Formal Synthesis of AB3217-A from Anisomycin Using a Directed Benzylic Oxidation

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Abstract: A formal synthesis of the insecticidal natural product AB3217-A involving an unusual diastereoselective benzylic oxidation is described.

Key words: natural product, anisomycin, AB3217-A, benzylic oxidation, insecticide

AB3217-A and its -B and -C congeners (Figure 1) were isolated in 1992 from the fermentation broth of *Streptomyces platensis* and were shown to have marked activity against two spotted spider mites as well as some herbicidal properties.[1] These compounds have a unique structure, consisting of deacetylanisomycin and β-D-xylofuranose linked through glycosidic and ether bonds to form a nine-membered ring containing three oxygen atoms.

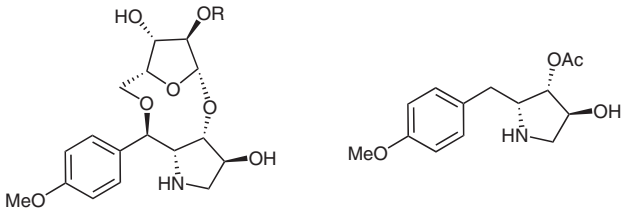
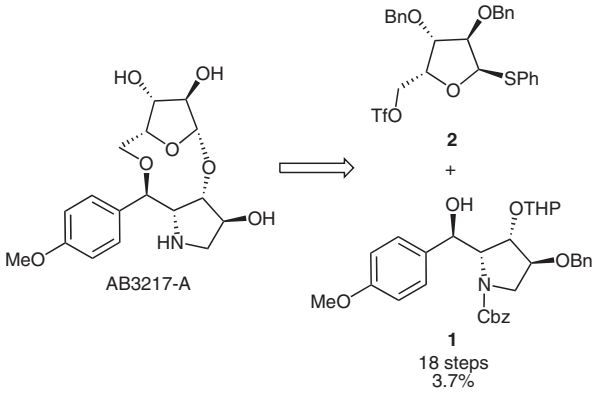


Figure 1 Structure of AB3217-A, -B, -C, and anisomycin

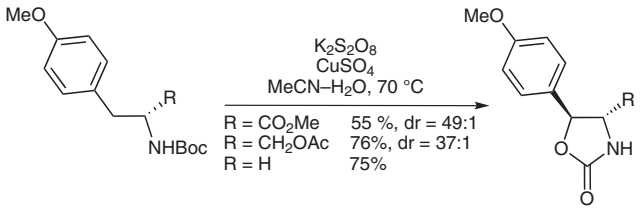
To date, only one total synthesis of AB3217-A has been published by Nakata et al.[2] The retrosynthetic approach adopted by this group is depicted below (Scheme 1). The anisomycin derivative **1** was connected to the β-D-xylofuranose unit **2** via alkylation of the benzylic alcohol followed by a diastereoselective intramolecular glycosylation.

The synthesis of intermediate **1** proposed by this group, starting from known (4*R*,5*R*)-4,5-bis(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (a derivative of L-tartrate),[3] comprises 18 steps with an overall yield of 3.7%. As we were interested in synthesizing gram quantities of compound **1**, we decided to embark on an alternative synthesis. We chose to explore the use of anisomycin[4] itself as a starting point, since it is commercially available and contains much of the required functionality of AB3217-A, with the exception of the benzylic hydroxy group.



Scheme 1 Synthetic plan proposed by Nakata et al.[2]

The key step of our synthesis was the application of the diastereoselective benzylic oxidation developed by Ohfune et al. (Scheme 2).[5] In this reaction, a benzylic cation is generated, which is then trapped intramolecularly by the carbonyl group of the carbamate to release the *tert*-butyl cation.



Scheme 2 Benzylic oxidation developed by Ohfune et al.[5]

Even though this methodology has so far been applied only to acyclic tyrosine and DOPA derivatives, we envisaged that it would be perfectly suited for our substrate which already has the optimal substituents in place. To that end, anisomycin was protected as its *tert*-butyl carbamate **3**. It was then subjected to the oxidative cyclisation conditions, and the bicyclic product **4** was formed in 62–65% yield with a 10:1 diastereoselectivity (Scheme 3). *p*-Anisaldehyde formed by overoxidation was identified as the major byproduct, but shortening the reaction time did not result in a significant yield increase.

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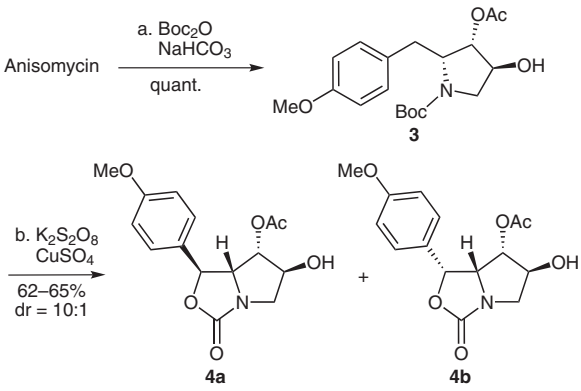


Scheme 3 Benzylic oxidation leading to compound **4**. *Reagents and conditions*: (a) Boc_2O (1.1 equiv), $NaHCO_3$ (1.1 equiv), THF–H_2O (1:1), r.t., 3 h 30, quant.; (b) $K_2S_2O_8$ (2 equiv), $CuSO_4$ (0.2 equiv) MeCN–H_2O (1:1), 70 °C, 3.5 h, 62–65%.

NOE experiments indicated that the undesired diastereomer **4a** was formed predominantly, and final confirmation was achieved by X-ray crystallographic analysis of a later derivative (see below). Following Ohfune's rationale, the selectivity of the reaction can be explained by considering steric factors in the two possible transition states (Figure 2). In the case of the minor diastereomer **4b**, a disfavored interaction is apparent between the acetate and the *ortho* proton of the aromatic ring, whereas no such interaction appears during the formation of the major diastereomer **4a**. However, the acetate group might stabilise the cation in both transition states, which could explain the relatively low level of diastereoselectivity obtained for substrate **3** compared to the acyclic examples described in the literature.[5]

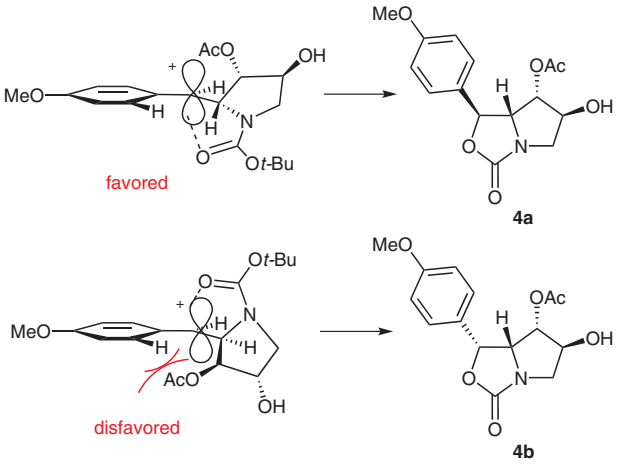
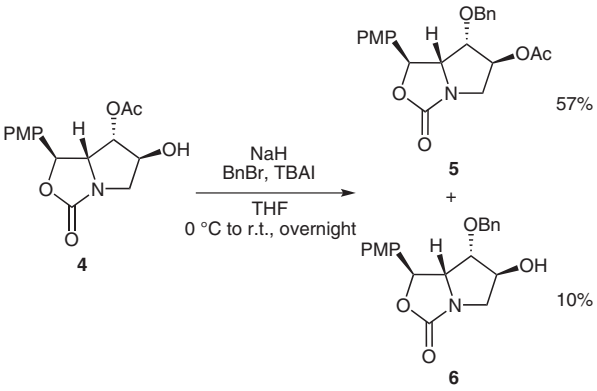


Figure 2 Possible transition states for the oxidative cyclisation

The decision was taken to proceed with the diastereomeric mixture and invert the stereochemistry of the benzylic centre at a later stage, as described by Nakata.[2] The next step was thus to benzylate the free hydroxy residue on the pyrrolidine ring. This reaction proved surprisingly challenging, as the acetyl group was observed to migrate prior to alkylation under basic conditions, even though the two hydroxy groups have an *anti* relationship.[6] Moreover, a minor byproduct was formed, which appeared to be the deacylated 'migrated' compound **6** (Scheme 4).



Scheme 4 Direct alkylation attempted on compound **4**. *Reagents and conditions*: BnBr (3 equiv), TBAI (0.1 equiv), NaH (1.1 equiv), THF, 0 °C to r.t.

Compound **5** was hydrolyzed to compound **6**, which was purified by crystallization. X-ray crystallography (Figure 3) confirmed the unexpected regioselectivity of the alkylation as well as the proposed stereochemistry for the benzylic position.[7]

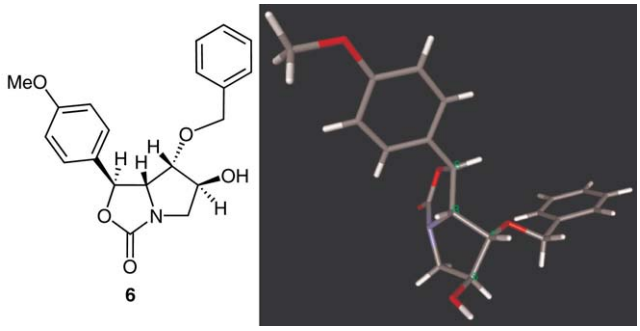
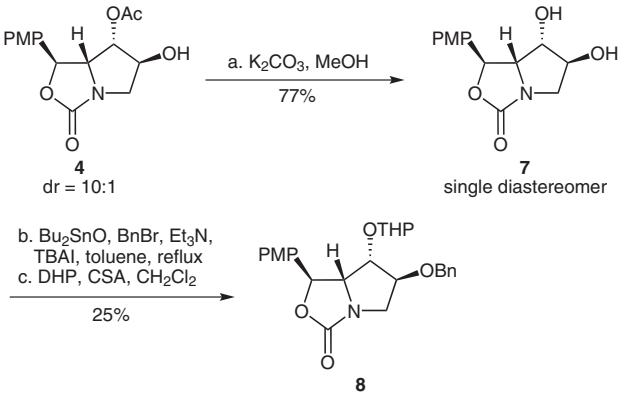


Figure 3 Crystal structure of compound **6**



Scheme 5 First synthesis of intermediate **8**. *Reagents and conditions*: (a) K_2CO_3 (2 equiv), MeOH, r.t., 24 h, 77%; (b) Bu_2SnO (2 equiv), Et_3N (1.5 equiv), BnBr (1.1 equiv), TBAI (0.1 equiv), toluene, reflux, overnight; (c) 3,4-dihydro-2*H*-pyran (DHP) (2 equiv), CSA (0.1 equiv), CH_2Cl_2, r.t., 3 h, 25% over two steps.

A number of conditions were then tried to alkylate alcohol **4** without migration, but all attempts were unsuccessful (see Table 1 in Experimental Section). Benzylation at an earlier stage (on the Boc-protected anisomycin) also failed.

In an alternative and ultimately successful approach, the 4-acetoxy group of intermediate **4** was hydrolyzed to give the corresponding diol **7**, which could be isolated as a single diastereomer in 77% yield. It was envisioned that the envelope shape of compound **7** would favour the regioselective alkylation of the least hindered hydroxy group. Attempts using the usual basic conditions gave mixtures of mono- and dibenzylated products. However, regioselective benzylation could be achieved using dibutyltin ester methodology and subsequent protection of the remaining alcohol as a tetrahydropyran (THP) ether afforded intermediate **8**, albeit in low overall yield (Scheme 5)

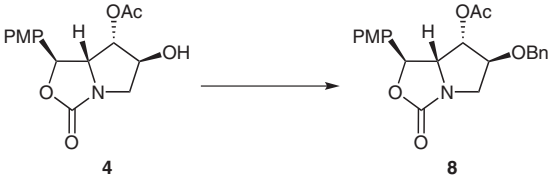
Alternatively it was found that silylation with *tert*-butyldimethylsilylchloride in DMF in the presence of imidazole and catalytic amounts of DMAP took place selectively at the least hindered hydroxy group. Subsequent formation of the THP ether of the remaining alcohol, deprotection, and benzylation afforded the protected diol **8** (Table 1) in an improved overall yield of 82% (Scheme 6).

Opening of the cyclic carbamate was achieved by hydrolysis under basic conditions, and subsequent re-protection of the pyrrolidine nitrogen as a benzyl carbamate furnished the intermediate alcohol **9**. Disappointingly, attempts to shorten the sequence by opening the carbamate with benzyl alcohol[9] to give the corresponding benzyl carbamate **9** failed, owing to the instability of the cyclic carbamate under the experimental conditions employed.

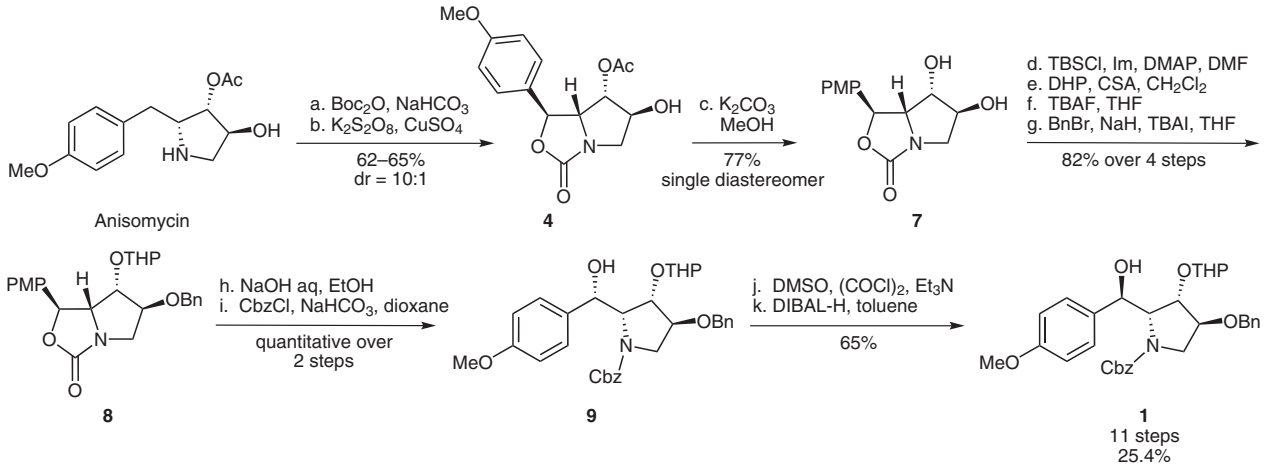
Final inversion of the benzylic alcohol in compound **9** was achieved in 65% yield using the oxidation–reduction protocol described by Nakata et al.[2]

In conclusion, we have achieved the synthesis of the advanced intermediate **1** in 11 steps from anisomycin, with an overall yield of 25.4%. This therefore represents a short and efficient formal total synthesis of the natural product AB3217-A.

Table 1 Summary of the Different Attempts To Benzylate Intermediate **4** To Obtain Directly Compound **8** under Basic, Acidic, or Neutral[8] Conditions



	Conditions	Comments
Basic conditions	NaH, BnBr, TBAI, THF	migrated product (57%)
	Ag_2O, BnBr, TBAI	complex mixture
Acidic conditions	$Cl_3C(NH)OBn$, TFA, CH_2Cl_2, 0 °C	traces, mostly starting material
	$Cl_3C(NH)OBn$, HBF_4, CH_2Cl_2, 0 °C	degradation
	$Cl_3C(NH)OBn$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C to 0 °C	complex mixture
	$Cl_3C(NH)OBn$, TfOH, CH_2Cl_2, –20 °C	complex mixture
Neutral conditions[8]	phenyl diazomethane, $SnCl_2$	no reaction
	benzyl triflate, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, –78 °C to 0 °C	3% isolated product
	AgOTf, BnBr, 2,6-di-*tert*-butylpyridine (solvent), r.t.	degradation



Scheme 6 Synthesis of **1** from anisomycin. *Reagents and conditions*: (a) Boc_2O (1.1 equiv), $NaHCO_3$ (1.1 equiv), THF–H_2O (1:1), r.t., 3.5 h, quant.; (b) $K_2S_2O_8$ (2 equiv), $CuSO_4$ (0.2 equiv), MeCN–H_2O (1:1), 70 °C, 3.5 h, 62–65%; (c) K_2CO_3 (2 equiv), MeOH, r.t., 24 h, 77%; (d) TBSCl (1.1 equiv), DMAP (0.3 equiv), imidazole (2 equiv), DMF, r.t., 24 h, 86%; (e) 4-dihydro-2*H*-pyran (DHP) (2 equiv), CSA (0.1 equiv), CH_2Cl_2, r.t., 3 h, 86%; (f) TBAF (2 equiv), THF, r.t., 3 h, 95%; (g) BnBr (2 equiv), TBAI (0.1 equiv), NaH (1 equiv), THF, r.t., 2 h, quant.; (h) 8 M aq NaOH (8 equiv), EtOH, reflux, 2 h; (i) benzyl chloroformate (1.1 equiv), 1 M aq $NaHCO_3$ (4 equiv), dioxane, r.t., quant. over 2 steps; (j) $(COCl)_2$ (2 equiv), DMSO (4 equiv), Et_3N (6 equiv), CH_2Cl_2, –78 °C to 0 °C, quant.; (k) DIBAL-H (2 equiv), toluene, –78 °C, 45 min, 65%.

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References and Notes

(1) (a) Kanbe, K.; Mimura, Y.; Tamamura, T.; Yatagai, S.; Sato, Y.; Takahashi, A.; Sato, S. *J. Antibiot.* **1992**, *45*, 548. (b) Kanbe, K.; Takahashi, A.; Tamamura, T.; Sato, K.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 568. (c) Kim, W.-G.; Kim, J.-P.; Park, D.-J.; Kim, C. h.-J.; Kwak, S. S.; Yoo, I.-D. *Agric. Chem. Biotech.* **1996**, *39*, 153.

(2) (a) Nakata, M.; Tamai, T.; Kamio, T.; Kinoshita, M.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3057. (b) Nakata, M.; Tamai, T.; Kamio, T.; Kinoshita, M.; Tatsuta, K. *Tetrahedron Lett.* **1994**, *35*, 3099.

(3) Hungerbuehler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.

(4) (a) Beereboom, J. J.; Butler, K.; Pennington, E.-C. *J. Org. Chem.* **1965**, *30*, 2334. (b) Butler, K. *J. Org. Chem.* **1966**, *31*, 317. (c) Sobin, B. A.; Tanner, F. W. *J. Am. Chem. Soc.* **1954**, *76*, 4053. (d) Macias-Silva, M.; Vazquez-Victorio, G.; Hernandez-Damian, J. *Curr. Chem. Biol.* **2010**, *4*, 124.

(5) (a) Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 5177. (b) For a recent example see: Bulman Page, P. C.; Buckley, B. R.; Rassias, G. A.; Blacker, A. J. *Eur. J. Org. Chem.* **2006**, 803.

(6) For precedents for *trans* intramolecular acetyl migration, see: (a) Deng, S.; Chang, C.-W. T. *Synlett* **2006**, 756. (b) Markad, S. D.; Schmidt, R. R. *Eur. J. Org. Chem.* **2009**, 5002.

(7) The hypothesis that the migration of the acetate proceeds via formation of an epoxide was ruled out. If an epoxide was formed and re-opened by the acetate, the stereochemistry of the two hydroxy groups on the pyrrolidine moiety would be inverted, which is not the case as can be observed on the crystal structure of **6** (Figure 3).

(8) For a recent example of benzylation using phenyl diazomethane, see: (a) Dake, G.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5668. For procedures using benzyl triflate, see: (b) Berry, J. M.; Hall, L. D. *Carbohydr. Res.* **1976**, *47*, 307. (c) Fleming, I.; Leslie, C. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1197.

(9) Haddad, M.; Imogaï, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680.