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A New Entry to 1,3-Polyols, 2-Amino 1,3-Polyols, and β -(1-Hydroxyalkyl)isoserines Using Azetidinone Frameworks as Chiral Templates via Iterative Asymmetric [2 + 2] Cycloaddition Reactions

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Summary: A new entry to polyfunctional compounds based on an iterative [2 + 2] asymmetric cycloaddition reaction of ketenes to O-protected α -hydroxy aldehyde derived imines is described for the first time.

The design of new synthetic strategies for the construction of polyfunctional target molecules with control of the stereochemistry at each of the newly created stereogenic centers constitutes one of the most important topics in organic synthesis.¹ As an example, the construction of homochiral 1,3-polyol chains by repetition of a few synthetic steps² has proved to be of considerable interest in the synthesis of polyoxomacrolide antibiotics.³ On the basis of this concept, we became interested in the design of a new iterative approach⁴ to 1,3-polyol compounds which, at the same time, would serve for the construction of other target molecules like 2-amino 1,3-polyol chains.⁵ We have previously reported on the utility of a 3-alkoxy β -lactam framework for the synthesis of β -phenyl isoserines.⁶ It seemed obvious therefore that 3-alkoxy-4-(1-alkoxyalkyl)- β -lactams (Figure 1) should be attractive



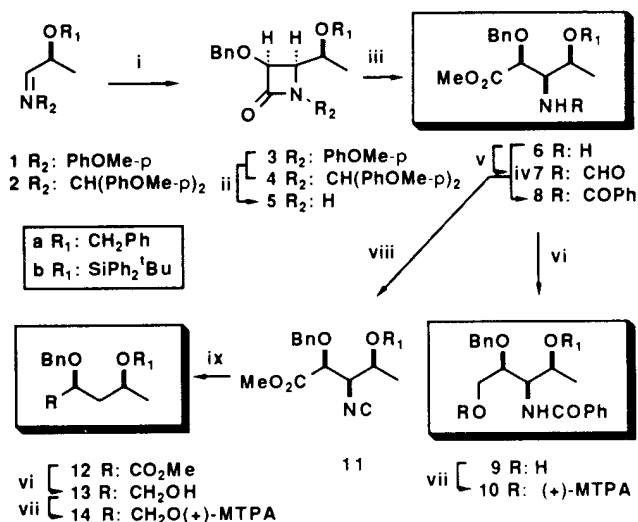
Figure 1.

precursors of β -(1-alkoxyalkyl)isoserines and, thus, 1,3-dihydroxy compounds, if an effective deamination could be achieved. Repetition of the process by converting the resulting α,γ -dialkoxy esters to the corresponding α,γ -dialkoxy aldehyde derived imines would give β -lactams elongated at C-4 position and, thus, more elaborate 1,3-polyols in an iterative fashion. Prior to the present work, Ojima and co-workers^{7,8} reported a synthesis of α -alkoxy esters through a selective hydrogenolysis of the N₁-C₄ β -lactam bond. This method, although remarkable, is limited to β -lactams carrying an aryl moiety at the C₄ position and, consequently, inappropriate for the synthesis of optically active α,γ -dialkoxy esters. Our approach to these compounds, Scheme I, relies on the high level of reaction diastereoselection observed for the Staudinger reaction using α -alkoxy aldehyde derived imines or analogs as the sources of chirality.⁹ In this paper we present our first results on the successful implementation of this new iterative strategy for the synthesis of polyfunctional compounds demonstrating its versatility and synthetic utility.¹⁰

Homochiral β -lactam 3 and 4, prepared by reaction of (benzyloxy)ketene with the readily available lactaldehyde derived imines 1 and 2, were first selected for development

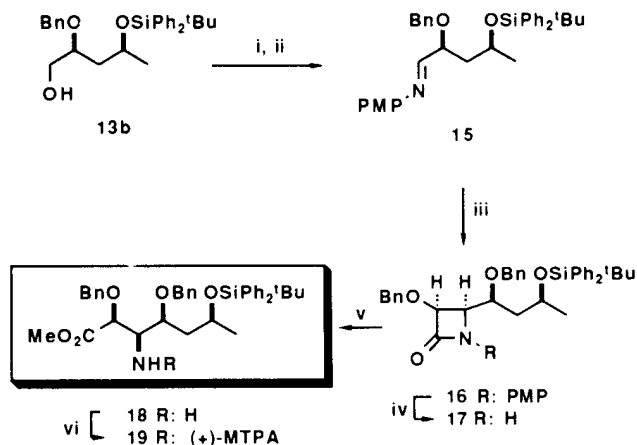
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Scheme I^a

^a Reagents and conditions: (i) BnOCH₂COCl, NEt₃, CH₂Cl₂, -78 °C → rt, 20–24 h (ref 9h); (ii) (NH₄)₂Ce(NO₃)₆, CH₃CN/H₂O, -5 °C, 15 min; (iii) ClSiMe₃, MeOH, 0 °C → rt, 2 h; (iv) PhCOCl, NEt₃, CH₂Cl₂, 0 °C → rt, 3 h; (v) Ac₂O-HCO₂H (vi) LiAlH₄, Et₂O, (vii) (+)-MTPA-Cl, NEt₃, CH₂Cl₂, DMAP cat; (viii) (Cl₃CO)₂CO, NEt₃, CH₂Cl₂, 0 °C, 15 h; (ix) (Me₃Si)₃SiH, AIBN, toluene, 80 °C, 30 min.

to test the effectiveness of the proposal.^{9h} Compound **3a** when subjected to N-dearylation with cerium(IV) ammonium nitrate (CAN)¹¹ afforded **5a** in 60% isolated yield. Treatment of **5a** with trimethylchlorosilane in methanol at room temperature for 2 h provided the β-[1-(benzyloxy)-ethyl]isoserine **6a** in 85% yield. The optical purity of the β-amino ester **6a** was checked by its transformation into the N-benzoyl derivative **8a** [syrup, [α]_D²⁵ = -29.3° (c = 1.0, CH₂Cl₂)] followed by LiAlH₄ reduction of the ester moiety and further acylation of the resulting hydroxy compound **9a** with (+)-MTPA acid chloride¹² and triethylamine overnight. Subsequent ¹⁹F-NMR (δ_F: 105.2 ppm) and HPLC analysis of the resulting ester **10a** proved the overall diastereomeric purity of the reaction sequences performed. Similarly, **3b** [70%, syrup, [α]_D²⁵ = -13.5° (c = 1.0, CH₂Cl₂)], when subjected to N-dearylation afforded **5b** in 56% yield [mp 104–105 °C (hexane), [α]_D²⁵ = -41.0° (c = 1.0, CH₂Cl₂)]. A better chemical yield was obtained when the N-deprotection¹³ was performed on the β-lactam **4b** to give the desired **5b** in 75% yield. At this stage, the next aspect we studied was the deamination of **6a** to provide the first member of the syn-1,3-polyol chain. This was accomplished by formylation of **6a** using acetic anhydride-formic acid¹⁴ followed by a simple dehydration-reduction sequence.¹⁵ The reduction of isocyanide **11a** using tributyltin hydride under Barton's conditions (5 h heating at 80 °C in toluene was necessary to ensure complete conversion) led to the desired α,γ-dialkoxy ester **12a** but only in 30% isolated yield after a difficult separation of butyltin byproducts. Among other alternative hydride reagents examined, triethylsilane and diphenylsilane were completely inefficient for this reac-

Scheme II^a

^a Reagents and conditions: (i) (Cl₃CO)₂CO, DMSO, NEt₃, CH₂Cl₂, (ii) 4-MeOC₆H₄NH₂, CH₂Cl₂, MgSO₄; (iii) BnOCH₂COCl, NEt₃, CH₂Cl₂ - 78 °C → rt, 20–24 h; (iv) (NH₄)₂Ce(NO₃)₆, CH₃CN/H₂O, -5 °C, 15 min; (v) ClSiMe₃, MeOH, 0 °C → rt, 2 h; (vi) (+)-MTPA-Cl, NEt₃, CH₂Cl₂. PMP group: 4-MeOC₆H₄.

tion.¹⁶ On the other hand, tris(trimethylsilyl)silane¹⁷ proved to be at the same time highly reactive and convenient for product isolation. Thus, when **11a** was treated with this reagent in the presence of AIBN in toluene at 80 °C for 30 min, the expected α,γ-dialkoxy ester **12a** was obtained in 80% yield. The absence of epimerization during the reaction sequences was primarily determined by ¹H NMR analysis of the crude compound **12a**, but further evidence was provided by reduction of the methoxycarbonyl group to the 1,3-polyol **13a** [α]_D²⁵ = -18.0° (c = 1.0, CH₂Cl₂) and subsequent acylation using Mosher acid chloride and triethylamine. The resulting Mosher ester **14a** showed a single set of signals in its ¹H, ¹³C, and ¹⁹F NMR spectra, proving that the synthesis and reactions proceeded without detectable racemization.

The second cycle of the iterative process is illustrated in Scheme II. The polyol **13b** was oxidized to the corresponding aldehyde using triphosgene-DMSO¹⁸ and transformed in the usual way into the derived imine **15**. Treatment of such an imine with (benzyloxy)acetyl chloride and triethylamine at -78 °C to room temperature overnight led¹⁹ to the β-lactam **16** in 75% yield as a single diastereomer as judged by ¹H NMR analysis of the crude compound. The stereochemistry of this adduct was established by ¹H NMR (*J*_{3,4} = 5.3 Hz) and its absolute

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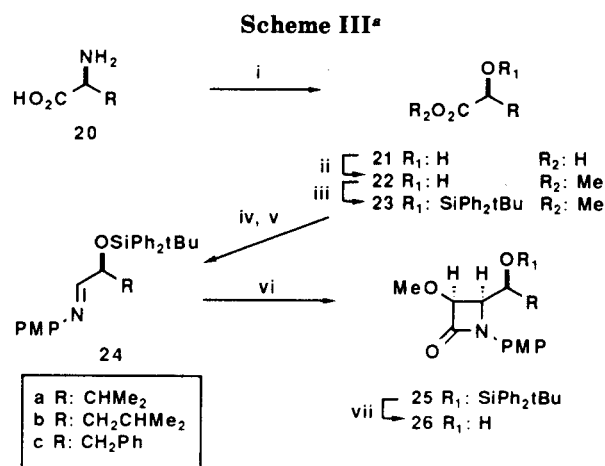
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configuration by analogy with compounds 3 and 4 vide supra. Subsequent treatment with CAN in acetonitrile-water furnished the corresponding N-unsubstituted β -lactam 17 in 50% yield which upon treatment with trimethylchlorosilane in methanol gave the β -amino α,γ,ϵ -polyol side chain 18 in nearly quantitative yield. The optical purity of 18 was determined by its conversion into the Mosher amide 19 which showed a single signal in the ^{19}F NMR spectrum. It should be pointed out that synthetic routes to amino polyols usually involve formation of polyhydroxylated chiral substrates followed by chemo- and stereoselective substitution of one hydroxyl group by the corresponding amino or cryptoamino functionality, thus requiring various selective protecting group manipulations.⁵ Consequently, a feature of the present method is not only the inverse mode of operation but also the possibility of constructing differentially protected polyhydroxylated chiral, nonracemic units by using different protecting groups on either the α -hydroxy ketene or imine partner for the cycloaddition step.

Within the above context, asymmetric induction in the Staudinger reaction from the imine component has usually been achieved using both sugar aldehydes and α -alkoxy aldehydes derived from commercially available α -hydroxy acids, i.e., lactic or mandelic acids.⁹ To extend the scope of the above approach to a variety of 2-amino 1,3-polyols, we decided to explore the behavior of a wider range of α -alkoxy aldehyde derived imines in such a cycloaddition reaction. Our plan was to take advantage of the facile conversion of α -amino acids 20 into the corresponding α -hydroxy acids 21 with overall retention of configuration.²⁰ Although this chemical transformation could be, in principle, applied to all natural as well as unnatural α -amino acids,²¹ three examples were selected to illustrate the proposal (Scheme III). Thus, each compound 21 was first esterified and the resulting α -hydroxy ester 22 protected as the silyl ether 23. Reduction of the methoxycarbonyl group was followed by formation of the corresponding imine 24 and treatment with methoxyacetyl chloride under established conditions.¹⁹ As Table I shows, the resulting β -lactams were isolated in the indicated yields after chromatographic purification on silica gel and in all cases a single diastereomer was observed by NMR spectroscopy of the corresponding crude compounds. These results clearly indicate that the proposed reaction methodology could be applied to the synthesis of a wide variety of structurally different homochiral β -(1-hydroxyalkyl)-isoserines and related compounds with virtually complete control of the stereochemistry at each newly created stereogenic center.²²

In conclusion, the introduction of the Staudinger



^a Reagents and conditions: (i) H₂SO₄ 2 N NaNO₂, H₂O, 0 °C (3 h) \rightarrow rt (15 h); (ii) H₂SO₄, MeOH, refl., 3 h; (iii) ^tBuPh₂SiCl, DBU, CH₂Cl₂ rt, 4 h; (iv) DIBAL 1 M, toluene, -78 °C, 5 min; (v) 4-MeO-C₆H₄NH₂, CH₂Cl₂, MgSO₄, 0 °C, 2 h; (vi) MeOCH₂COCl, NEt₃, CH₂Cl₂ -78 °C \rightarrow rt, 20–24 h; (vii) ^tBu₄NF, THF, rt 20 h.

Table I. Asymmetric [2 + 2] Cycloaddition of Methoxyketene to Imines 24^a

compd	R	yield, ^b %	mp, °C	[α] _D ²⁵ (deg)
25a	CHMe ₂	65	oil	-35.8 ^d
25b	CH ₂ CHMe ₂	65	117–8 ^e	-18.0
26b	CH ₂ CHMe ₂	78	90 ^f	-170.1
25c	CH ₂ Ph	71	oil ^g	
26c	CH ₂ Ph	75	140 ^f	-155.3

^a Reaction conducted on a 10 mmol scale. ^b Isolated yield of pure compounds. ^c Measured in methylene chloride at c = 1.0. ^d Purified by preparative HPLC. ^e Crystallization solvent: CH₂Cl₂/hexane. ^f Crystallization solvent: MeOH. ^g Characterized by conversion into 26c.

reaction in an iterative fashion in the asymmetric synthesis of polyfunctional compounds constitutes the main feature of the present chemistry. Further applications of this methodology to the chemical synthesis of natural products are underway in our laboratory.

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Supplementary Material Available: Experimental procedures and spectral data for 3a,b, 4a, 5a,b, 6a,b, 12a,b, 16–18, 25a–c, and 26b,c (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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