(Table II). Lower temperatures were found to have a deleterious effect on the stereochemical outcome of these reductions. It is possible that a decrease in reaction temperature retards the rate of H_2 evolution and boronic ester generation, but has a weaker influence on the rate of the hydride addition, and thus leads to diminished diastereocontrol. Since we had independently made the observation that Wilkinson's catalyst strongly accelerates borate ester formation between alcohols and catecholborane, we evaluated the effect of this catalyst on reaction stereoselectivity (Table II). Accordingly, in the presence of 5% of the rhodium catalyst under otherwise identical conditions (-35 °C), ketone **1** is reduced with 20:1 syn selectivity, and the stereoselection in the reduction of **3** is improved from 3:1 to 10:1. The positive influence of the catalyst on the reaction stereoselection may be attributed, at least in part, to the ability of the transition-metal complex to catalyze the formation of the boronic ester.

In summary, catecholborane is an effective reagent for the syn-selective reduction of β-hydroxy ketones; in certain cases, the levels of diastereoselection can be improved by catalytic amounts of $Rh(PPh_3)_3Cl$. It is anticipated that the mildness and convenience of this reaction will render it a useful method in synthesis.

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

Supplementary Material Available: Experimental data for compounds described in this paper (3 pages). Ordering information is given on any current masthead page.

Studies Directed toward the Total Synthesis of Lonomycin A (Emericid). Asymmetric Synthesis of the C_1–C_{11} Synthon

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Summary: The asymmetric synthesis of the lonomycin A C_1–C_{11} synthon **2** is described, in which the absolute stereochemical relationships were established through the use of β-keto imide aldol bond constructions, internally directed β-hydroxy ketone reduction, and diastereoselective rhodium-catalyzed hydroboration.

Lonomycin A, also known as emericid, is one of the most structurally complex of the polyether antibiotics isolated to date.[1] In addition to the 23 resident stereogenic centers, the latent instability of the carboxyl terminus of this ionophore renders lonomycin a substantial challenge as a target for synthesis. In this paper, we describe the successful construction of the C_1–C_{11} polypropionate portion of this molecule (structure **2**, Scheme I). Recent methodology developed in this laboratory for the assemblage of polypropionate structures utilizing chiral β-keto imides[2] has been exploited to control all pivotal stereochemical relationships and C–C bond constructions in the synthesis of **2**.

The initial stages of the synthesis are illustrated in Scheme II. All absolute stereochemical control in this sequence is ultimately derived from the Sn(II) enolate of β-keto imide **4**. Stannous triflate mediated aldol coupling between **4** and methacrolein ($Sn(OTf)_2$, Et_3N, **4**, CH_2Cl_2, -20 °C, 1 h; 3–5 equiv of RCHO, -78 °C, 30 min) provided adduct **5** (78%, de = 90%). Subsequent anti reduction[3] of the β-hydroxy ketone ($NaBH(OAc)_3$, HOAc, 25 °C, 1 h) provided diol **6** (93%, de = 94%). Refunctionalization to aldehyde **7** was achieved by the straightforward sequence of acetonide formation (2,2-dimethoxypropane, Dowex-50, CH_2Cl_2, 25 °C, 1 h), $LiAlH_4$ reduction of the carboximide (THF, -78 °C, 1 h), and reoxidation using the technique of Parikh and Doering[4] (SO_3·py, DMSO/CH_2Cl_2, -5 °C, 1 h) in 80% overall yield. A second β-keto imide aldol reaction between **4** and aldehyde **7** (2 equiv each $Sn(OTf)_2$, Et_3N, and **4**, CH_2Cl_2, -20 °C, 1 h; 1 equiv **7**, -78 °C, 30 min) provided **8** (79% yield), which contains all of the carbon atoms and seven of the eight asymmetric centers present in the C_1–C_{11} synthon. It is noteworthy that the required stereochemical relationship of the labile C_2 methyl group is also secured in this synthesis plan.

At this point we faced the task of methylating the aldol adduct **8** without promoting retro-aldol cleavage or epimerization of the C_2 methyl-bearing stereocenter. The use of methyl triflate (15 equiv, 30 equiv 2,6-di-*tert*-butylpyridine, $CDCl_3$, 80 °C, 4 h) proved to be an efficient solution to this problem,[5] providing **9** in 83% yield. It was gratifying that no detectable C_2 diastereomization occurred during this methylation, even when the reaction mixture was heated at reflux in chloroform for an extended time period. The success of this transformation is a testament to the stability imparted to the β-keto imide stereocenter by allylic strain control elements.[6]

To complete the preparation of **2**, we hoped to introduce the C_{10} stereocenter through a rhodium-catalyzed hydroboration[7] which would also serve to introduce the required oxygenation at C_{11} needed for eventual aldol coupling to

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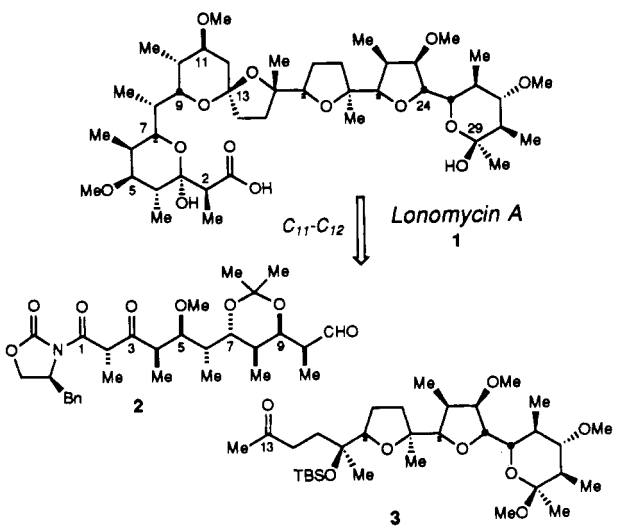
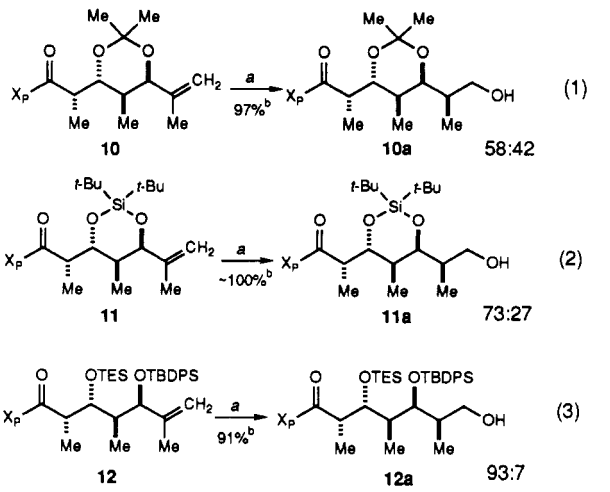
Scheme I



the C_{12}–C_{30} fragment **3**. Several protected derivatives of diol **6** were examined (2–3 equiv of catecholborane, 3–5 mol % $ClRh(PPh_3)_3$, THF, 25 °C, 8 h; 30% H_2O_2, THF/EtOH/H_2O, pH 7, 25 °C, 12 h) as model systems to evaluate the feasibility of this approach (eqs 1–3). Since earlier studies from this laboratory on the catalyzed hydroboration of such allylic alcohols had supported the trend that enhanced hydroboration diastereoselection is coupled with increased size of the allylic oxygen substituent, the trends noted below (eqs 1–3) were consistent with



(1)

(2)

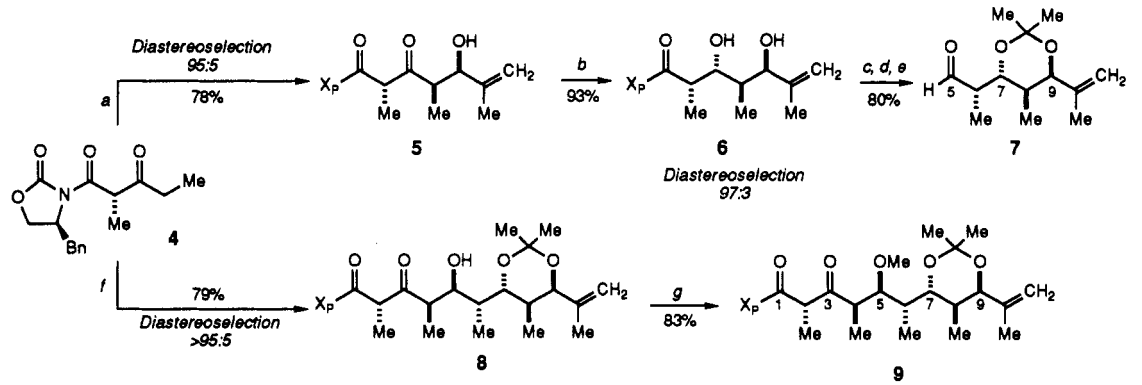
(3)

(a) Catecholborane, $ClRh(Ph_3)_3$; H_2O_2; (b) Isolated yield of both diastereomers. Diasteromer ratios determined by HPLC analysis.

previous findings.[7]

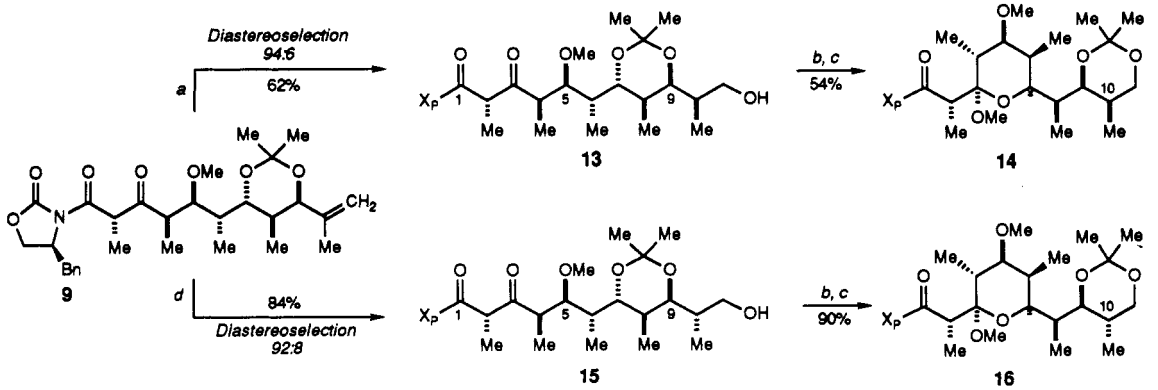
Application of the catalyzed hydroboration reaction to the advanced intermediate **9** (Scheme III) constituted the penultimate step in the construction of the C_1–C_{11} synthon **2**. Based on the closely related model reaction (eq 1), we were not prepared for the high diastereoselectivity observed in the *catalyzed hydroboration* of this olefin to the desired C_{11} alcohol **13** (**13**:**15** = 94:6). The corresponding *uncatalyzed hydroboration* of **9** (disiamylborane, THF, 25 °C) provided the diastereomeric alcohol **15** (84%; **13**:**15** = 8:92) as anticipated by literature precedent.[8]

Scheme II[a]



[a] (a) $Sn(OTf)_2$, Et_3N, 2-methylpropenal; (b) $NaBH(OAc)_3$, HOAc; (c) 2,2-dimethoxypropane, Dowex-50, CH_2Cl_2; (d) LAH, THF, −78 °C; (e) SO_3·pyridine, DMSO, CH_2Cl_2; (f) $Sn(OTf)_2$, Et_3N, **7**; (g) MeOTf, 2,6-di-*tert*-butylpyridine, $CDCl_3$, Δ.

Scheme III[a]



[a] (a) Catecholborane, $ClRh(Ph_3)_3$; H_2O_2; (b) Dowex-50, $HC(OMe)_3$/MeOH; (c) Dowex-50, 2,2-dimethoxypropane/CH_2Cl_2; (d) Sia_2BH; H_2O_2, $NaHCO_3$.

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

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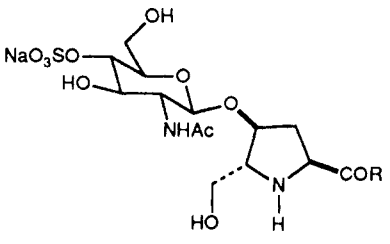
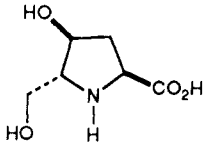
Summary: The first total synthesis of bulgecin C has been achieved in 18 linear steps from (2*R*,4*S*)-hydroxyproline. Transformations of note include the regioselective electrochemical methoxylation of a 4-acetoxyproline carbamate, a stereospecific free radical substitution reaction to incorporate the 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



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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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