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# Total Synthesis of AB3217-A, a Novel Anti-mite Substance, via Intramolecular Glycosylation

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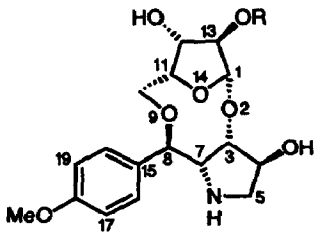
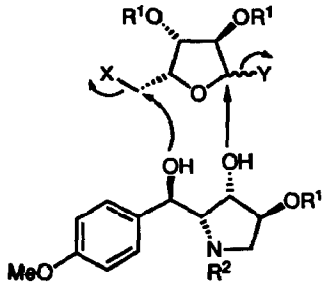
***Abstract:*** **The first total synthesis of AB3217-A, a novel anti-mite substance, has been achieved via intermolecular etherification and intramolecular glycosylation as the key steps for the formation of the nine-membered ring.**

AB3217-A (**1a**) was isolated in 1992 from the fermentation broth of the strain of *Streptomyces platensis* AB3217.[1] Two new substances, AB3217-B (**1b**) and AB3217-C (**1c**), the C13-ester derivatives of **1a**, were also isolated from the same strain.[2] They showed marked activity against the two spotted spider mite.[1,2] The structure of **1a** was determined by spectroscopic means and its absolute configuration was determined by X-ray crystallographic analysis.[1] The characteristic structure is a novel nine-membered ring built of deacetylanisomycin and β-D-xylofuranose, which are linked through glycosidic and ether bonds. We wish to describe here the first total synthesis of **1a** via intermolecular etherification and intramolecular glycosylation as the key steps for the formation of the nine-membered ring. Although glycosylations are among the most widely-used reactions in the synthesis of biologically active substances,[3] intramolecular glycosylation has been rarely used in the synthesis of natural products.[4]

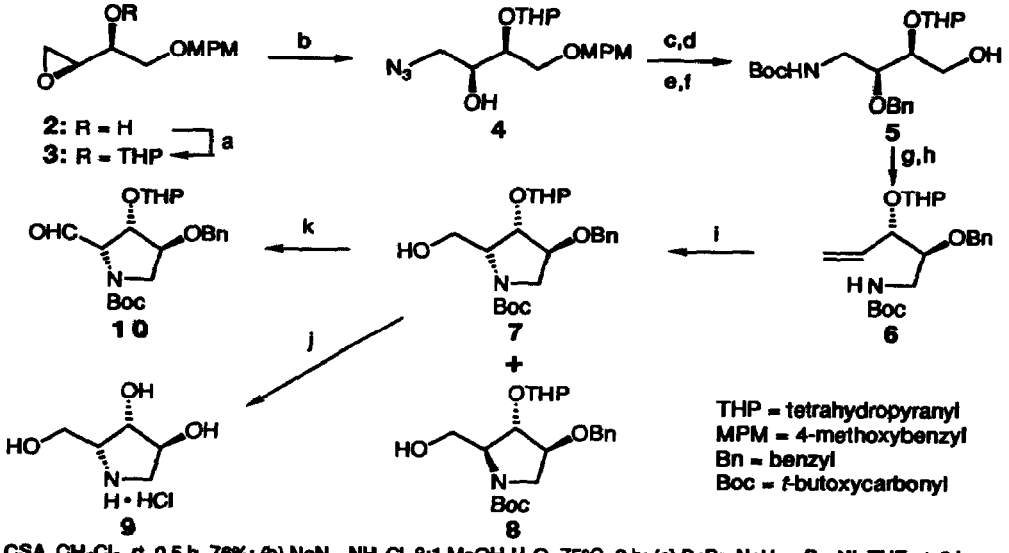



**AB3217-A (1a):** R = H
**AB3217-B (1b):** R = $C(O)(CH_2)_4C(OH)Me_2$
**AB3217-C (1c):** R = $C(O)(CH_2)_2CHMe_2$



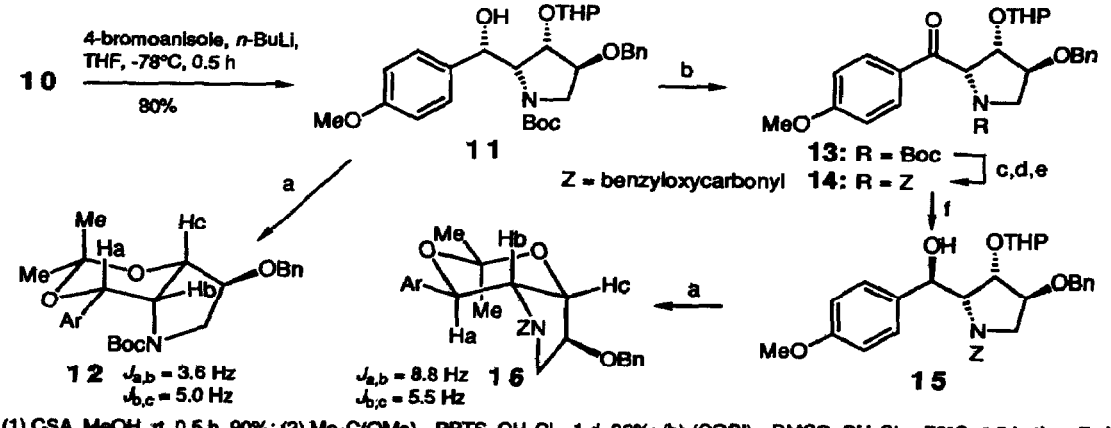

Synthesis of the pyrrolidine unit began with epoxy-alcohol **2**[5] which was prepared from dimethyl L-tartrate in six steps by the modified Seebach procedures.[6] Protection of **2** [3,4-dihydro-2*H*-pyran (DHP), CSA, 76% yield] followed by the epoxide-opening of the resulting **3**[7] with $NaN_3$-$NH_4Cl$[8,9] gave azidoalcohol **4** as a single isomer. The four-step manipulation of the crude **4** gave **5**[5] in 85% overall yield from **3**. Swern oxidation of **5** followed by Wittig methylenation ($Ph_3P{=}CH_2$) gave olefin **6**[5] in 60% yield. Pyrrolidine-ring formation was realized by the conceptually similar method to the Joullié's[10] or Takahata-Momose's one.[11] Namely, epoxidation of **6** with MCPBA followed by $BF_3{\cdot}OEt_2$-treatment gave pyrrolidines **7**[5] and **8** in 45%

and 15% yield, respectively.[12] The newly generated stereocenter in the major pyrrolidine **7** was confirmed by its conversion to the known hydrochloride of 1,4-dideoxy-1,4-imino-D-xylitol (**9**).[13] Swern oxidation of **7** gave aldehyde **10** in 82% yield.




(a) DHP, CSA, $CH_2Cl_2$, rt, 0.5 h, 76%; (b) $NaN_3$, $NH_4Cl$, 8:1 MeOH-$H_2O$, 75°C, 2 h; (c) BnBr, NaH, *n*-$Bu_4NI$, THF, rt, 2 h; (d) $Ph_3P$, THF, 50°C, 2 h, then $H_2O$, 2 h; (e) $(Boc)_2O$, $NaHCO_3$, $CH_2Cl_2$, rt, 1 h; (f) DDQ, 18:1 $CH_2Cl_2$-$H_2O$, rt, 2 h, 85% (5 steps); (g) $(COCl)_2$, DMSO, $CH_2Cl_2$, -78°C, 0.5 h, then $Et_3N$, -78 to 0°C, 0.5 h; (h) $Ph_3P{=}CH_2$, benzene, 0°C to rt, 60% (2 steps); (i) (1) MCPBA, $CH_2Cl_2$, rt, 2 d; (2) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, -78°C, 5 min, 45% (for **7**), 15% (for **8**); (j) (1) $H_2$, $Pd(OH)_2$, MeOH, rt, 0.5 h; (2) 1M aq HCl, THF, 50°C, 0.5 h, 95% (2 steps); (k) $(COCl)_2$, DMSO, $CH_2Cl_2$, -78°C, 0.5 h, then $Et_3N$, -78 to 0°C, 0.5 h, 82%.

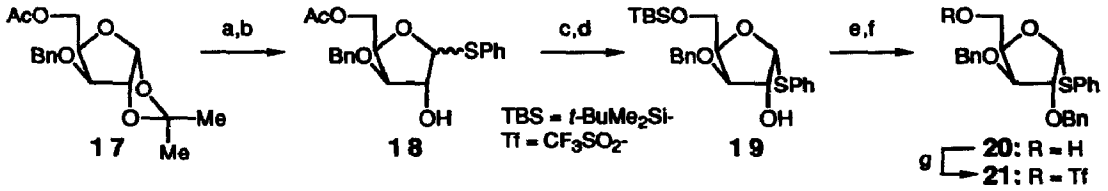
The above aldehyde **10** was coupled with 4-anisyllithium (4-bromoanisole, *n*-BuLi)[11] to afford **11**[5] in 80% yield as a single isomer. The configuration at the benzylic stereocenter was determined by the $^1H$ NMR *J* analysis of acetonide **12**. This remarkable, but undesirable, facial selectivity may arise from *N*-assisted addition of anisyllithium to the aldehyde.




(a) (1) CSA, MeOH, rt, 0.5 h, 90%: (2) $Me_2C(OMe)_2$, PPTS, $CH_2Cl_2$, 1 d, 90%; (b) $(COCl)_2$, DMSO, $CH_2Cl_2$, -78°C, 0.5 h, then $Et_3N$, -78 to 0°C, 0.5 h, 88%; (c) 1:3 TFA-$CH_2Cl_2$, rt, 0.25 h; (d) ZCl, $K_2CO_3$, aq THF, rt, 0.5 h; (e) DHP, CSA, $CH_2Cl_2$, rt, 0.5 h, 85% (3 steps); (f) DIBAL, toluene, -78°C, 0.5 h, 91%.

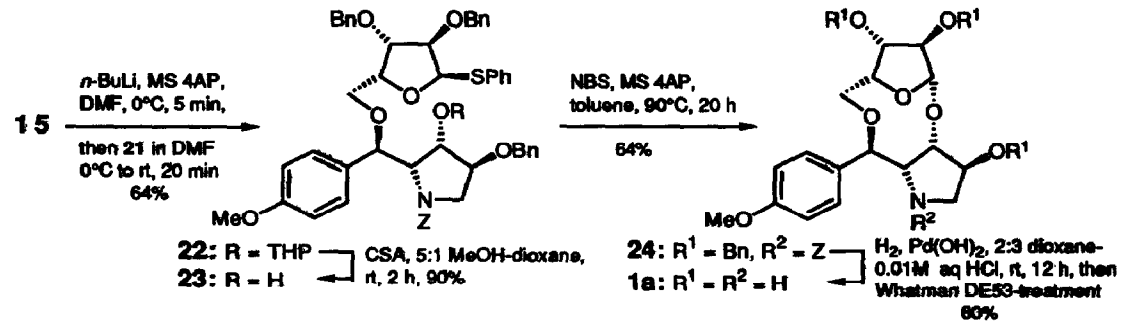
To invert the configuration, **11** underwent Swern oxidation to give **13** in 88% yield. Acidic treatment of **13** followed by successive *N*-benzyloxycarbonylation[14] and *O*-protection provided **14** in 85% yield. Finally, DIBAL reduction of **14** afforded **15**[5] in 91% yield as a single isomer. The newly created stereocenter in **15** was confirmed by the $^1$H NMR *J* analysis of acetonide **16**.

Synthesis of the D-xylose unit was initiated from **17** which was derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in the five steps.[15] After deacetonization (aq AcOH) of **17**, the resulting free sugar was treated with $(PhS)_2$ and *n*-$Bu_3P$[16,17] to afford a 1 : 1.8 mixture of α : β anomers **18** in 70% combined yield. Since this mixture could not be separated, it was subjected to deacetylation and silylation to afford α-phenyl thioglycoside **19**[5] (34%) together with its β-anomer (60%). Benzylation and subsequent de-*O*-silylation of **19** gave **20**[5] in 95% yield.[18] Finally, introduction of a leaving group to **20** was realized by treatment of **20** with triflic anhydride ($Tf_2O$) and $Et_3N$ to afford the extreamly rabile triflate **21**,[19] which was immediately subjected to the next reaction.




(a) 50% aq AcOH, 100°C, 2.5 h; (b) $(PhS)_2$, *n*-$Bu_3P$, THF, rt, 0.5 h, 70% (2 steps); (c) NaOMe, MeOH, rt, 0.5 h; (d) TBSCl, imidazole, DMF, 0°C, 0.5 h, 34% (for **19**) (2 steps); (e) BnBr, NaH, *n*-$Bu_4NI$, THF, rt, 2 h; (f) *n*-$Bu_4NF$, THF, rt, 0.5 h, 95% (2 steps); (g) $Tf_2O$, $Et_3N$, $CH_2Cl_2$, -78°C, 5 min.

With both units in hand, we turned our attention to the exciting task of creating a nine-membered ring. Of a variety of conditions investigated for connecting both units, the most satisfied one was the following: *n*-BuLi in hexane (1.5 equiv) was added to a mixture of **15** (1 equiv) and molecular sieves 4A powder (MS 4AP) in DMF at 0°C (5 min) and to this was added **21** (1.5 equiv) in DMF and then the mixture was stirred at rt for 20 min, providing **22**[5] in 64% yield and a 20% yield of the recovered **15**.[20] Acidic treatment of **22** afforded **23** in 90% yield. The ultimate intramolecular glycosylation of **23** was best accomplished by *N*-bromosuccinimide (NBS) in toluene[17,21] (90°C) to afford **24**[5] in 64% yield. A final deprotection of **24** furnished AB3217-A (**1a**) in 60% yield. The synthetic **1a** was identical in all respects ($^1$H NMR, IR, UV, mp, $[\alpha]_D$, and TLC mobilities) with the natural AB3217-A.[1,22]



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## References and Notes


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5. Satisfactory spectroscopic data were obtained for all new compounds.
6. Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.
7. All compounds having THP ether in this letter consist of a 1 : 1 anomeric mixture, which were not separated.
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9. The same reaction of **3** (R = TBS) resulted in a concomitant migration of the silyl protecting group.
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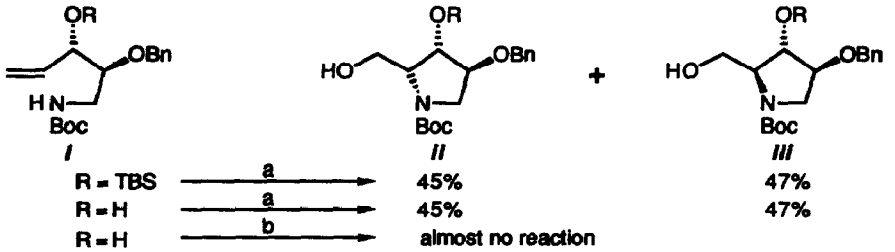
11. Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240.
12. A nonstereoselective pyrrolidine-ring formation or no reaction was observed when *i* was subjected to the following conditions.




(a) (1) MCPBA, $CH_2Cl_2$, rt, 2 d; (2) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, -78°C, 5 min (see ref. 10).
(b) D-(-)-DIPT, TBHP, $Ti(O\text{-}i\text{-}Pr)_4$, MS 3AP, $CH_2Cl_2$, -20°C, 15 d (see ref. 11).

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14. It was necessary to alter the *N*-protecting group from *t*-butoxycarbonyl to benzyloxycarbonyl group because final deprotection of **24** ($R^2$ = Boc, *vide infra*) under acidic conditions resulted in failure.
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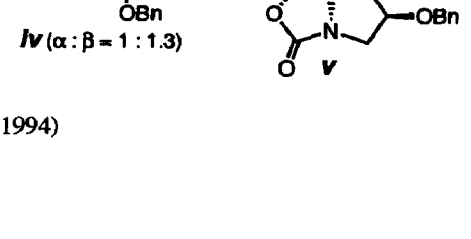
18. The anomeric configurations of **20** and its β-isomer were determined by their $^1H$ NMR NOE measurements (for **20**: H-1→H-2, 9.7%. for β-anomer: H-1→H-2, 4.0%; H-1→H-3, 2.1%; H-1→H-4, 2.3%).
19. Etherification of **21** (R = Ms or Ts, or OR = I) with 4-methoxybenzyl alcohol or 1-(4-methoxyphenyl)-2-methyl-1-propanol under a variety of conditions was unsuccessful, giving either recovered **21** or decomposition depending on the conditions employed. Triflation of the corresponding β-anomer of **20** was also unsuccessful, giving *iv* via 1,5-PhS group migration. For 1,2-PhS group migration, see: Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466. Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1992**, *33*, 2063. Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501.
20. The use of other bases in this etherification was less satisfactory. In some cases, the cyclic urethane *v* was obtained as the major product.
21. Toluene was the best solvent. Acetonitrile could be also used (rt, 24 h), albeit in lower yield (30%).
22. Mp of the synthetic **1a**: 238-239°C (lit,[1] 241°C). Optical rotation of the synthetic **1a**: $[\alpha]_D^{30}$ -45° (c 0.41, $H_2O$) (lit,[1] $[\alpha]_D^{24}$ -52.5° (c 1.0, $H_2O$)).




*iv* (α : β = 1 : 1.3) *v*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