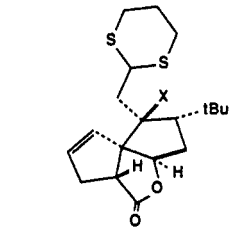
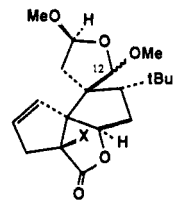
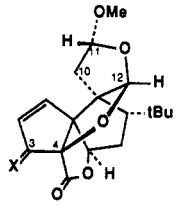


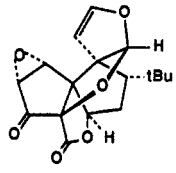
13 X = CH_2OH
14 X = CHO



15 X = H
16 X = OH



17 X = H_2
18 X = O



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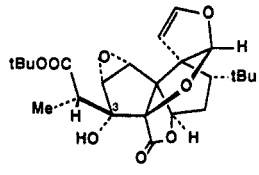

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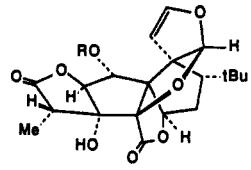
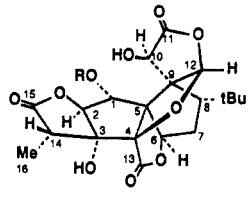


21 R = H
22 R = TBMS



23 R = TBMS
1 R = H

nylsulfonyl)-3-phenyloxaziridine[16] (2 equiv, 0 °C for 30 min) to form the α-hydroxylacetone **16**, mp 115-116 °C, and (2) reaction with a solution of CSA in methylene chloride (20 mg/100 mL) at 23 °C for 24 h to afford **17**, mp 151-153 °C (75%).[20] The introduction of an oxo function at C(3) was accomplished in 50% overall yield by the following transformations: (1) allylic bromination with 1.3 equiv of *N*-bromosuccinimide in carbon tetrachloride (0.02 M) under external tungsten lamp irradiation at 10 °C for 2-3 h (monitored by SG TLC) to give a mixture of 60% of the C(3) brominated product (Br^3), 30% of the C(1) brominated product (Br^1), and 10% of the 3,3-dibrominated product ($Br^{3,3}$); (2) reaction of the mixture with 10 M silver nitrate in acetonitrile at 23 °C for 15 min which generates a mixture of the enone **18**, mp 267-268 °C (from $Br^{3,3}$), the 1-nitrate ester (from Br^3), and the 3-nitrate ester (from Br^1), easily separated by SGC; (3) conversion of the 3-nitrate ester to **18** by nitrate cleavage with zinc-acetic acid followed by oxidation of the resulting C(3) alcohol with PDC in methylene chloride at 23 °C for 5 h; (4) conversion of the 1-nitrate ester to **18** by exposure to 20 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene and 20 equiv of water in 10:1 benzene-methanol at 23 °C for 30 h followed by oxidation of the resulting C(3) alcohol (from overall S_N2' reaction) by PDC.

The final γ-lactone ring was affixed starting with epoxy ketone **19** which was obtained from **18** in the following two steps: (1) elimination of methanol from C(10)-C(11) by heating **18** under argon with 5 equiv of pyridinium tosylate and 2.5 equiv of dry pyridine in chlorobenzene at 135 °C for 16 h (80% yield)[21,22] and (2) enone epoxidation with triphenylmethyl hydroperoxide (5 equiv) and benzyltrimethylammonium isopropoxide (0.5 equiv) in THF at -10 °C for 3 h to give after reduction of excess hydroperoxide by trimethyl phosphite (10 equiv) and SGC 72% of **19**. Reaction of **19** with 7 equiv of the lithium enolate of *tert*-butyl propionate (from LDA) in 4:1 THF-hexamethylphosphorictriamide, at -78 °C to -30 °C for 2 h and then at -30 °C for 10 h, furnished the desired aldol adduct **20** in 60% yield after SGC.[23] Exposure of **20** to 4 equiv of CSA in methylene chloride (23 °C for 15 h) afforded bis-lactone **21** (82%) which was converted to the *tert*-butyldimethylsilyl (TBMS) ether **22** upon treatment with 2.5 equiv of TBMS triflate and 5 equiv of 2,6-lutidine in acetonitrile at 23 °C for 1 h (89%). Hydroxylation of **22** using osmium tetroxide in pyridine followed by oxidation of the resulting product with excess iodine in methanol in the presence of $CaCO_3$ (23 °C for 12 h) produced trilactone **23** (ca. 40% from **22**)[21] along with a small amount of the C(10) epimer. Desilylation of **23** (5 equiv of $BF_3 \cdot Et_2O$ in methylene chloride at 23 °C for 14 h) gave 89% yield of (±)-ginkgolide B (**1**), identical with an authentic sample by 500-MHz ^1H NMR, FT-IR, SG-TLC analysis in several solvent systems, and mass spectral comparison.[24]

Supplementary Material Available: Spectral data for compounds **1-23** (6 pages). Ordering information is given on any current masthead page.

(19) The observed course of the functionalization to give **12** suggests that steric repulsion between the *tert*-butyl substituent at C(8) and the hydrogens at C(10) and C(11) causes puckering of the C(5)-C(9) ring so as to bring H-C(8) into proximity to O-C(4).

(20) The configuration at C(11) of **17** follows clearly from chemical and NOE studies not reported herein.

(21) The yields given for this and remaining steps in the synthesis are probably not optimum since these reactions have been conducted only a few times without systematic attempts at further improvement.

(22) This product and also **21** and **1** are solids which decompose before melting; **22** and **23** are colorless oils.

(23) A small amount of C(3) epimer (ca. 7%) was also obtained; the C(3) epimer became the major product from reaction in THF alone at -78 °C.

(24) We are grateful to Dr. P. Braquet, Institute Henri Beaufour, Paris and Dr. K. Yamada of Kagoya University for samples of ginkgolide B, to Dr. Ashvinikumar V. Gavai and Dr. Yi Bin Xiang for valuable experimental assistance, and to Francis J. Hannon for determination of mass spectra. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

Asymmetric Synthesis on Carbohydrate Templates: Stereoselective Ugi Synthesis of α-Amino Acid Derivatives

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Experiences from the chemical synthesis of glycopeptides[1] revealed that carbohydrates exhibit considerable complexing abilities toward cations. This stimulated the concept to utilize this complexation together with the high chirality of the carbohydrates for the stereochemical control of reactions.[2] The present paper reports a stereoselective formation of α-amino acid derivatives by using the Ugi four-component condensation.[3]

In contrast to the recently developed stereoselection methods for synthesis of α-amino acids[4] based on the electrophilic ami-

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(3) Ugi, I.; Offermann, K.; Herlinger, H.; Marquarding, D. *Justus Liebigs Ann. Chem.* **1967**, 709, 1 and references therein.

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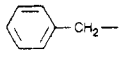
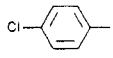
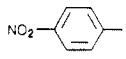
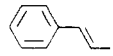
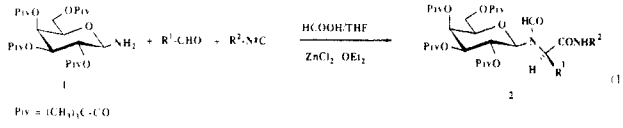
Table I. Diastereoselective Ugi Synthesis of *N*-Galactosylamino Acid Amides **2** (Eq 1)[f]

product	R^1	R^2	reactn temp[c]/ time[d,e]	kinetic ratio[a] (2*R*:2*S*)	yield (%) of pure (2*R*)-**2**
2a	CH_3-$(CH_2)_2$	$(CH_3)_3C$	−78/2[d]	94:6	80
2b	$(CH_3)_2$-CH	$(CH_3)_3C$	−78/2[d]	95:5	86
2c	$(CH_3)_3C$	$(CH_3)_3C$	−25/3[d]	96:4[b]	80
2d		$(CH_3)_3C$	−78/8[e]	95:5	80
2e		$(CH_3)_3C$	−25/24[e]	95:5	90
2f		$(CH_3)_3C$	−25/24[e]	96:4	93
2g		$(CH_3)_3C$	0/8[e]	91:9	81
2h		$(CH_3)_3C$	−25/24[e]	97:3	92
2i		$(CH_3)_3C$	0/4[e]	94:6	91
2j		$(CH_3)_3C$	−25/24[e]	95:5	75
2k	$N{\equiv}C$-$(CH_2)_3$-	Ph	−25/24[e]	94:6	81

[a] HPLC (diode array detection) directly taken from the reaction mixtures after treatment with water. [b] At −78 °C: (2*R*:2*S*) > 100:1. [c] Temperature is measured in °C. [d] Time is measured in days. [e] Time is measured in hours. [f] In all cases the yields of diastereomeric mixture 2*R*/2*S* are >95%.

nation[4b-e] or alkylation[4a,g] of corresponding enolates, the Ugi reaction circumvents the use of organometallic intermediates. Ugi and his co-workers achieved asymmetric induction in their reactions by the application of α-phenyl- or α-ferrocenylalkylamines.[3,5] However during hydrogenolytic removal, the chirality of these auxiliaries is destroyed. Furthermore, α-amino acids sensitive to hydrogenation (e.g., phenylglycine, amino acids with sulfur containing or alkene side chain) cannot be synthesized by this procedure.

The Ugi reaction with the 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**)[6] (eq 1) as the chiral auxiliary described here proceeds in a simple one-pot procedure.



(1)

In a typical experiment, a solution of 4 mmol of **1**, 4.1 mmol of the corresponding aldehyde, 4.4 mmol of a carboxylic acid, and 4.2 mmol of an aliphatic or aromatic isocyanide in 30 mL of tetrahydrofuran is cooled to the temperature quoted in Table I. To this solution is added 4 mmol of zinc chloride (as the etherate). After the reaction is finished (monitoring by TLC), a conventional isolation and recrystallization delivers diastereomerically pure products **2** (Table I). Formic acid (or acetic acid) is used preferably as the carboxylic acid in order to accelerate the reactions. At room temperature, the α-amino acid derivatives are formed almost quantitatively in a few minutes. Even under these conditions, the (β-D,*R*)-diastereomers **2** are preferred in ratios of 8–10:1. At −25 °C the reactions require about 24 h. At −78 °C and with sterically demanding aldehydes about 3 days are necessary to complete the reaction. However, then the diastereoselectivity increases to 15–35:1 in favor of the (β-D,*R*)-**2** diastereomers (Table I). In particular, at −78 °C from pivaldehyde the (2*R*)-diastereomer of the *tert*-leucine derivative **2c** is formed exclusively. Even by 400-MHz proton NMR and by analytical HPLC the other diastereomer cannot be detected. In all cases, the pure (β-D,*R*)-diastereomers **2** are obtained in yields of 75–95% after one simple recrystallization from heptane or dichloromethane/heptane.

Table II. Two-Step Hydrolysis of Compounds **2** (eq 2) and Synthesis of (*R*)-Amino Acids **5**

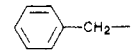
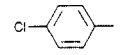
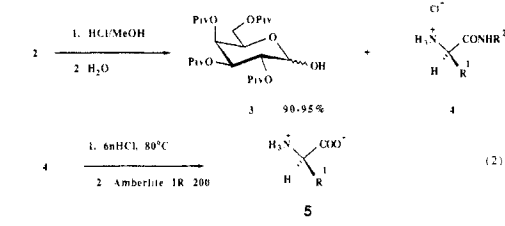
product	R^1	overall yield (%)	$[\alpha]^{22}_D$
5a	$(CH_3)_3C$	90	−8.8 (*c* 2, 1.5 N HCl); lit.[8] $[\alpha]^{22}_D$ −7 ± 1 (*c* 5, 5 N HCl)
5b		82	+6.5 (*c* 1, 1.5 N HCl); lit.[9] $[\alpha]^{25}_D$ = +7.07 (*c* 1, 1 N HCl)
5c		85	−157 (*c* 1, 1 N HCl); lit.[10] $[\alpha]^{20}_D$ = −155 (*c* 1, 1 N HCl)
5d		90	−140.5 (*c* 0.5, 1 N HCl); lit.[10] $[\alpha]^{20}_D$ = −138.7 (*c* 1, 1 N HCl)
5e	HOOC-$(CH_2)_3$-	85	−21.5 (*c* 0.7, 2 N HCl); lit.[11] $[\alpha]^{16}_D$ = −25 (*c* 0.7, 6 N HCl)

Table I illustrates that α-amino acid derivatives **2** having unbranched **2a**, branched **2b,c**, benzylic **2d**, functionalized **2k**, and unsaturated **2j** side chains are accessible efficiently by this method in enantiomerically pure form. It is a particular advantage of this reaction that aryl and heteroaryl glycine derivatives, even such ones containing sulfur **2f** or strongly acidifying moieties **2i**, can be synthesized stereoselectively in high yields. The *N*-galactosylamino acid amide derivatives **2** can be transformed into a series of valuable chiral products, e.g., 1,2-diamines and β-amino alcohols. Most interesting among these are the (*R*)-amino acids themselves.

The conversion of the pure (β-D,*R*)-diastereomers **2** into the corresponding (*R*)-amino acids **5** is achieved by use of an acidic two-step hydrolysis (eq 2). After acidolytic cleavage of the



(2)

N-glycosidic bond the *O*-pivaloyl-galactose **3** is reisolated in 90–95% yield. It can easily be transformed into the starting chiral auxiliary **1**.[6] Hydrolysis of the amino acid amides **4** and subsequent deprotonation delivers the free (*R*)-α-amino acids **5** (Table II). (*S*)-Enantiomers cannot be detected in the products (TLC control using "chiral plate"[7]).

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