Soc., **99**, 943 (1977).
(9) P. Bischof, R. Gleiter, R. T. Taylor, A. R. Browne, and L. A. Paquette, unpublished work.
(10) The Ohio State University Dissertation Fellow, 1975–1976.

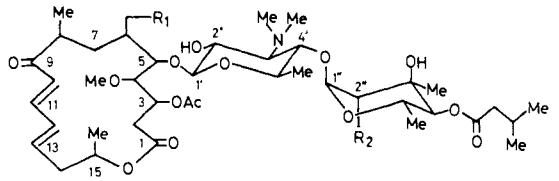
Richard T. Taylor,[10] Leo A. Paquette*
Evans Chemical Laboratories
The Ohio State University, Columbus, Ohio 43210
Received April 27, 1977

Synthesis of Carbomycin B. Introduction of the Amino Disaccharide onto the 16-Membered-Ring Aglycone

Sir:

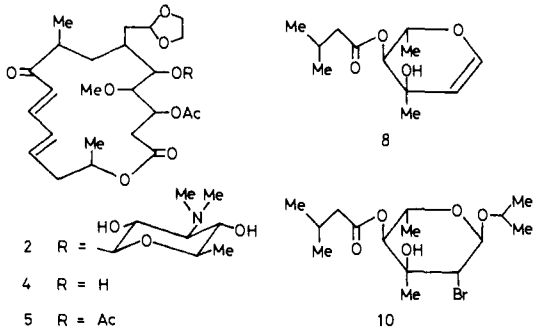
Sixteen-membered-ring macrolides[1] are an important class of antibiotics and most of their structures contain an amino disaccharide, namely 4-*O*-(α-L-mycarosyl)-D-mycaminose which seems to be indispensable for their antibacterial activities. It is apparent, therefore, that regio- and stereoselective introduction of this disaccharide onto the macrolide aglycone constitutes an essential part of the total synthesis of the macrolide antibiotics. We now wish to report a synthesis of carbomycin B,[2-4] a representative antibiotic of this class, by introduction of the amino disaccharide onto the 16-membered-ring aglycone of carbomycin B. This synthesis was achieved by using a new method[5] for the synthesis of 2-deoxy-α-glycosides, including diaxial opening of glycals with alcohols in the presence of a brominating agent.

Carbomycin B (**1**),[6] upon treatment with ethylene glycol and *p*-toluenesulfonic acid in acetonitrile (23 °C, 1 h), afforded



1 R_1 = ^{18}CHO R_2 = H
9 R_1 =  R_2 = Br
11 R_1 = CHO R_2 = Br

the ethylene acetal **2**[7] (84% yield), mp 102–106 °C (amorphous from acetone–hexane), $[\alpha]^{16}_D$ +13° (*c* 1.3, $CHCl_3$), and 2′-hydroxylethyl 4-*O*-isovalerylmycaroside (**3**,[7] 91% yield).



2 R =
4 R = H
5 R = Ac

8

10

Oxidation[8] of **2** with *m*-chloroperbenzoic acid (1.05 equiv, $CHCl_3$, 23 °C, 10 min) provided the *N*-oxide as a solid. The *N*-oxide, without purification, was treated with acetic anhydride (3 equiv, $CHCl_3$, reflux, 1 h) followed by treatment with sodium bicarbonate, affording the 16-membered-ring lactone **4**,[7] the aglycone part of carbomycin B (57% overall yield from **2**), mp 72–75 °C (amorphous from ether–hexane), $[\alpha]^{21}_D$ +10° (*c* 1.0, $CHCl_3$); the acetate **5**[7] (Ac_2O, pyridine, 45 °C, 14 h),[9] mp 220.5–221.5 °C (needles from chloroform–ether).

Condensation of **4** with 1-α-bromo-2,4-diacetylmycaminose hydrobromide[10] (5 equiv) in the presence of mercuric cyanide in nitromethane (20 °C, 10 h) gave the β-glycoside **6**[7] identical with the per-*O*-acetate (Ac_2O, pyridine, 23 °C, 1 h) of **2**, mp 103–110 °C (amorphous from ether–hexane), $[\alpha]^{20}_D$ −14° (*c* 1.0, $CHCl_3$), in 16% yield after column chromatography on silica gel.

Selective deacetylation of **6** by using its own basicity in methanol (23 °C, 14 h) quantitatively gave the product **2**[7] identical with the above-mentioned degradation product.

The glycal **8**,[7] $[\alpha]^{26}_D$ −148° (*c* 2.4, $CHCl_3$), was prepared by hydrolysis of the glycoside **3** (0.5 N hydrochloric acid, in aqueous dioxane, 40 °C, 4 h) to give 4-*O*-isovalerylmycarose **7**,[7] mp 74–75 °C (EtOAc–hexane), followed by treatment of **7** with *p*-toluenesulfonyl chloride (1.4 equiv) and triethylamine (2.8 equiv) in acetonitrile (23 °C, 5 h), in 51% overall yield. Reaction[5] of **8** with 1 equiv of the acetal **2** and 1 equiv of 1,3-dibromo-5,5-dimethylhydantoin in a mixture of acetonitrile and benzene (from −20 to 23 °C, 4 h) afforded, after column chromatography on silica gel (benzene–EtOAc followed by EtOAc–acetone–EtOH), a single condensed product and unreacted starting material **2** (recovered in 65% yield). Recrystallization (ether–hexane) of the product afforded needles of pure **9**[7] (11% yield,[11] mp 194–196 °C, $[\alpha]^{16}_D$ −18° (*c* 1.2, $CHCl_3$). The chemical shifts and coupling constants of H-1″ and H-2″ in the ^{1}H NMR were practically the same as those of the 2-bromo-α-L-altropyranoside **10**[12] and the signal due to C-4′ in the ^{13}C NMR was deshielded about 4.5 ppm in comparison with that of **2**, supporting that **9** possesses an α-glycosidic linkage at C-4′ with diaxially opening of the olefin group of **8**.[5]

Although the glycosidic linkage of 2-deoxyglycosides is generally cleaved under acidic conditions, the presence of a bromine atom at C-2 induces the glycoside to resist even drastic acid hydrolysis. Thus, deprotection of **9** with 90% trifluoroacetic acid (5 °C, 15 min) gave rosettes of 2″-bromocarbomycin B (**11**)[7] in nearly quantitative yield, mp 172–174 °C (ether–hexane), $[\alpha]^{21}_D$ −20° (*c* 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23 000), without cleavage of the α-glycosidic linkage.

Debromination[5] of **11** by using tri-*n*-butyltin hydride (1.2 equiv) in benzene (60 °C, 1 h under argon) with α,α′-azobisisobutyronitrile as catalyst completed the synthesis, giving carbomycin B (**1**)[13] (90% yield) identical with that obtained from natural sources by IR ($CHCl_3$), UV (MeOH), ^{1}H NMR and mass spectra, and antimicrobial activity.

The utility of the masked macrolide aglycone **4** for regioselective glycosylation is thus demonstrated.

Acknowledgment. The authors are grateful to Dr. Hamao Umezawa, Director of the Institute of Microbial Chemistry, for his support and encouragement and to Dr. Hiroshi Naganawa of the Institute for NMR studies.

References and Notes

(1) S. Ōmura and A. Nakagawa, *J. Antibiot.*, **28**, 401 (1975), and references cited therein.
(2) (a) F. A. Hochstein and K. Murai, *J. Am. Chem. Soc.*, **76**, 5080 (1954); (b) L. A. Freiberg, R. S. Egan, and W. H. Washburn, *J. Org. Chem.*, **39**, 2474 (1974).
(3) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957); R. B. Woodward, L. S. Weiler, and P. C. Dutta, *J. Am. Chem. Soc.*, **87**, 4662 (1965).
(4) M. Kuehne and B. W. Benson, *J. Am. Chem. Soc.*, **87**, 4660 (1965).
(5) K. Tatsuta, K. Fujimoto, M. Kinoshita, and S. Umezawa, *Carbohydr. Res.*, **54**, 85 (1977). For another approach to the synthesis of 2-deoxy disaccharides, see R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43**, 2190 (1965).
(6) Prepared from josamycin[1] (leucomycin A_3, the C-9 hydroxyl derivative of **1**) by oxidation with sulfur trioxide–pyridine complex and triethylamine in Me_2SO in 86% yield, mp 193–195 °C (prisms from acetone–hexane), $[\alpha]^{21}_D$ −36° (*c* 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23 000),[2b] although in 30% yield by oxidation with MnO_2.[1]
(7) All compounds gave satisfactory combustion analyses, IR, UV, NMR, and mass spectra consistent with the reported structures. ^{1}H and ^{13}C NMR (δ, parts per million from TMS) were in $CDCl_3$ solution and the latter was analyzed in comparison with data of 16-membered macrolide antibiotics

reported by S. Omura, A. Nakagawa, A. Neszmélyi, S. D. Gero, A.-M. Sepulchre, F. Piriou, and G. Lukacs, *J. Am. Chem. Soc.*, **97**, 4001 (1975). Melting points were uncorrected. Significant NMR spectral data are listed herein. **2**: ^{13}c nmr 202.6 (C-9), 105.3 (C-1′), 103.6 (C-18), 84.8 (C-5), 73.4 (C-5′), 68.5 (C-4′). **4**: ^{13}C NMR 103.6 (C-18), 84.0 (C-4), 72.6 (C-5), 64.8 and 64.3 (ethylene carbons of the acetal). **6**: ^{13}C NMR 103.4 (C-18), 100.6 (C-1′), 85.5 (C-5). **8**: ^{1}H NMR 6.38 (d, J = 6 Hz, H-1), 4.82 (d, H-2). **9**: ^{1}H NMR 5.25 (d, $J \sim 1$ Hz, H-1″), 3.97 (d, H-2″); ^{13}C NMR 105.3 (C-1′), 103.8 (C-18), 100.2 (C-1″), 73.0 (C-4′), 72.5 (C-5′), 53.4 (C-2″). **10**: ^{1}H NMR 5.21 (d, $J \sim 1$ Hz, H-1), 3.97 (d, H-2). **11**: ^{13}C NMR 200.9 (C-18), 104.0 (C-1′), 100.3 (C-1″), 53.4 (C-2″).

(8) S. Ōmura, A. Nakagawa, K. Suzuki, T. Hata, A. Jakubowski, and M. Tishler, *J. Antibiot.*, **27**, 147 (1974).

(9) The drastic condition required for the acetylation of **4** suggests that the C-5 hydroxyl group has little reactivity for the glycosylation because of some hindrance.

(10) Prepared by treatment of tri-*O*-acetylmycaminose[2a] with hydrogen bromide in methylene chloride (23 °C, 1 h), ^{1}H NMR 6.77 (d, J = 3.5 Hz, H-1).

(11) Improvements of the yield will be sought in further experimentation. It should be noted, however, that the glycosylation was achieved without protection of the C-2′ and C-3″ hydroxyl and C-3′ dimethylamino groups.

(12) Prepared from isopropyl alcohol and **8** in the same manner as described above (91%), $[\alpha]^{21}_{D}$ −65° (*c* 1.0, $CHCl_3$).[5]

(13) Synthetic carbomycin B has mp 193–195 °C (prisms from acetone–hexane). Anal. Calcd for $C_{42}H_{67}NO_{15}$: C, 61.07; H, 8.18; N, 1.70. Found: C, 61.10; H, 8.09; N. 1.64.

Kuniaki Tatsuta,* Akihiro Tanaka
Koichi Fujimoto, Mitsuhiro Kinoshita
Department of Applied Chemistry, Keio University
832 Hiyoshi, Yokohama, Japan 223

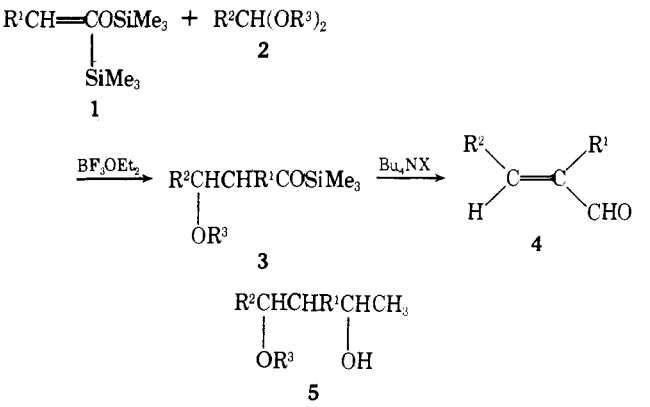
Sumio Umezawa
Institute of Bioorganic Chemistry
1614 Ida, Nakahara, Kawasaki, Japan 211

Received February 23, 1977

An Effective Preparative Method of α,β-Unsaturated Aldehydes via β-Alkoxyacylsilanes

Sir:

Formal "directed aldol coupling" between two types of aldehydes to afford α,β-unsaturated aldehyde, RCH=CR′CHO, is one of the most versatile synthetic organic reactions and a number of masked carbonyl equivalents have hitherto been devised.[1] Brook's pioneering works on acylsilane types of compounds have shown that silylcarbonyl groups can also be used as formyl synthon.[2] Unfortunately, their characteristic features have not been fully utilized yet for synthetic purpose because of limited applicability with moderate success. We have recently developed a method for effective conversion of 1,1-bis(trimethylsilyl)alkan-1-ol[3] into the trimethylsilyl enol ether of the corresponding trimethylacylsilane **1**.[4] This paper



describes the reaction of this silyl enol ether **1**, which provides a facile preparative method of α,β-unsaturated aldehyde effected through the following two stages: (1) preparation of β-alkoxyacylsilane **3** by BF_3·OEt_2-catalyzed[5] reaction of acetal **2** with the silyl enol ether **1** and (2) its conversion into α,β-unsaturated aldehyde **4** under the influence of catalytic amounts of quaternary ammonium hydroxide or substituted phenoxides. Both of these reactions proceed under very mild conditions in high yield. This makes this method of considerable synthetic interest. The following procedures are illustrative. The trimethylsilyl enol ether of propionyltrimethylsilane (1.010 g, 5 mmol) and benzaldehyde diethyl acetal (0.900 g, 5 mmol) in methylene chloride (10 mL) were added to a methylene chloride (5 mL) solution of BF_3·OEt_2 (0.710 g, 5 mmol) at −78 °C under an argon atmosphere. After stirring for 1 h at −78 °C and 2 h at −30 °C, the reaction mixture was quenched with aqueous $NaHCO_3$ and was extracted with ether. Removal of the solvent and distillation afforded the corresponding adduct **3**[6] ($R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = C_2H_5$) (1.214 g, 92%, bp 105~106 °C (2 mm). The alkoxyacylsilane (1.056 g, 4 mmol) thus obtained was treated with a 25% methanolic solution of tetrabutylammonium hydroxide (0.832 g, 0.8 mmol) in acetonitrile (15 mL) at room temperature for 15 min. The reaction mixture was then neutralized with dilute HCl, washed with aqueous $NaHCO_3$, and extracted with ether. Removal of the solvent followed by bulb-to-bulb distillation gave 2-methyl-3-phenylpropenal (0.549 g, 94%). Various acetals react similarly to afford the corresponding unsaturated aldehyde **4** in good yield by the above-mentioned two successive procedures, while ketals usually fail to react with the silyl enol ether **1** under the reaction conditions described above.[7] The aldehydes obtained are usually the *E* isomers exclusively.[8]

Stronger Lewis acids, e.g., $TiCl_4$, $AlCl_3$, or $SnCl_4$, cannot

Table I. Preparation of β-Alkoxyacylsilane **3** and Its Conversion into α,β-Unsaturated Aldehyde **4**

Reactant			**3**[a],		**4**,
R^1	R^2	R^3	% yield	X	% yield
CH_3	C_3H_7	CH_3	87	OH[b]	91[f]
	C_6H_5	C_2H_5	92	OH[c]	94
	$C_6H_5CH{=}CH$	C_2H_5	86	OH[c]	89
C_2H_5	C_3H_7	CH_3	81	OH[b]	85
$C_6H_5CH_2$	CH_3	C_2H_5	90	OH[c]	71
				F[d]	45[g]
				o-$CH_3OC_6H_4$-O[e]	81
	C_3H_7	CH_3	75	OH[b]	92
	C_6H_5	C_2H_5	88	OH[c]	93[h]
				F[d]	98[i]
	$C_6H_5CH{=}CH$	C_2H_5	87	OH[c]	90[j]
				F[d]	92[k]

[a] All of the reactions were carried out under the same condition described in the text. [b] The reaction was performed for 50 min in the presence of 25% methanolic solution of Bu_4NOH (0.2 equiv). [c] The reaction was performed for 15~20 min in the presence of 25% methanolic solution of Bu_4NOH (0.2 equiv). [d] The reaction was performed for 12 h in the presence of Bu_4NF (0.08 equiv) and methanol (4 equiv). [e] The reaction was performed for 46 h in the presence of *o*-methoxyphenoxide (0.4 equiv) and methanol (4 equiv). [f] The *E* isomer was formed exclusively, otherwise noted. [g] Methyl transfer product **5** was also formed in 5% yield. [h] *E*:*Z*, 89:4. [i] *E*:*Z*, 90:8. [j] *E*:*Z*, 85:5. [k] *E*:*Z*, 84:8.