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Cyclic Phenylboronates as Hydroxyl Protecting Groups in the Synthesis of Monoesters of Macrolide Aglycones

Thomas J. Perun,* Jerry R. Martin, and Richard S. Egan

Division of Antibiotics and Natural Products, Abbott Laboratories, North Chicago, Illinois 60064

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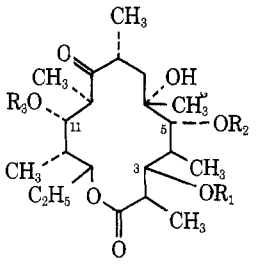
Benzeneboronic acid reacts readily with the cis-related 1,3-diols present in 14-membered macrolide aglycones. These cyclic phenylboronates were found to be useful protecting groups of the C-3 and C-5 hydroxyls of erythronolides, allowing the esterification of the C-11 hydroxyl. Removal of the phenylboronate from the erythronolide 11-esters was not possible under the usual hydrolytic conditions, so the protecting group was removed by treatment with dilute peroxide and hydrolysis of the presumed borate ester intermediate. Attempts to prepare 11-acetylerythromycin by microbial conversion of 11-acetylerythronolide B or its 6-deoxy analog were unsuccessful. The major product in both cases was 3-*O*-(α-L-mycarosyl)-11-acetylerythronolide B.

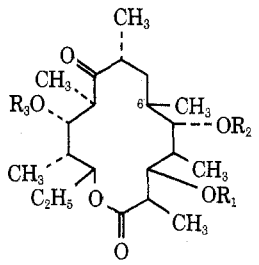
In our studies of the chemistry and conformation of erythromycin aglycones[1] we had need for monoacetyl derivatives of the three secondary hydroxyls in the erythronolide and 6-deoxyerythronolide molecules (**1** and **6**). Such compounds might also serve as potential substrates for microbial transformation in the study of blocked mutants of *S. erythreus*.[2] We were successful in obtaining monoacetylation of the hydroxyls at C-3 and C-5 as well as diacetylation at these positions using reaction conditions less strenuous than that necessary for triacetylation.[1a] Mixtures of these compounds could be separated conveniently by chromatography on Sephadex LH-20. The relative reactivity of the C-11 hydroxyl prevented selective acetylation at this position, however; so a cyclic phenylboronate ester was selected as a possible means of protecting the C-3 and C-5 hydroxyls during acetylation.

Cyclic phenylboronates have been used for protecting glycoside hydroxyls during acetylation[3] because of their facile formation from 1,2- and 1,3-diols[4] and their easy removal with water or polyalcohols.[3,4] Cyclic phenylboronate esters have also proven to be useful derivatives in the macrolide aglycone series[1c,2b] because of their selective and nearly quantitative reaction with the cis-related or 1,3-syn-periplanar diols present in these compounds. The preparation of erythronolide B 3,5-phenylboronate (**11**) occurred readily by refluxing an equimolar mixture of the macrolide and benzeneboronic acid in acetone for a short time. Other macrolide aglycones were similarly reactive. The aglycone of lankamycin,[5] 11-acetyllankolide, reacted with benzeneboronic acid to give the 3,5-phenylboronate **16** in good yield. This compound was prepared to study the conformational similarity among macrolide aglycones. The nmr analysis of phenylboronates has been discussed in detail in a separate communication.[6]

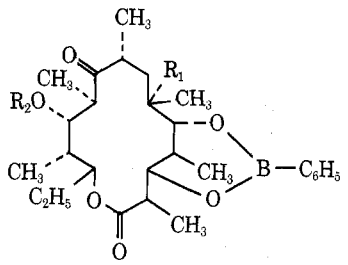
The formation of the 11-acetyl-3,5-phenylboronates of erythronolide B (**12**) and 6-deoxyerythronolide B (**15**) with acetic anhydride in pyridine proceeded smoothly using the fairly lengthy times necessary for acetylating the unreactive C-11 hydroxyl. Acetylation of this hydroxyl could also be accomplished with other acid anhydrides or acid chlorides. For instance, 11-benzoylerythronolide B 3,5-phenylboronate (**13**) could also be prepared in good yield. When attempts were made to hydrolyze the phenylboronate ester of these derivatives, however, using hydrolytic conditions normally successful for removing this group,[3,4] no reaction occurred. The presence of an ester function at C-11 apparently was responsible for preventing hydrolysis, since a 3,5-phenylboronate group on erythronolide B was easily removed under these conditions. It thus became necessary to find another mild method for removing phenylboronate protecting groups without destroying the macrolide ring.



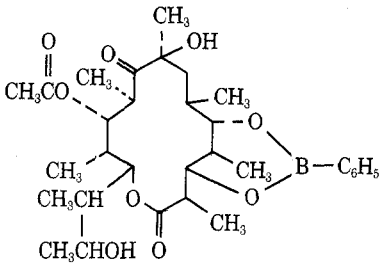
	R_1	R_2	R_3
1	H	H	H
2	CH_3CO	H	H
3	H	CH_3CO	H
4	H	H	CH_3CO
5	CH_3CO	CH_3CO	H



	R_1	R_2	R_3
6	H	H	H
7	CH_3CO	H	H
8	H	CH_3CO	H
9	H	H	CH_3CO
10	CH_3CO	CH_3CO	H



	R_1	R_2
11	OH	H
12	OH	CH_3CO
13	OH	C_6H_5CO
14	H	H
15	H	CH_3CO



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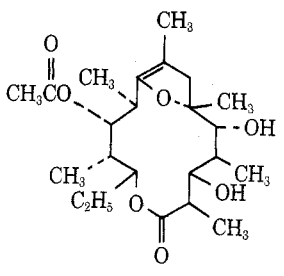

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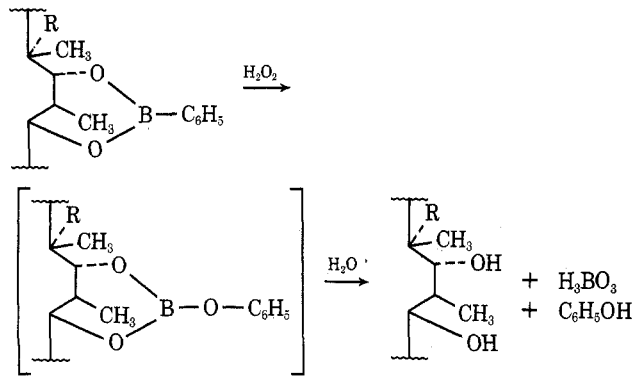
Earlier studies of the chemistry of benzeneboronic acid had shown that this compound reacts quite readily with dilute hydrogen peroxide, the products being boric acid and phenol resulting from insertion of an oxygen between boron and the aromatic carbon followed by hydrolysis.[7] It seemed reasonable to expect that phenylboronate esters would react in the same manner with peroxide. If this occurred with the erythronolide phenylboronates, the resulting borate esters might be more readily hydrolyzed than their precursors (Scheme I).

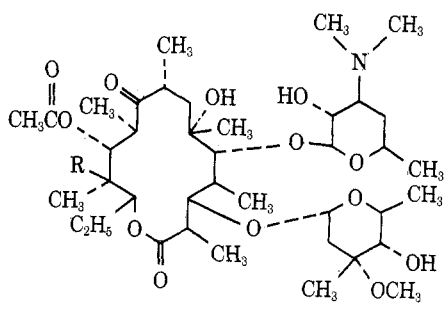
Treatment of 11-acetylerythronolide B 3,5-phenylboronate with hydrogen peroxide in aqueous ethanol did indeed produce detectable amounts of phenol. The product obtained from the reaction, however, was not the desired 11-acetylerythronolide B (4) but its 6,9-enol ether derivative 17. The formation of the enol ether apparently resulted from the presence of the boric acid formed in the reaction, since acidic conditions are known to catalyze the formation of enol ethers in the erythronolide and erythromycin series.[1a,8] To overcome this problem the reaction was conducted with suspended $NaHCO_3$ as a buffering agent. In this manner 11-acetylerythronolide B (4) was obtained. The presence of phenol sometimes prevented crystallization of the product; so the most convenient method for obtaining the 11-acetyl derivative was by chromatographic purification. A similar procedure was used to prepare 11-acetyl-6-deoxyerythronolide B (9).

Scheme I

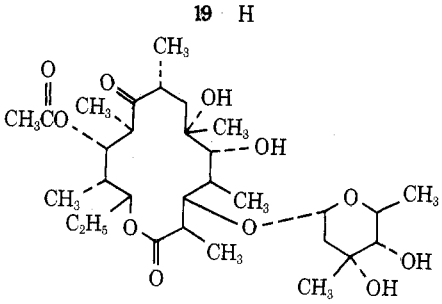


The nmr chemical shifts for the acetate esters of erythronolide B and 6-deoxyerythronolide B are shown in Table I. These compounds proved to be valuable for the conformational analysis of the erythronolide ring. Detailed examination of the nmr spectra and circular dichroism spectra of these compounds has been discussed by Egan in a separate communication.[6]

The 11-acetylerythronolides 4 and 9 were used as potential substrates for microbiological conversion to 11-acetylerythromycins A or B (18 and 19) by addition of these



	R
18	OH
19	H



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compounds to fermentations of early blocked mutants of *S. erythreus* capable of converting known erythromycin progenitors to the complete antibiotic. While there was evidence for conversion of each of these substrates to a mixture of basic antibiotics, the major product in both cases was the neutral glycoside 3-*O*-(α-L-mycarosyl)-11-

Table I
Chemical Shifts of Acetyl Esters of Erythronolide B and 6-Deoxyerythronolide B

Compd	Compd no.	δ (CDCl₃, ambient) CH₃CO	H-3	H-5	H-11
3-Acetylerythronolide B	**2**	2.09	5.07	3.54	3.84
5-Acetylerythronolide B	**3**	2.10	3.79	4.52	3.79
11-Acetylerythronolide B	**4**	2.02	3.96	4.05	4.89
3,5-Diacetylerythronolide B	**5**	2.02, 2.08	5.23	4.60	3.83
3,5,11-Triacetylerythronolide B[a]		2.02, 2.05, 2.07	5.40	4.70	5.13
3-Acetyl-6-deoxyerythronolide B	**7**	2.08	5.19	3.49	3.67
5-Acetyl-6-deoxyerythronolide B	**8**	2.08	3.73	4.68	3.37
11-Acetyl-6-deoxyerythronolide B	**9**	2.00	3.92	4.07	4.91
3,5-Diacetyl-6-deoxyerythronolide B	**10**	2.00, 2.10	5.19	4.71	3.58
3,5,11-Triacetyl-6-deoxyerythronolide B[b]		2.02, 2.03, 2.07	5.20	4.79	4.89
6-Deoxyerythronolide B	**6**		3.90	3.98	3.69

[a] Reference 1a. [b] Reference 2b.

acetylerythronolide B (**20**). The elemental analysis of this compound indicated an empirical formula of $C_{30}H_{52}O_{11}$, and the high-resolution mass spectrum contained peaks at *m/e* 570, corresponding to the loss of water from the parent, and at *m/e* 443 and 427 due to cleavage of mycarose (with and without the glycosidic oxygen)[9] from the parent molecule. The appearance of a fragment ion due to loss of H_2O at the highest mass is a common occurrence in the mass spectrum of neutral macrolides.[10] The uv spectrum of this compound contained a normal peak at 285 nm due to the carbonyl at C-9, and the nmr spectrum showed a close correspondence with those of other mycarosylerythronolides.[2a,c] Particularly important was the resonance at 5.05 ppm ($CDCl_3$) due to the anomeric proton of mycarose, and the coupling constants of this proton ($J_{1,2}$ = <1, 3.0) provided evidence for the α configuration.[2a,2c]

The inability to produce major amounts of 11-acetylerythromycins by a combination chemical-microbiological synthesis was a disappointment. Subsequently, a chemical route was found to produce these compounds in good yield.[11]

Experimental Section

Melting points were determined with a microscope hot stage. Ir spectra were obtained as $CHCl_3$ solutions by Mr. W. H. Washburn and associates on a Perkin-Elmer Model 521 instrument. Uv spectra were recorded for 95% EtOH solutions with a Cary Model II spectrophotometer. Nmr spectra were determined in $CDCl_3$ on a Varian HA-100 instrument. High-resolution mass spectra were obtained by Mrs. S. Mueller with an AEI MS-9 instrument. CD data (EtOH) were provided by Dr. L. A. Mitscher, The Ohio State University.

Acetylation of Erythronolide B (1). Erythronolide B (2.0 g) was dissolved in 30 ml of pyridine and 3.0 ml of acetic anhydride was added. The reaction mixture was allowed to stand at room temperature for 6.5 hr, then poured into ice-water and extracted with ethyl acetate. The extracts were washed with water, dried ($MgSO_4$), and evaporated. Residual pyridine was removed by azeotroping with benzene, giving 2.25 g of oil. Tlc examination of the oil showed starting material and three faster moving components. The oil was chromatographed on a column (2.5 × 35 cm) of silica gel prepared in $CHCl_3$. Elution with increasing concentrations of CH_3OH in $CHCl_3$ gave fractions examined by tlc. Those fractions containing a single component were pooled and evaporated to dryness. The first component eluted (233 mg) was **3,5-diacetylerythronolide B (5).** Crystallization from ethyl acetate–hexane gave colorless needles: mp 204–205°; $[\theta]_{292}$ −11,103; $[\theta]_{216}$ +3170.

Anal. Calcd for $C_{25}H_{42}O_9$: C, 61.71; H, 8.70. Found: C, 61.44; H, 8.71.

The second component eluted (546 mg) was **5-acetylerythronolide B (3).** The compound was obtained as a glass which resisted crystallization, $[\theta]_{288}$ −10,750, $[\theta]_{216}$ −1234.

Anal. Calcd for $C_{23}H_{40}O_8$: C, 62.13; H, 9.07. Found: C, 61.95; H, 9.34.

The third component eluted (479 mg) was **3-acetylerythronolide B (2).** Crystallization from ethyl acetate–hexane gave needles, mp 187–189°, $[\theta]_{290}$ −11,626.

Anal. Calcd for $C_{23}H_{40}O_8$: C, 62.13; H, 9.07. Found: C, 61.98; H, 9.13.

Acetylation of 6-Deoxyerythronolide B (6). 6-Deoxyerythronolide B (1.0 g) was acetylated in 15 ml of pyridine with 3.0 ml of acetic anhydride for 6 hr at ice-bath temperature. Work-up as above gave 977 mg of oily residue. Tlc examination showed the presence of starting material and three faster moving components. The mixture of three products was separated from starting material by chromatography on silica gel prepared in $CHCl_3$. Elution with 0.3% CH_3OH in $CHCl_3$ gave 469 mg of glassy residue. The glassy residue was fractionated by passage through a column (2.0 × 90 cm) of Sephadex LH-20 prepared in $CHCl_3$. Elution with $CHCl_3$ first gave fractions containing **3,5-diacetyl-6-deoxyerythronolide B (10).** Crystallization from ethyl acetate–hexane gave 172 mg: mp 130–131°; $[\theta]_{291}$ −16,260; $[\theta]_{230}$ −1305.

Anal. Calcd for $C_{25}H_{42}O_8$: C, 63.81; H, 9.00. Found: C, 64.08; H, 9.23.

The second component eluted was **5-acetyl-6-deoxyerythronolide B (8).** Crystallization as above gave 124 mg: mp 142–143°; $[\theta]_{289}$ −16,371; $[\theta]_{212}$ −5300.

Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.46; H, 9.41. Found: C, 64.22; H, 9.34.

The third component eluted was **3-acetyl-6-deoxyerythronolide B (7).** Crystallization gave 102 mg: mp 160–162°; $[\theta]_{289}$ −17,128; $[\theta]_{220}$ −2320.

Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.46; H, 9.41. Found: C, 64.51; H, 9.19.

Erythronolide B 3,5-Phenylboronate (11). A solution of 10.0 g (25 mmol) of erythronolide B (1) and 3.0 g (25 mmol) of benzeneboronic acid in 500 ml of anhydrous acetone was refluxed for 3–5 hr. The solution was then concentrated to a volume of about 75 ml and cooled to room temperature, yielding 8.4 g of crystalline product, mp 160–165°. Further concentration gave an additional 3.2 g. The total yield was 86% as the acetone solvate. The acetone could be removed by drying under vacuum at 140°. The ir spectrum contained a band at 1310 cm^{-1} characteristic for phenylboronates;[3a] $[\theta]_{292}$ −15,690.

Anal. Calcd for $C_{27}H_{41}O_7B$: C, 66.39; H, 8.46; O, 22.93; B, 2.22. Found: C, 66.50; H, 8.49; O, 23.14; B, 2.03.

The phenylboronate group of **11** could be removed easily by refluxing in a 1:1 acetone–water solution containing mannitol and sodium bicarbonate.[4a]

11-Acetylerythronolide B 3,5-Phenylboronate (12). A solution of 3.0 g of **11** (as the solvate) and 3.0 ml of acetic anhydride in 30 ml of anhydrous pyridine was allowed to stand at room temperature under a drying tube for 2 days. The solution was then poured into ice water and the precipitate was collected, washed with water, and dried, giving 2.3 g, mp 142–147°. A recrystallization from ethanol–water gave 1.9 g (65%): mp 150–153°; ir 1315 cm^{-1} (B–O); nmr δ 2.03 (CH_3CO); $[\theta]_{292}$ −33,290.

Anal. Calcd for $C_{29}H_{43}O_8B$: C, 65.66; H, 8.17; B, 2.04. Found: C, 65.48; H, 8.38; B, 1.78.

11-Acetyl-6-deoxyerythronolide B 3,5-Phenylboronate (15). The procedure above was used to prepare **15** from 5.0 g of 6-deoxyerythronolide B 3,5-phenylboronate[2b] (**14**), giving 4.0 g (74%) of crystalline product: mp 133–134°; ir 1315 cm^{-1} (B–O); nmr δ 2.00 (CH_3CO); $[\theta]_{294}$ −24,060.

Anal. Calcd for $C_{29}H_{43}O_7B$: C, 67.71; H, 8.42; B, 2.10. Found: C, 67.78; H, 8.49; B, 2.30.

11-Benzoylerythronolide B 3,5-Phenylboronate (13). A solution of 2.0 g (4 mmol) of **11** in 20 ml of anhydrous pyridine was cooled in ice while 1.15 ml (10 mmol) of benzoyl chloride was added. The solution was kept at 0° for 1 hr, then at room temperature for 24 hr, after which it was poured into ice water. The gummy solid obtained was allowed to stand in the aqueous solution overnight until it became crystalline. The solid was filtered, washed with water, and suspended in 5% $NaHCO_3$ solution for a few hours, then filtered, washed with water, and dried, giving 2.5 g of product. A recrystallization from 95% ethanol gave 1.6 g (74%), mp 191–193, ir 1315 cm^{-1} (B–O).

Anal. Calcd for $C_{34}H_{45}O_8B$: C, 68.92; H, 7.65; B, 1.83. Found: C, 68.81; H, 7.71; B, 2.08.

11-Acetyllankolide 3,5-Phenylboronate (16). A solution of 50 mg of 11-acetyllankolide[5a] and 12 mg of benzeneboronic acid in benzene was refluxed for 2 hr. The benzene was removed by distillation and the oil obtained was crystallized from $CHCl_3$–hexane, giving 27 mg, mp 150–155°.

Anal. Calcd for $C_{31}H_{47}O_9B$: C, 64.81; H, 8.25. Found: C, 64.61; H, 8.30.

11-Acetylerythronolide B (4). A solution of **12** (6.7 g) in 200 ml of 95% ethanol was stirred with suspended $NaHCO_3$ while 4.5 ml of 30% H_2O_2 was added. Stirring was continued for 23 hr and then a small amount of platinum oxide was added and the suspension was stirred for 7 hr more. The solid was filtered and 100 ml of water was added to the filtrate. The clear solution was reduced in volume *in vacuo* until a solid began to precipitate. The product which crystallized from the solution was filtered, giving 4.4 g: mp 163–165° (79%); uv λ_{max} 285 nm (ϵ 46); $[\theta]_{292}$ −17,875; $[\theta]_{218}$ −3200.

Anal. Calcd for $C_{23}H_{40}O_8$: C, 62.13; H, 9.07; O, 28.80. Found: C, 62.29; H, 8.95; O, 28.84.

The presence of phenol in the reaction solution sometimes prevented crystallization of the product. In this case the aqueous solution was extracted with ether and the oil obtained from the evaporated extract was chromatographed on Sephadex LH-20 prepared in CH_3OH. The product was crystallized from EtOH–H_2O.

When the reaction was conducted under the same conditions but without adding bicarbonate to control the pH, the product obtained was **8,9-anhydro-11-acetylerythronolide B 6,9-hemiacetal (17):** mp 215–218°; nmr δ 2.06 (CH_3CO), 1.56 ($CH_3C{=}C$); uv no λ_{max} at 260–350 nm.

Anal. Calcd for $C_{23}H_{38}O_7$: C, 64.76; H, 8.98; O, 26.26. Found: C, 64.89; H, 8.96; O, 26.08.

11-Acetyl-6-deoxyerythronolide B (9). The procedure used to prepare **4** was followed. From 5.2 g of **15** was obtained 3.3 g of **9**: mp 155–157° (76%); $[\theta]_{290}$ −17,400; $[\theta]_{222}$ −3815.

Anal. Calcd for $C_{23}H_{40}O_7$: C, 64.46; H, 9.41; O, 26.13. Found: C, 64.71; H, 9.71; O, 26.14.

Fermentation of 11-Acetyl-6-deoxyerythronolide B (9) by a Blocked Mutant of *Streptomyces erythreus* (Abbott 2NU153). *Streptomyces erythreus* (Abbott 2NU153) was grown in complex fermentation medium as previously described.[2] Finely divided **9** (900 mg) was evenly distributed among 36 500-ml Erlenmeyer flasks each containing 50 ml of a 24-hr fermentation culture. Incubation was continued for 144 hr, then the flask contents were pooled and clarified as described previously. The clarified fermentation broth at pH 7.2 was extracted with one-half volume of ethyl acetate. The ethyl acetate extract was partitioned two times with one-half volumes of 0.1 *M* phosphate buffer at pH 4.5, washed with water, and dried (Na_2SO_4). Removal of the ethyl acetate *in vacuo* left 1.23 g of yellow oil. The oil was chromatographed on a column of silica gel (3.0 × 35 cm) prepared in chloroform. Elution with increasing concentrations of methanol in chloroform gave fractions containing only a material with R_f 0.35–0.39. These fractions were combined and the solvent was removed, leaving 598 mg of light yellow oil. The oil was dissolved in methanol and treated with Darco G60. Crystallization from ethyl acetate–hexane gave 310 mg of 3-*O*-(α-L-mycarosyl)-11-acetylerythronolide B (**20**) as colorless needles. An analytical sample had mp 212–214°; ir 3605, 3500, 1733, 1705 cm^{-1}; uv λ_{max} 285 nm (ϵ 41.5); $[\theta]_{290}$ −12,950; $[\theta]_{218}$ −2340.

Anal. Calcd for $C_{30}H_{52}O_{11}$: C, 61.20; H, 8.90. Found: C, 61.06; H, 8.98.

Fermentation of 11-Acetylerythronolide B (4) by a Blocked Mutant of *Streptomyces erythreus* (Abbott 2NU153). 11-Acetylerythronolide B (1.2 g) was incubated with *S. erythreus* (Abbott 2NU153) as described above. Ethyl acetate extraction of the clarified broth gave 1.52 g of yellow oil. Chromatography of the neutral fraction gave 862 mg of light yellow oil which was treated with Darco G60 in methanol. Crystallization from ethyl acetate–hexane gave 521 mg of 3-*O*-(α-L-mycarosyl)-11-acetylerythronolide B (**20**), mp 208–210°. The identity of this compound with that from the previous fermentation was confirmed by all physical and spectroscopic data.

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