Total Synthesis

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Asymmetric Allylboration of *vic*-Tricarbonyl Compounds: Total Synthesis of (+)-Awajanomycin**

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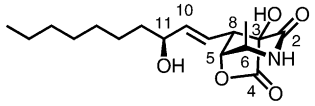
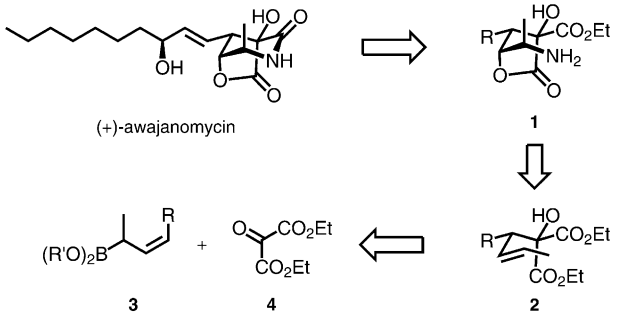
(+)-Awajanomycin was isolated from the marine fungus *Acremonium* sp. AWA16-1, which was collected from sea mud off Awajishima Island (Japan).[1] Its bioactivity (IC_{50} for A549 cells: 27.5 $\mu g\,mL^{-1}$) and its unique γ-lactone, δ-lactam core structure brought the compound to the attention of synthetic chemists. So far, one total synthesis[2] and two approaches to the bicyclic core[3] have been reported.



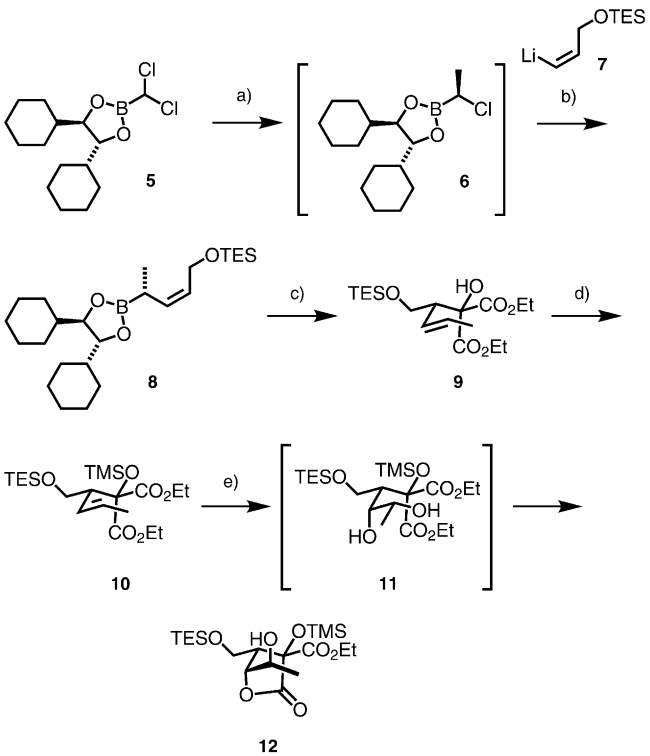
(+)-awajanomycin

A synthetic strategy for awajanomycin in which an asymmetric allylboration of a *vic*-tricarbonyl compound is the key step is shown in Scheme 1. The bicyclic core of the natural product could be assembled from the amino ester **1** by lactam formation. The step from olefin **2** to the γ-lactone **1** requires the stereoselective aminohydroxylation of the double bond and differentiation of the diastereotopic ester groups. Compound **2** could be accessible by the stereocontrolled addition of the α,γ-disubstituted allylboronate **3** to diethyl ketomalonate **4**. While the stereocontrolled allylboration of aldehydes and α-keto esters is an established methodology,[4] the allylboration of *vic*-tricarbonyl compounds has neither been explored nor applied to natural product synthesis. Chiral *Z*-pentenylboronates are among the most efficient allylborating reagents for aldehydes,[5] and thus compounds of type **3** should be good candidates for the present challenge. 1,2-Dicyclohexylethane-1,2-diol is an excellent chiral director for the introduction of the stereocenter in the α,γ-disubstituted allylboronate **3**.[5,6]

The one-pot preparation of allylboronate **8**, a compound suitable for the awajanomycin synthesis, started with the dichloromethylboronate **5** (Scheme 2).[5] Reaction with methyllithium and $ZnCl_2$ resulted in the intermediate **6**, which upon addition of the *Z*-alkenyllithium reagent **7**[7] gave the desired chiral Z-pentenylboronate **8**.[5,8] Treatment of allylboronate **8** with 2.5 equiv of the *vic*-tricarbonyl compound **4** without solvent at room temperature for nine days gave the allylboration product **9** in 85% yield with 92% *ee* (deter-



Scheme 1. Retrosynthetic analysis for (+)-awajanomycin with an allylboration as a key step.



Scheme 2. Stereocontrolled allylboration, dihydroxylation, and differentiation of the diastereotopic ester groups. a) MeLi, $ZnCl_2$, THF, −78→20°C; b) **7**, −78→ 20°C, 72%; c) 2.5 equiv diethyl mesoxolate, 9 d, 85%; d) TMSCl, imidazole, CH_2Cl_2, 89%; e) 5 mol% K_2OsO_4-$(OH_2)_2$, 2.5 equiv NMO, *t*BuOH/H_2O 2:1, 86%. NMO = 4-methylmorpholine *N*-oxide, TMS = trimethylsilyl.

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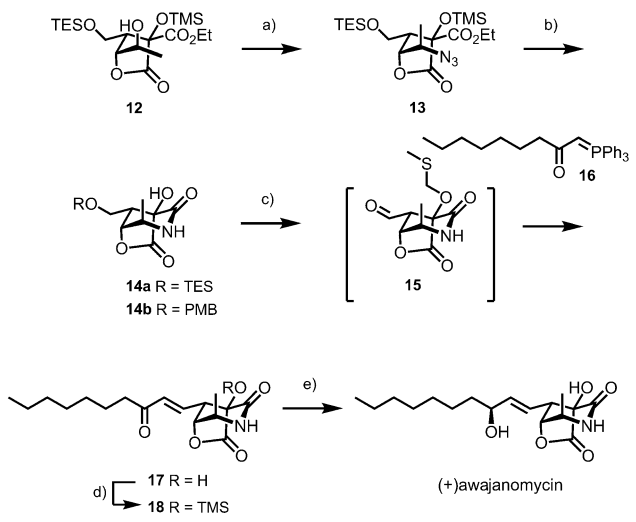
mined by ^{19}F NMR analysis of the Mosher ester derived from hydroxy lactone **12**). The dihydroxylation of alkene **9** led to a complex mixture of stereoisomeric γ- and δ-lactones. This situation changed completely upon TMS protection of the tertiary hydroxy group. The resulting homoallylic TMS ether **10** exhibited a clear conformational bias which allowed the substrate-controlled dihydroxylation of the *E* alkene. The product of the dihydroxylation, **11**, underwent direct cyclization to give the γ-lactone **12**. Only one of the diastereotopic ester groups in **11** was attacked by the diol to produce selectively the lactone **12**. Thus, the introduction of the TMS group led to stereoselective dihydroxylation and subsequent differentiation of the diastereotopic ester groups. Clearly, the protecting group determines the preferred conformation and contributes actively to the success of this reaction sequence.

The secondary alcohol **12** was converted into azide **13** under Mitsunobu conditions (Scheme 3).[9] For the subsequent formation of the δ-lactam, the TMS group on the tertiary hydroxy group at C3 had to be removed first. Then, the catalytic hydrogenation of the azide gave an amine which spontaneously cyclized to give the desired lactam **14a**. The structural assignment of the bicyclic structure of compound **14a** was possible by comparison with the spectroscopic data of the corresponding *p*-methoxybenzyl (PMB) analogue, *rac*-**14b**. Compound *rac*-**14b** was synthesized along the same route and its structure was verified by X-ray structural analysis (Figure 1).[10]



Scheme 3. δ-Lactam formation and completion of the awajanomycin synthesis. a) PPh_3, DIAD, DPPA, THF, 88%; b) $NEt_3 \cdot 3HF$, CH_2Cl_2; TESCl, imidazole, CH_2Cl_2, 84% over 2 steps; Pd/C, H_2, K_2CO_3, EtOAc, 79%; c) $(COCl)_2$, DMSO, NEt_3, −50→20 °C; ylene **16**, 50 °C; *p*TsOH 50 °C, 76%; d) TMSCl, Et_3N, THF, 94% e) (*R*)-methyl-CBS-oxazaborolidine, $BH_3 \cdot$THF, toluene, −80 °C; $NEt_3 \cdot 3HF$, THF, 83%. DIAD = diisopropyl azodicarboxylate, DPPA = diphenylphosphoryl azide, TES = triethylsilyl, TsOH = *p*-toluenesulfonic acid.

The endgame of the synthesis consisted of the introduction of the side chain. Swern oxidation[11] of the primary TES ether **14a** gave the corresponding labile aldehyde **15**, which was not purified but subjected directly to a Wittig reaction with ylene **16**[12] to deliver the enone **17**. The tertiary hydroxyl group in compound **14** was converted at the aldehyde stage into the S,O acetal, which was cleaved before purification of the enone **17**. The final task in the synthesis required the stereoselective reduction of the enone tor give the allylic alcohol with *S* configuration. Attempted substrate-controlled reduction of compound **17** with $NaBH(OAc)_3$ was diastereoselective. The CBS reduction of enone **17** bearing the free tertiary alcohol resulted in 3:1 selectivity.[13] Optimal stereoselective CBS reduction (> 95:5) was possible when TMS ether **18** was used as the starting material. The spectroscopic properties and optical rotations of synthetic (+)-awajanomycin were identical to those for the natural product.[1]

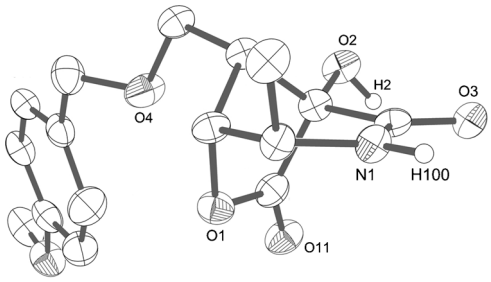


Figure 1. X-ray crystal structure of compound *rac*-**14b** showing the bicyclic core structure of awajanomycin.

In conclusion, an efficient stereoselective total synthesis of (+)-awajanomycin was achieved (22.5% yield over 10 steps (from **4**) compared to 3.8% yield over 13 steps in Ref. [2 < -litr b >]). Key steps were an asymmetric allylboration of a *vic*-tricarbonyl compound, a substrate-controlled alkene dihydroxylation with subsequent differentiation of diastereotopic ester groups, and a catalyst-controlled reduction of an enone. The crucial role of the silyl protecting group on the tertiary alcohol in the introduction of three out of the five stereocenters is noteworthy.

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