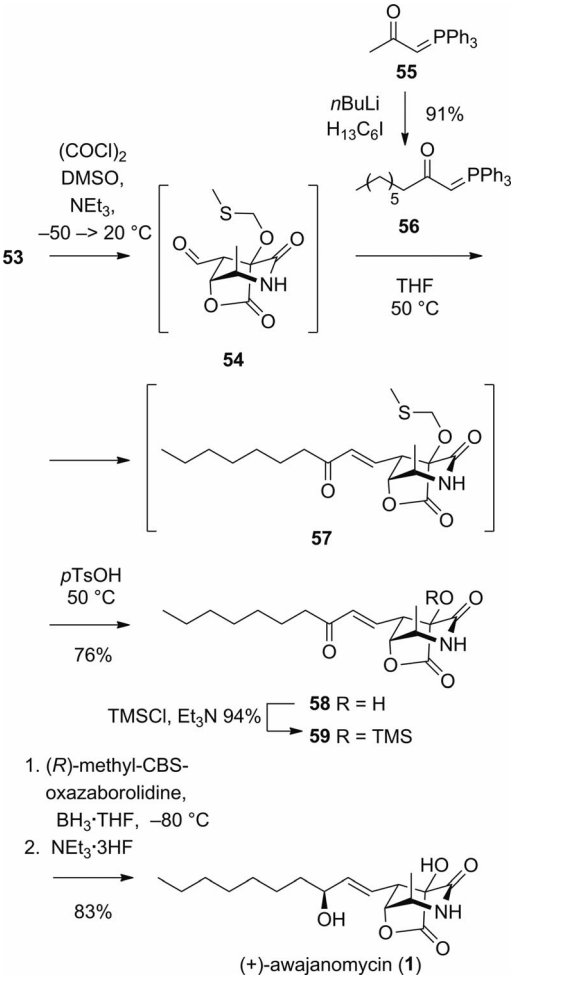


Scheme 7. Formation of lactams *rac*-**49** and **53**.

Attachment of the C-8 Side-Chain and Final Steps

The final part of the synthesis required the introduction of the C-8 side-chain. The deprotection of the PMB ether in compound *rac*-**49** was unexpectedly problematic. Neither oxidative (DDQ) nor hydrogenolytic (Pd/C) conditions gave satisfactory or reproducible yields. One cause of the problem could have been the high polarity and low solubility of the primary alcohol in organic media. To avoid the isolation of the free alcohol, the synthetic plan was revised to use the TES ether instead of the PMB ether. A primary TES ether can be oxidized directly to the aldehyde by avoiding the isolation of the alcohol.[17] Oxidation of the primary TES ether **53** under Swern conditions gave the intermediate aldehyde **54**, which was directly converted with the ylene **56** into enone **58** (Scheme 8). The tertiary hydroxy group in compound **53** was converted at the aldehyde stage into the S,O-acetal, which was cleaved before purification of enone **57**. Enone **58**, the product of this Swern/Wittig sequence was isolated in 76% yield. The ylene **56** was accessible by alkylation of ylene **55**.[18]

The final task in the synthesis required the stereoselective reduction of the ketone. A substrate-controlled reduction of compound **58** with $NaBH(OAc)_3$ showed no diastereoselectivity. Next, a CBS reduction[19] was examined, which gave unsatisfactory diastereoselectivity (2:1) in the presence of the free tertiary alcohol. An optimal stereoselective CBS reduction (>95:5) was possible when the TMS ether **59** was



Scheme 8. Attachment of the C-8 side-chain and completion of the synthesis.

used as the starting material (Scheme 8). After TMS deprotection, the target compound (+)-awajanomycin (**1**) was obtained. The spectral properties and optical rotation of synthetic (+)-awajanomycin (**1**) were identical to those reported for the natural product.[1]

Conclusions

An efficient, versatile, and enantioselective route to the natural product (+)-awajanomycin (**1**) has been developed. [22.5% over 10 steps (from **13**) compared with 3.8% over 13 steps in ref.[3]]. The key steps in this procedure are the asymmetric allylboration of a *vic*-tricarbonyl compound, a substrate-controlled alkene dihydroxylation with subsequent differentiation of the diastereotopic ester groups, and a catalyst-controlled reduction of an enone. The crucial role of the silyl protecting group on the tertiary alcohol in achieving the introduction of three out of the five stereocenters is noteworthy.

Experimental Section

Representative Allylboration of a *vic*-Tricarbonyl Compound (40 + 13 → 42): Boronic ester **40** (2.76 g, 3.65 mmol) was added to diethyl mesoxolate (**13**; 1.4 mL, 9.13 mmol), and the mixture was stirred in a sealed tube at 20 °C for 9 d. The reaction mixture was subjected to chromatographic purification (silica gel, 150 g; pentane/acetone, 20:1) to yield olefin **42** (2.02 g, 5.40 mmol, 85%) as a colorless oil. TLC (pentane/acetone, 20:1): R_f = 0.31. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.64 (dq, J = 15.3, 6.4 Hz, 1 H, 4′-CH), 5.35 (ddd, J = 15.4, 9.4, 1.6 Hz, 1 H, 3′-CH), 4.36–4.11 (m, 5 H, 2 OCH_2CH$_3$, 2-OH), 3.73 (dd, J = 10.0, 7.6 Hz, 1 H, 1′-CH_aH$_b$), 3.61 (dd, J = 9.9, 5.8 Hz, 1 H, 1′-CH$_a$$H_b$), 3.24 (ddd, J = 9.2, 7.5, 5.9 Hz, 1 H, 2′-CH), 1.63 (dd, J = 6.4, 1.5 Hz, 3 H, 4′-CH$_3$), 1.27 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 1.24 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 0.92 [t, J = 7.8 Hz, 9 H, Si(CH$_2$CH_3)$_3$], 0.56 [q, J = 7.9 Hz, 6 H, Si(CH_2CH$_3$)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 and 170.0 (CO), 130.6 (3′-CH), 126.0 (4′-CH), 80.8 (2-C$_q$), 63.2 (1′-CH$_2$), 62.3 and 62.3 (2 C, 2 OCH_2CH$_3$), 49.7 (2′-CH), 18.2 (4′-CH$_3$), 14.2 and 14.1 (2 C, 2 OCH$_2$$CH_3$), 6.8 [3 C, Si(CH$_2$-$CH_3$)$_3$], 4.3 [3 C, Si($CH_2CH_3$)$_3$] ppm. FTIR (neat): $\tilde{\nu}$ = 3496 (br. w), 2955 (w), 2912 (w), 2877 (w), 1738 (s), 1461 (w), 1414 (w), 1368 (w), 1299 (m), 1248 (m), 1213 (s), 1150 (s), 1099 (s), 1007 (m), 968 (m), 923 (m), 863 (w), 818 (m), 794 (m), 725 (s), 668 (w), 448 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{34}O_6SiNa$ [M + Na]$^+$ 397.2017; found 397.2008. Specific rotations (c = 1.02, $CHCl_3$, T = 22 °C): $[\alpha]_D$ = –27.7, $[\alpha]_{578}$ = –28.8, $[\alpha]_{546}$ = –32.9, $[\alpha]_{436}$ = –59.0, $[\alpha]_{365}$ = –97.4.

Supporting Information (see footnote on the first page of this article): Full experimental details and spectroscopic characterizations of all new compounds.

Acknowledgments

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[1] J.-H. Jang, K. Kanoh, K. Adachi, Y. Shizuri, *J. Nat. Prod.* **2006**, *69*, 1358–1360.
[2] R. Fu, J. Chen, L. C. Guo, J. L. Ye, Y. P. Ruan, P. Q. Huang, *Org. Lett.* **2009**, *11*, 5242–5245.
[3] R. Fu, J. L. Ye, X.-J. Dai, Y. P. Ruan, P. Q. Huang, *J. Org. Chem.* **2010**, *75*, 4230–4234.
[4] K. Hiroya, K. Kawamoto, K. Inamoto, T. Sakamoto, T. Doi, *Tetrahedron Lett.* **2009**, *50*, 2115–2118.
[5] D. R. Pritchard, J. D. Wilden, *Tetrahedron Lett.* **2010**, *51*, 1819–1821.
[6] a) M. Wohlfahrt, K. Harms, U. Koert, *Angew. Chem.* **2011**, *123*, 8554–8556; *Angew. Chem. Int. Ed.* **2011**, *50*, 8404–8406; b) M. Wohlfahrt, K. Harms, U. Koert, *Angew. Chem.* **2011**, *123*, 10945; *Angew. Chem. Int. Ed.* **2011**, *50*, 10742.
[7] H. Lachance, D. G. Hall, *Org. React.* **2008**, *73*, 1–608.
[8] R. W. Hoffmann, K. Ditrich, G. Köster, R. Stürmer, *Chem. Ber.* **1989**, *122*, 1783–1789.
[9] M. W. Andersen, B. Hildebrandt, G. Köster, R. W. Hoffmann, *Chem. Ber.* **1989**, *122*, 1777–1782.
[10] W. C. Hiscox, D. S. Matteson, *J. Org. Chem.* **1996**, *61*, 8315–8316.
[11] a) Z. Li, X. Lu, S. Ma, *J. Org. Chem.* **1992**, *57*, 709–713; b) E. Piers, T. Wong, P. D. Coish, C. Rogers, *Can. J. Chem.* **1994**, *72*, 1816–1819.
[12] K.-S. Masters, B. L. Flynn, *J. Org. Chem.* **2008**, *73*, 8081–8084.
[13] A. G. Myers, B. Zheng, M. Movassaghi, *J. Org. Chem.* **1997**, *62*, 7507.

[14] D. S. Matteson, *Acc. Chem. Res.* **1988**, *21*, 294–300.
[15] P. G. M. Wuts, P. A. Thompson, *J. Organomet. Chem.* **1982**, *234*, 137–141.
[16] a) P.-O. Johansson, Y. Chen, A. K. Belfrage, M. J. Blackman, I. Kvarnström, K. Jansson, L. Vrang, E. Hamelink, A. Hallberg, A. Rosenquist, B. Samuelsson, *J. Med. Chem.* **2004**, *47*, 3353–3366; b) K. Ninomiya, T. Shioiri, S. Yamada, *Tetrahedron* **1974**, *30*, 2151–2157.
[17] A. Rodriguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett.* **1999**, *40*, 5161–5164.
[18] M. P. Cooke Jr., *J. Org. Chem.* **1973**, *38*, 4082–4084.
[19] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

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