# 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 steps[2] 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 approach[4] 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 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 $N_1$–$C_4$ β-lactam bond. This method, although remarkable, is limited to β-lactams carrying an aryl moiety at the $C_4$ 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]

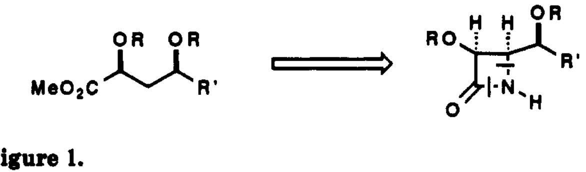

**Figure 1.**

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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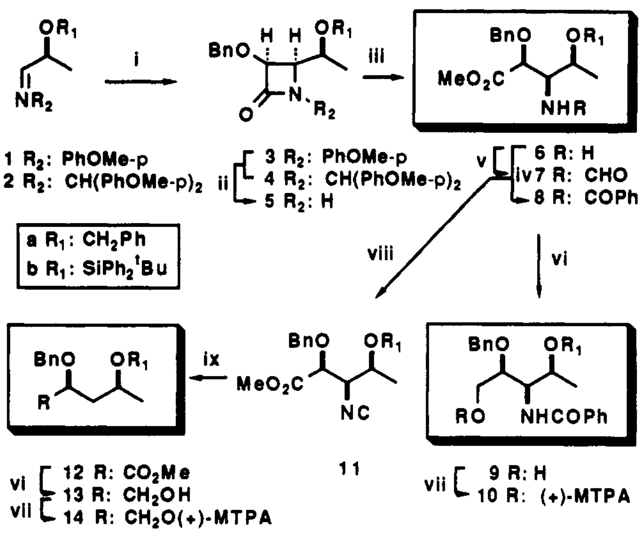
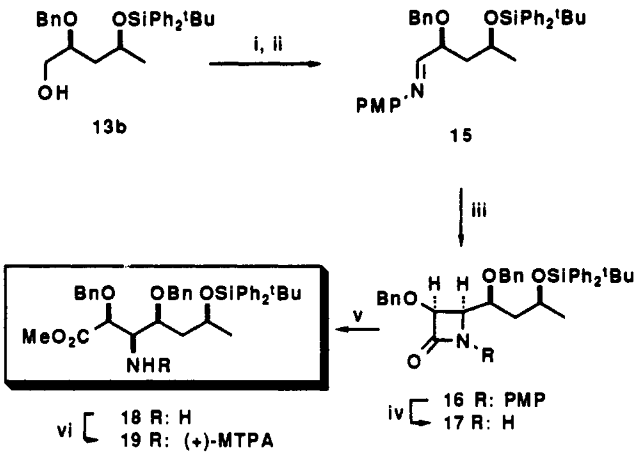
Scheme I[a]



[a] Reagents and conditions: (i) BnOCH$_2$COCl, NEt$_3$, CH$_2$Cl$_2$, −78 °C → rt, 20–24 h (ref 9h); (ii) (NH$_4$)$_2$Ce(NO$_3$)$_6$, CH$_3$CN/H$_2$O, −5 °C, 15 min, (iii) ClSiMe$_3$, MeOH, 0 °C → rt, 2 h; (iv) PhCOCl, NEt$_3$, CH$_2$Cl$_2$, 0 °C → rt, 3 h; (v) Ac$_2$O–HCO$_2$H (vi) LiAlH$_4$, Et$_2$O, (vii) (+)-MTPA-Cl, NEt$_3$, CH$_2$Cl$_2$, DMAP cat; (viii) (Cl$_3$CO)$_2$CO, NEt$_3$, CH$_2$Cl$_2$, 0 °C, 15 h; (ix) (Me$_3$Si)$_3$SiH, AIBN, toluene, 80 °C, 30 min.

Scheme II[a]



[a] Reagents and conditions: (i) (Cl$_3$CO)$_2$CO, DMSO, NEt$_3$, CH$_2$Cl$_2$, (ii) 4-MeOC$_6$H$_4$NH$_2$, CH$_2$Cl$_2$, MgSO$_4$; (iii) BnOCH$_2$COCl, NEt$_3$, CH$_2$Cl$_2$ − 78 °C → rt, 20–24 h; (iv) (NH$_4$)$_2$Ce(NO$_3$)$_6$, CH$_3$CN/H$_2$O, −5 °C, 15 min; (v) ClSiMe$_3$, MeOH, 0 °C → rt, 2 h; (vi) (+)-MTPA-Cl, NEt$_3$, CH$_2$Cl$_2$. PMP group: 4-MeOC$_6$H$_4$.

to test the effectiveness of the proposal.[9h] Compound **3a** when subjected to N-dearylation with cerum(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, $[\alpha]^{25}_D = -29.3°$ ($c$ = 1.0, CH$_2$Cl$_2$)] followed by LiAlH$_4$ reduction of the ester moiety and further acylation of the resulting hydroxy compound **9a** with (+)-MTPA acid chloride[12] and triethylamine overnight. Subsequent $^{19}$F-NMR ($\delta_F$: 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, $[\alpha]^{25}_D = -13.5°$ ($c$ = 1.0, CH$_2$Cl$_2$)], when subjected to N-dearylation afforded **5b** in 56% yield [mp 104–105 °C (hexane), $[\alpha]^{25}_D = -41.0°$ ($c$ = 1.0, CH$_2$Cl$_2$)]. A better chemical yield was obtained when the N-deprotection[13] 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 acid[14] 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 reaction.[16] On the other hand, tris(trimethylsilyl)silane[17] 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 $^1$H NMR analysis of the crude compound **12a**, but further evidence was provided by reduction of the methoxycarbonyl group to the 1,3-polyol **13a** $[\alpha]^{25}_D = -18.0°$ ($c$ = 1.0, CH$_2$Cl$_2$) and subsequent acylation using Mosher acid chloride and triethylamine. The resulting Mosher ester **14a** showed a single set of signals in its $^1$H, $^{13}$C, and $^{19}$F 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–DMSO[18] 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 led[19] to the β-lactam **16** in 75% yield as a single diastereomer as judged by $^1$H NMR analysis of the crude compound. The stereochemistry of this adduct was established by $^1$H NMR ($J_{3,4}$ = 5.3 Hz) and its absolute

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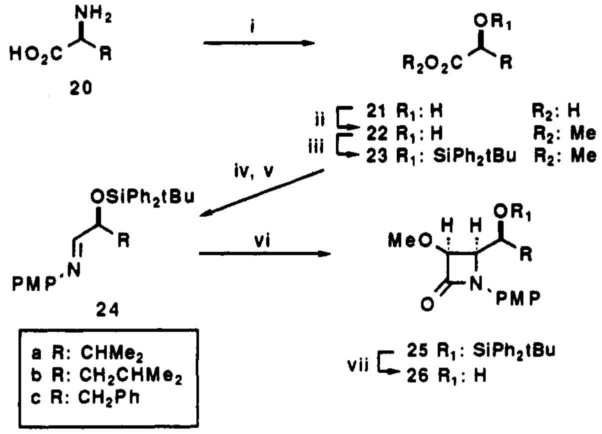
(19) The imines used in this work were prepared by treating equimolar amounts of the corresponding aldehyde with the amine at 0 °C for 4 h in methylene chloride as solvent in the presence of MgSO$_4$. The resulting imine solutions were used immediately in the cycloaddition reactions. In a typical example, a solution of alkoxyacetyl chloride (11.5 mmol) in methylene chloride (7 mL) was added dropwise to a cooled (−78 °C) solution of the corresponding imine **1**, **2**, **15**, or **24** (10 mmol) and triethylamine (3.19 mL, 23 mmol) in the same solvent (25 mL). After the addition, the resulting suspension was left to warm to room temperature and was stirred for 15–20 h. The reaction mixture was poured into methylene chloride (40 mL) and washed successively with water (30 mL), 0.1 N HCl (20 mL), aqueous NaHCO$_3$ (saturated solution, 20 mL), and water (30 mL). The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure, and the resulting crude product was purified by column chromatography (silica gel, eluant: CH$_2$Cl$_2$/hexane (1/5)) to afford pure (3*S*,4*R*)-3-alkoxy-4-[(1*S*)-(benzyloxy)alkyl]- or [(1*S*)-[(*tert*-butyldiphenylsilyl)oxy]alkyl]-1-(*p*-methoxyphenyl)- or [1-(di-*p*-methoxyphenyl)methyl]azetidin-2-ones **3**, **4**, **16**, or **25**.

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 facilie 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]

**Scheme III**[a]



[a] Reagents and conditions: (i) $H_2SO_4$ 2 N $NaNO_2$, $H_2O$, 0 °C (3 h) → rt (15 h); (ii) $H_2SO_4$, MeOH, refl., 3 h; (iii) $^tBuPh_2SiCl$, DBU, $CH_2Cl_2$ rt, 4 h, (iv) DIBAL 1 M, toluene, −78 °C, 5 min, (v) 4-MeO–$C_6H_4NH_2$, $CH_2Cl_2$, $MgSO_4$, 0 °C, 2 h; (vi) $MeOCH_2COCl$, $NEt_3$, $CH_2Cl_2$ −78 °C → rt, 20–24 h; (vii) $^tBu_4NF$, THF, rt 20 h.

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

| compd | R | yield,[b] % | mp, °C | $[\alpha]^{25}{}_D$[c] (deg) |
|---|---|---|---|---|
| **25a** | $CHMe_2$ | 65 | oil | −35.8[d] |
| **25b** | $CH_2CHMe_2$ | 65 | 117–8[e] | −18.0 |
| **26b** | $CH_2CHMe_2$ | 78 | 90[f] | −170.1 |
| **25c** | $CH_2Ph$ | 71 | oil[g] | |
| **26c** | $CH_2Ph$ | 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: $CH_2Cl_2$/hexane. [f] Crystallization solvent: MeOH. [g] Characterized by conversion into **26c**.

In conclusion, the introduction of the Staudinger 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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