The stereochemical assignments of both **13** and **15** were secured by conversion of each compound to the illustrated lactol ethers **14** and **16** where the stereochemical relationship between the C_9 oxygen and C_{10} methyl group was unequivocally determined by NMR spectroscopy along with the relevant NOE studies. With the stereochemical outcome of the hydroboration reaction thus confirmed, **13** was oxidized to aldehyde **2** in 89% yield using the Dess-Martin reagent[9] (CH_2Cl_2, 25 °C, 15 min), providing the C_1-C_{11} synthon in an overall yield of 21% from β-keto imide **4**.

Acknowledgment. Support has been provided by the National Institutes of Health and Merck. A postdoctoral fellowship to G.S.S. from the NIH is gratefully acknowledged. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

Supplementary Material Available: All experimental procedures and spectral data (9 pages). Ordering information is given on any current masthead page.

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Total Syntheses of Bulgecinine and Bulgecin C from (2*S*,4*R*)-Hydroxyproline

Anthony G. M. Barrett* and Daniel Pilipauskas

Department of Chemistry, Northwestern University, Evanston, Illinois 60208

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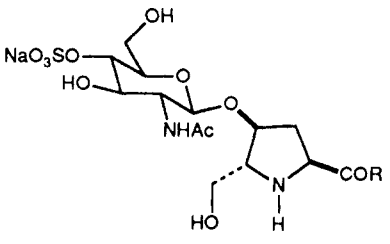
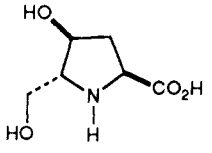
Summary: The first total synthesis of bulgecin C has been achieved in 18 linear steps from (2*R*,4*S*)-hydroxyproline. Transformations of note include the regioselective electrochemical methoxylation of a 4-acetoxyproline carbamate, a stereospecific free radical substitution reaction to incorporate the C-5 hydroxymethyl group, and a β-stereoselective, trichloroacetimidate-mediated glycosylation using a 2-azido-2-deoxy-D-glucopyranose derivative.

The bulgecins A (**1**), B (**2**), and C (**3**) are a group of potent β-lactam synergists produced during the fermentation of *Pseudomonas acidophila* and *P. mesoacidophila*.[1] These natural products, although devoid of antibacterial activity, mediate, in concert with β-lactams, the development of a curious morphological change in the cell wall of Gram-negative bacteria. This bulge formation is accompanied by an increased sensitivity of the organism to inhibition and, as a result, bacteria are killed at lower β-lactam concentrations. Recently, *Chromobacterium violaceum* has been shown to produce two structurally related glycopeptide sulfates, SQ-28505 and SQ-28546.[2] These substances are also β-lactam antibiotic potentiators.



1 R = $NHCH_2CH_2SO_3H$
2 R = $NHCH_2CH_2CO_2H$
3 R = OH



4

As a consequence of their biological effects and structural novelty, the bulgecins have been the subject of synthetic investigations. The bulgecin aglycon bulgecinine (**4**) has been synthesized from D-glucose,[3] D-glucuronic acid,[4] pyroglutamic acid,[5] and an L-allylglycine derivative.[6] Additionally, Shiba and co-workers have reported the synthesis of bulgecin A (**1**) and two analogues.[7] Herein we report the first total synthesis of bulgecin C (**3**) from (2*S*,4*R*)-4-hydroxyproline using electrochemical and radical transformations to prepare a bulgecinine derivative and subsequent trichloroacetamidate-mediated glycosylation.

(2*S*,4*R*)-4-Hydroxyproline (**5**) was esterified and N-protected as the *O*-(2-(trimethylsilyl)ethyl) carbamate.[8] Subsequent inversion of the C-4 stereochemistry was readily accomplished by esterification using the Mitsunobu reaction[9] to give the (4*S*)-acetate **6**. Anodic oxidation according to the excellent Shono protocol[10] gave the 5-methoxy compound **7** in a 64% yield as a mixture of diastereoisomers (1:1).[11] In contrast to the successful anodic oxidation of *N*-(*tert*-butyloxycarbonyl)-[12] and *N*-(benzyloxycarbonyl)proline methyl esters,[12,13] the corresponding *N*-Boc and *N*-Cbz analogues of **6** produced complex reaction mixtures of electrochemical oxidation and gave only low yields (<20%) of the corresponding 5-methoxylated derivatives.

Acetolysis of **7** gave the corresponding 5-acetate (77%), which was smoothly converted into the 5-phenylseleno compound **8** (86%) by reaction with benzeneselenol under acidic conditions. Adduct **8** was isolated as a mixture of diastereoisomers (2:1). Irradiation of the selenide **8** in the

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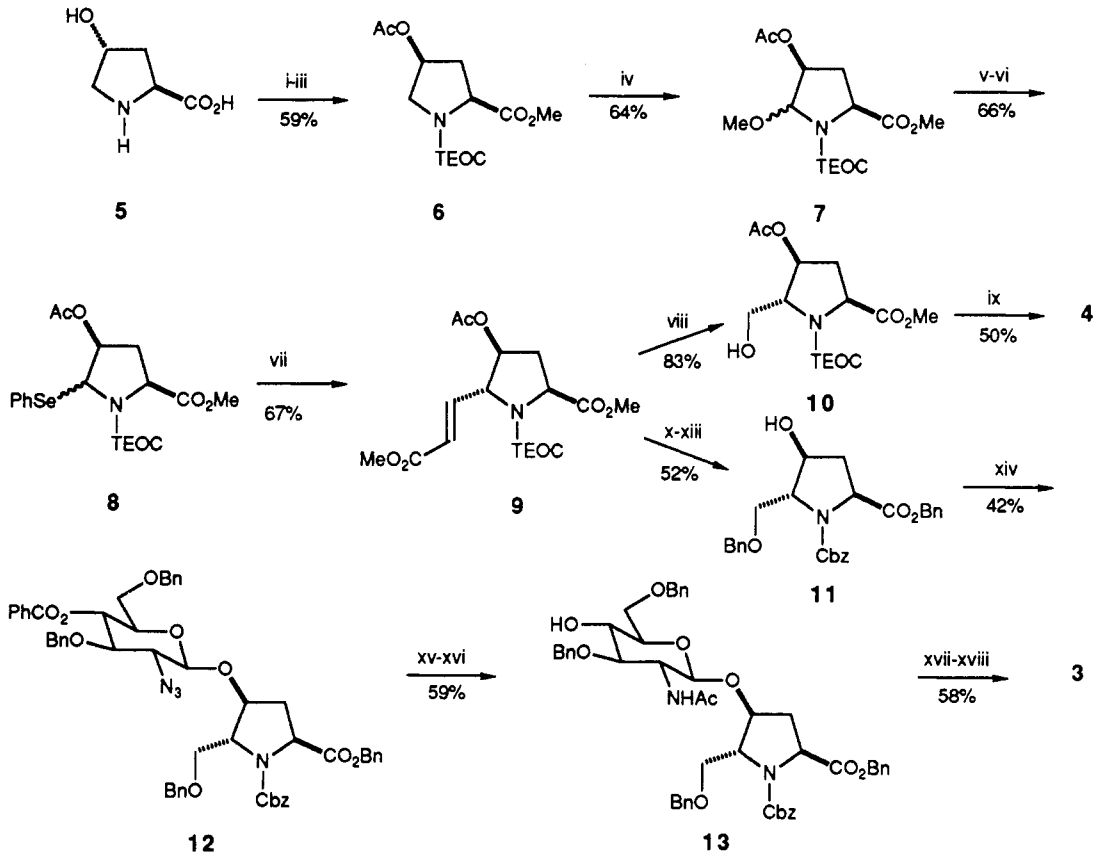
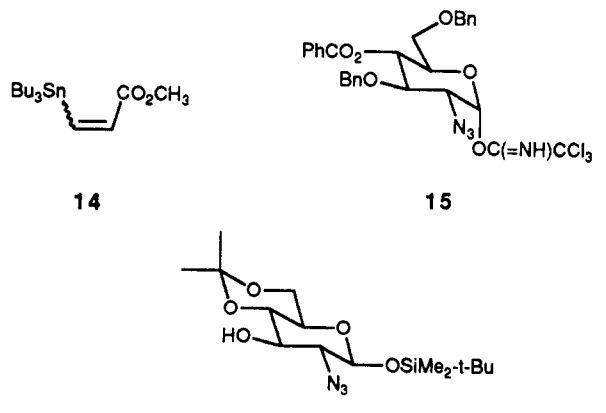
Scheme I[a]



TEOC = $Me_3SiCH_2CH_2OCO$

[a] (i) MeOH/$SOCl_2$, 100%; (ii) TEOC-N_3, Et_3N, CH_3CN, 90%; (iii) PPh_3, $EtO_2CN{=}NCO_2Et$, AcOH, THF, 65%; (iv) Et_4NOTs, MeOH, graphite electrodes, 5.5 F mol^{-1}, then Ac_2O, Et_3N, CH_2Cl_2, 64%; (v) Ac_2O, AcOH, H_2SO_4 (cat.), 77%; (vi) PhSeH, TsOH (cat.), 86%; (vii) (*E*)- or (*Z*)-$MeO_2CCH{=}CHSn(Bu)_3$, $(Bu_3Sn)_2$, 250 W sunlamp, Pyrex filter, 67%; (viii) O_3, MeOH-CH_2Cl_2; $NaBH_4$, 83%; (ix) NaOH, MeOH, then TBAF, 50%; (x) TFA, then BnOCOCl, aqueous $NaHCO_3$, CH_2Cl_2, 82%; (xi) O_3, MeOH-CH_2Cl_2; $NaBH_4$, 97%; (xii) BnBr, Ag_2O, CH_2Cl_2, reflux, 91%; (xiii) BnOH, $Ti(O\text{-}i\text{-}Pr)_4$ (cat.), 110 °C, 72%; (xiv) **15**, 0.1 equiv of $BF_3{\cdot}Et_2O$, -40 °C, 4-Å sieves, 42% β; (xv) AcSH, 80%; (xvi) KOH, H_2O, MeOH, 74%; (xvii) pyridine·SO_3, DMF, 73%; (xviii) Pd, 1:1 95% HCO_2H-MeOH, 80%.

presence of methyl (*Z*)- or (*E*)-2-(tributylstannyl)acrylate (**14**)[14] in benzene gave the radical substitution product **9**. Much to our delight this was formed as a *single diastereoisomer* in a 67% yield.[15] The stereospecificity of this free radical C-5 homologation is undoubtedly a consequence of steric approach control. In contrast, all our attempts to incorporate C-5 carbon substituents via the acyliminium cation derived from either **7** or the corresponding acetate and allyltrimethylsilane derivatives proceeded with little or no stereochemical control. Ozonolysis of the α,β-unsaturated ester **9** followed by a reductive workup with sodium borohydride afforded the (5*R*)-hydroxymethyl compound **10** (83%). Subsequent removal of the protecting groups gave the amino acid **4** which was identified with bulgecinine (**4**) in all respects.[16] For the synthesis of bulgecin C (**3**), the bulgecinine derivative **9** was readily converted[17] into the *N*-Cbz protected amino acid **11** and glycosylated using the 2-azido-2-deoxy-α-D-glucopyranosyl trichloroacetimidate derivative **15**.[18] This provided the corresponding β-glycoside **12** (42%), which was formed with good anomeric diastereo-



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(15) The 5-phenylthio analogue was slow to react under these conditions.

(16) ^{13}C and ^1H NMR spectra, melting point, and optical rotation data observed for **4** agreed exactly with those reported for the natural material; see ref 1.

(17) For the use of titanium tetraisopropoxide as a catalyst for transesterification see: Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenburger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.

(18) The α-trichloroacetimidate **15** was prepared from the known azide **16** (Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 1537) by the sequential reaction with (a) NaH, $PhCH_2Br$, THF (84%); (b) CF_3CO_2H, H_2O, THF (74%); (c) $(Bu_3Sn)_2O$, $PhCH_2Br$, Bu_4NBr, PhMe (82%) (Veyrieres, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1626); (d) PhCOCl, Et_3N, DMAP, CH_2Cl_2 (90%); (e) Bu_4NF, AcOH (86%); and (f) CCl_3CN, DBU, 4-Å molecular sieves, CH_2Cl_2, -30 °C (65% α, 14% β) (Tavecchia, P.; Trumtel, M.; Veyrieres, A.; Sinay, P. *Tetrahedron Lett.* **1989**, *30*, 2533). See also Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257.

selectivity (α:β = 1:3). Attempts to glycosylate the alcohol **11** using an oxazolidine derivative were unsuccessful presumably because of steric congestion at the secondary hydroxyl group. Reductive acetylation of the azide **12** using thiolacetic acid[19] and selective saponification gave the 4′-alcohol **13** (59%). Finally, sulfation of **13** using sulfur trioxide·pyridine in DMF[20] (73%) and global catalytic debenzylation gave bulgecin C (**3**) (80%). The material was identical in all respects (TLC, IR, ^{1}H NMR, ^{13}C NMR, FAB HRMS, and $[\alpha]_D$) with an authentic sample of the natural product.

It is clear from these results that the radical substitution of pyrrolidine derivatives provides a convenient method for the stereospecific generation of bulgecinine (**4**). Additionally the electrochemical/radical strategy and the glycosylation technology are applicable to the synthesis of alternative bulgecin systems. Further aspects of these studies will be published in due course.

Acknowledgment. We thank the National Institutes of Health for support of our program (AI-23034) and for the purchase of a 400-MHz NMR spectrometer (RR-01672) and a high-resolution mass spectrometer (RR-03245) used in these studies. We additionally thank Takeda Chemical Industries, Ltd., for providing an authentic sample of bulgecin C (**3**) and G. D. Searle and Company for the microanalysis of new compounds.

Supplementary Material Available: Experimental data for **3** and **4** (2 pages). Ordering information is given on any current masthead page.

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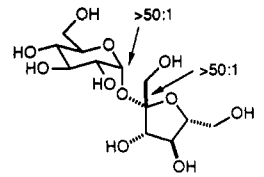
Redox Glycosidation: A Stereoselective Synthesis of Sucrose‡

Anthony G. M. Barrett,*,[1] Barend C. B. Bezuidenhoudt, and Laura M. Melcher
Department of Chemistry, Northwestern University, Evanston, Illinois 60208
Received July 16, 1990

Summary: Sucrose was stereoselectively prepared from D-glucose by esterification using D-arabinoic acid and subsequent methylenylation, iodoetherification, and radical-mediated substitution.

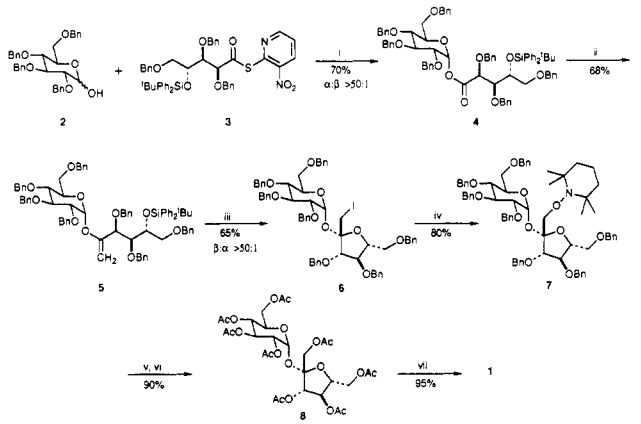
The construction of glycosides is frequently nontrivial in consequence of poor α- versus β-diastereoselectivities and low chemical yields. Classically glycosides are prepared by the Koenig–Knorr reaction of a protected glycosyl halide with a sugar alcohol in an alkylation process mediated by a silver (I) or mercury (II) salt.[2] In the past decade numerous variations of this alkylation strategy have been developed.[3] However, there is, as yet, no generally reliable method available such that the assembly of oligosaccharides is routine and straightforward.[4] Recently we described a procedure whereby disaccharides were assembled via glycosyl aldonic esters, Tebbe methylenylation, and subsequent cyclization.[5] Additionally we observed that disaccharides could be prepared via glycosyl aldonic acid thionoesters, reductive S-methylation, and cyclization.[6] These redox glycosidation procedures provide novel methods[7] for the elaboration of the glycosidic bond.

Sucrose is a target considerable historic importance[8] that is not straightforward to synthesize. It contains two synthetically challenging units: a cis α-glucopyranoside and a β-fructofuranoside residue, which contains a tertiary glycosyl oxygen. Herein we report the application of the titanium redox glycosidation methodology for the total synthesis of sucrose from D-glucose and D-arabinoic acid. The approach is noteworthy in consequence of the outstanding kinetic stereoselectivities achieved in the construction of both anomeric centers.



‡ Dedicated to Professor Leonard N. Owen on the occasion of his 76th birthday.

Scheme I[a]



[a] Reagents: (i) nBuLi (1.6 M), THF, −78 °C; (ii) $TiCl_4$, TMEDA, Zn, CH_2Br_2, THF; (iii) Bu_4NF on silica, THF; I_2, KO^{t}Bu, THF; (iv) TEMPO, Bu_3SnH, PhH, $h\nu$; (v) Na, NH_3, THF; (vi) Ac_2O, pyridine; (vii) NaOMe, MeOH.

Sequential reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**2**)[9] with *n*-butyllithium and the thioester **3**[10] gave

(1) Address correspondence to the author at the Department of Chemistry, Colorado State University, Fort Collins, CO 80523.
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(4) In contrast to oligosaccharide chemistry, syntheses of oligonucleotides and polypeptides are now highly sophisticated. For examples, see: Letsinger, R. L. "Chemical Synthesis of Oligodeoxyribonucleotides; A Simplified Procedure" In *Genetic Engineering: Principles and Methods*; Setlow, J. K., Hollaender, A., Eds.; Plenum Press: New York, 1983; Vol. 5, pp 191–209. Merrifield, B. *Science* **1986**, *232*, 341.
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