JOC The Journal of Organic Chemistry

Note

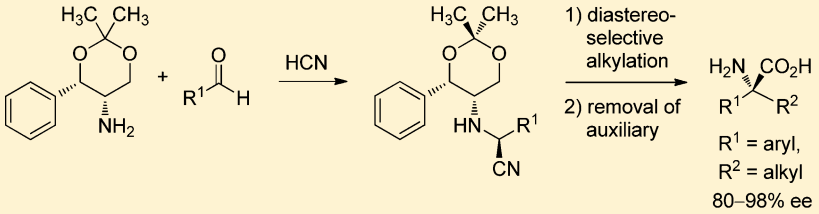
pubs.acs.org/joc

Enantioselective Synthesis of α-Quaternary Amino Acids by Alkylation of Deprotonated α-Aminonitriles

Isabelle Netz, Murat Kucukdisli, and Till Opatz*

Institute of Organic Chemistry, Johannes Gutenberg-University, Duesbergweg 10-14, 55128 Mainz, Germany

Supporting Information



ABSTRACT: A series of α-quaternary arylglycines were prepared in high optical purity (up to 98% ee) by α-alkylation of deprotonated α-aminonitriles derived by the Strecker reaction from (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane. The procedure includes only chromatographic purification of the final products and is devoid of chromatography or crystallization operations on intermediates to raise the optical purity.

α-Amino acids play a key role in the machinery of life. Consequently, their asymmetric synthesis has become an important task for synthetic organic chemists.[1−5] Whereas α-quaternary α-amino acids are nonproteinogenic, they do occur in nature and have proven to be useful as pharmaceuticals (e.g., methyldopa) and as building blocks for the construction of peptidomimetics.[6,7] Consequently, a variety of synthetic methods have been developed for their synthesis, both in racemic and nonracemic forms.[8−18] The pioneering chemical synthesis of α-amino acids reported by Adolph Strecker in 1850 made use of their close relationship with α-aminonitriles, and even today, the Strecker synthesis is still used for the industrial scale synthesis of α-amino acids like methionine.[19] Because of the strong anion stabilizing capacity of the nitrile group and the latent iminium ion reactivity,[20−23] α-aminonitriles are not only useful precursors to amino acids but also versatile building blocks for the synthesis of a wide variety of nitrogen-containing compounds,[24,25] including diverse *N*-heteroarenes,[26−28] aliphatic amine derivatives[29,30] and alkaloids.[31−39] We found that *N*-mono- and *N*-unsubstituted α-aminonitriles derived from aromatic or heteroaromatic aldehydes can be deprotonated quantitatively in the α-position to furnish stabilized α-aminocarbanion equivalents. In contrast to their counterparts derived from aliphatic aldehydes, no *N*-protection is required.[40] Because the resulting anions should be suitable for the synthesis of α-quaternary α-amino acids through C-alkylation and subsequent hydrolysis, several removable nitrogen-bound auxiliaries were tested for controlling the stereochemistry of the alkylation step. The use of various substituted 1-phenylethylamine-type auxiliaries were met with limited success, and diastereoselectivities of 10:1 were not surpassed. However, (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**1**) proved to be highly effective and provided excellent diastereoselectivities of up to 99:1. In contrast to the also highly efficient 2-sulfinylarene-type auxiliary employed by Ruano and co-workers,[41] it can be removed by oxidation after hydrolysis of the nitrile function, permitting straightforward access to α-quaternary arylglycines.[42,43]

Auxiliary **1** had been successfully employed by Weinges et al.[42−44] for the synthesis of α-amino acids by means of a diastereoselective crystallization of its Strecker products with aldehydes or ketones followed by hydrolysis and oxidative degradation of the chiral template. Being readily available from acetone, nitromethane, formaldehyde, and benzaldehyde as a byproduct of an industrial-scale synthesis of the antibiotic chloramphenicol, the recycling of **1** is expendable. In the 1990s, the Enders group employed Strecker products derived from the *N*-methyl analogue of **1** as chiral acyl anion equivalents for diastereoselective 1,4-additions to α,β-unsaturated carbonyl compounds.[45−47]

The reaction of the hydrochloride salt of **1** with benzaldehyde (**2a**) and 2-napththaldehyde (**2b**) in the presence of KCN furnished the aminonitriles **3a** and **3b** as single diastereomers after crystallization from the reaction medium in 82 and 67% yields, respectively. Their deprotonation with potassium bis(trimethylsilyl)amide (KHMDS) in THF at −78 °C furnished the corresponding potassium keteneiminates, which were α-alkylated with various alkyl and benzyl halides to α-quaternary aminonitriles **4** (Scheme 1).

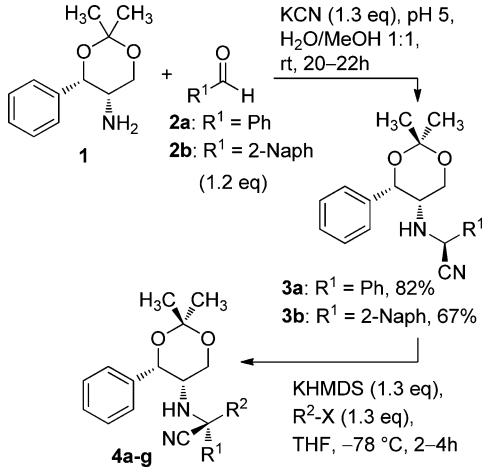
The diastereoselectivity of the alkylation was determined by ^{1}H NMR spectroscopy as well as by HPLC-MS of the crude reaction mixture after an extractive workup (vide infra).

Because the alkylation products were prone to spontaneous dehydrocyanation during attempted chromatographic purification and inert to acetylation, tosylation, and alkoxycarbonyla-

Received: April 18, 2015
Published: May 29, 2015

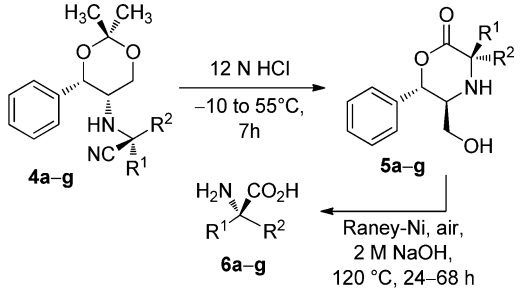
DOI: 10.1021/acs.joc.5b00868
J. Org. Chem. 2015, 80, 6864−6869

Scheme 1. Synthesis of α-Aminonitriles 4 by α-Alkylation



tion to increase their stability, they were directly subjected to acidic hydrolysis of the nitrile group as well as oxidative removal of the auxiliary. As already reported by Weinges et al.,[42−44] lactones **5** were formed upon treatment of compounds **4** with hydrochloric acid. Double oxidative C−C-bond cleavage catalyzed by Raney−Nickel with aerial oxygen as the stoichiometric oxidant produced the α-amino acids **6**, which were purified by preparative HPLC (Scheme 2). Although compounds **5** were obtained in low purity as judged by NMR, the purity increased upon removal of the auxiliary.

Scheme 2. Hydrolysis and Oxidative Removal of the Auxiliary to Produce Amino Acids 6



The optical purity of the products was determined by derivatization with Marfey's reagent (1-fluoro-2,4-dinitrophenyl-5-L-alanine amide) and analytical HPLC.[48,49] The racemic products used as HPLC standards were synthesized via a Bucherer−Bergs reaction of the corresponding ketones for comparison.[50,51] The results are summarized in Table 1.

With the sole exception of isopropyl-substituted compound **6e** (Table 1, entry 5), all products were obtained with enantioselectivities of 91 to >98% ee, demonstrating the high degree of stereocontrol exerted by the Weinges auxiliary.

Comparison of the optical rotation of compounds **6a−e** with literature values confirmed the *R*-configuration in each case (all compounds except for **6c** are levorotatory). Presumably, the shielding of the Re face of the keteneiminate β-carbon by the phenyl group of the auxiliary is responsible for the observed asymmetric induction (Figure 1).

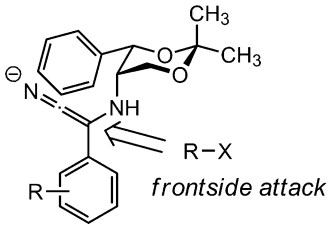
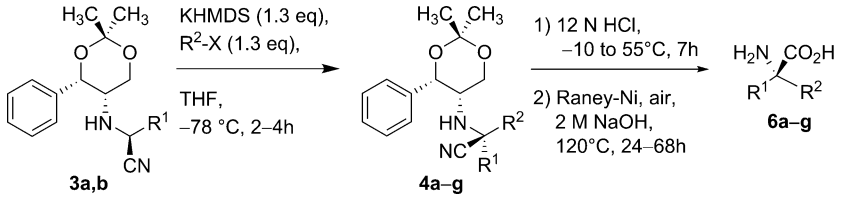


Figure 1. Model for the stereoselective alkylation.

The direction of attack and position of the other arene moiety are identical to the model for Weinges' diastereoselective HCN addition to arylaldimines derived from **1**.[24,44] A highly similar spatial arrangement is also reflected in the X-ray structure of the THF-complex of the lithiated *N*-methyl derivative of **1** published by Enders et al.[52] who consistently observed Si-side attack in their 1,4-additions.

In summary, a highly effective diastereoselective auxiliary-controlled synthesis of α-quaternary arylglycines based on the α-alkylation of deprotonated α-aminonitriles derived from (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane was developed. The products were obtained in high optical purity without the need for the purification of intermediates by chromatography or crystallization. To the best of our knowledge, this represents the first stereoselective alkylation of deprotonated *N*-monosubstituted α-aminonitriles for the

Table 1. Auxiliary-Controlled Synthesis of α-Quaternary Arylglycines 6



entry	product	R^1	R^2–X	yield from Strecker product **3**	er[a]	ee[a]
1	**6a**	Ph	MeI	33%	96:4	92%
2	**6b**	Ph	EtBr	74%	98.5:1.5	97%
3	**6c**	Ph	BnBr	68%	95.5:4.5	91%
4	**6d**	Ph	*n*-PrBr	33%	98:2	96%
5	**6e**	Ph	*i*-PrBr	21%	90:10[b]	80%[b]
6	**6f**	Ph	MOMCl	81%	>99:1	>98%
7	**6g**	2-naph	EtBr	49%	97:3	94%

[a]Determined by HPLC of the α-amino acids after derivatization with Marfey's reagent. [b]Approximate value due to the presence of impurities.

DOI: 10.1021/acs.joc.5b00868
J. Org. Chem. 2015, 80, 6864−6869

preparation of α-amino acids. Although the synthesis of purely aliphatic α-amino acids requires the introduction of a removable *N*-protecting group (e.g., benzyl or PMP), high inductions have already been demonstrated for the *N*-methyl derivative of the Weinges auxiliary.

EXPERIMENTAL SECTION

Materials and Methods. All reactions requiring the exclusion of air and/or moisture were conducted in flame-dried glassware under an argon atmosphere. THF was distilled from potassium/benzophenone under an argon atmosphere. DCM was dried over calcium hydride and distilled under an argon atmosphere. Ethyl acetate and cyclohexane were purchased in technical quality and were purified by distillation. All other chemicals and solvents were purchased from commercial suppliers and used without prior purification unless otherwise stated. Flash chromatography was performed on silica of 25−40 μm particle size. Alternatively, an automatic gradient flash chromatographic system with integrated UV detector was used. NMR spectra were recorded on 300, 400, and 600 MHz spectrometers using standard pulse sequences. Chemical shifts are expressed in ppm relative to tetramethylsilane referenced to the residual solvent signals ($CDCl_3$: ^1H, δ = 7.26 ppm; ^{13}C, δ = 77.16 ppm. D_2O: ^1H, δ = 4.79 ppm. CD_3OD: ^1H, δ = 3.31 ppm; ^{13}C, δ = 49.00 ppm). HPLC-MS- and ESI-MS-analyses were performed on high pressure gradient systems with diode array detectors. ESI-HRMS was performed on a Q-TOF instrument with a dual source and a suitable external calibrant. Analytical HPLC: ACE3-C18PFP (3 μm particle size, 150 × 4.6 mm), 1.0 mL/min flow, 40 °C. Preparative HPLC: ACE5-C18PFP-column (5 μm particle size, 150 × 30 mm), 37.5 mL/min flow, 21 °C. TLC was performed on alumina-backed silica plates (0.25 mm, 60 F254). IR spectra were recorded on an FTIR with a diamond ATR unit. Optical rotations were measured at 546 and 578 nm and were extrapolated to 589 nm using the Drude equation. Melting points were measured on an electrothermal apparatus with a digital thermometer.

General Procedure for the Synthesis of Aminonitriles 3. The title compounds were prepared according to a modified protocol by Enders et al.[45] (4*S*,5*S*)-(+)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**1**) was dissolved in methanol/water 1:1 and was acidified with hydrochloric acid (1 M) to pH 5. Under cooling (ice bath), the respective aldehyde and KCN were added, and the mixture was stirred until TLC indicated complete conversion. Gaseous HCN was removed with a stream of argon (CAUTION!), and the reaction mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo.

*(2S,4′S,5′S)-(+)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-phenylacetonitrile (**3a**).* The title compound was prepared according to the general procedure from amine **1** (2.98 g, 14.4 mmol) in H_2O/MeOH (30 mL each), benzaldehyde (1.74 mL, 17.3 mmol), and KCN (1.28 g, 18.7 mmol) over 20 h at room temperature. Yield: 3.78 g (11.7 mmol, 82%) as colorless crystals. Mp 111.4−112.0 °C (from EtOH), lit.[44] mp 114 °C. R_f = 0.52 (cyclohexane/ethyl acetate 3:1). IR (ATR, cm^{-1}) $\tilde{\nu}$: 3330, 2992, 2873, 1451, 1381, 1198, 1072, 845, 743, 698. ^1H NMR, COSY, NOESY (400 MHz, $CDCl_3$): δ 7.45−7.08 (m, 10H, H_{ar}), 5.17 (s, 1H, *H*-4′), 4.30 (d, *J* = 11.9 Hz, 1H, *H*-6′$_a$), 4.06 (d, *J* = 11.9 Hz, 1H, *H*-6′$_b$), 3.89 (s, 1H, *H*-2), 2.94 (s, 1H, *H*-5′), 2.14 (s, 1H, N*H*), 1.56 (s, 3H, CH_3-a), 1.51 (s, 3H, CH_3-b). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ 139.6 (*C*1‴), 134.9 (*C*1″), 129.0 (*C*4″), 128.8 (*C*3″,5″), 128.4 (*C*4‴), 127.7 (*C*3‴,5‴), 127.6 (*C*2″,6″), 126.1 (*C*2‴,6‴), 119.8 (*C*1), 99.4 (*C*2′), 73.3 (*C*4′), 64.9 (*C*6′), 54.8 (*C*5′), 54.0 (*C*2), 29.6 (*C*H$_3$-b), 18.7 (*C*H$_3$-a). ESI-HRMS (*m*/*z*): calcd for $[C_{20}H_{22}N_2O_2 + H]^+$, 323.1760; found, 323.1764.

The analytical data are in accordance with those reported in the literature.[44]

*(2S,4′S,5′S)-(+)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-(2-naphthyl)-acetonitrile (**3b**).* The title compound was prepared according to the general procedure from amine **1** (770 mg, 3.71 mmol) in H_2O/MeOH (10 mL each), 2-naphthaldehyde (696 mg, 4.46 mmol), and KCN (314 mg, 4.83 mmol) over 22 h at room temperature. Yield: 925 mg (2.48 mmol, 67%) as a colorless crystalline solid. Mp 122.5−123.2 °C (from EtOH). R_f = 0.45 (cyclohexane/ethyl acetate 3:1). IR (ATR, cm^{-1}) $\tilde{\nu}$: 3340, 2992, 2872, 2246, 1693, 1451, 1380, 1198, 1073, 738, 700. ^1H NMR, COSY (400 MHz, $CDCl_3$): δ 7.85−7.71 (m, 3H, H_{ar}), 7.58 (d, *J* = 1.7 Hz, 1H, H_{ar}), 7.54−7.47 (m, 2H, H_{ar}), 7.47−7.37 (m, 5H, H_{ar}), 7.12 (dd, *J* = 8.5, 1.9 Hz, 1H, H_{ar}), 5.18 (d, *J* = 2.2 Hz, 1H, *H*-4′), 4.29 (dd, *J* = 12.0, 2.1 Hz, 1H, *H*-6′$_a$), 4.14−4.07 (m, 2H, *H*-6′$_b$, *H*-2), 2.96 (m, 1H, *H*-5′), 2.22 (t, *J* = 7.7 Hz, 1H, N*H*), 1.56 (s, 3H, CH_3-a), 1.50 (s, 3H, CH_3-b). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ 139.7 (*C*1‴), 133.5 ($C_{q,naph}$), 133.0 ($C_{q,naph}$), 132.3 (*C*2″), 128.8 (C_{ar}), 128.5 (*C*3‴,5‴), 128.2 (C_{ar}), 127.8 (C_{ar}), 127.8 (C_{ar}), 126.9 (C_{ar}), 126.8 (C_{ar}), 126.7 (C_{ar}), 126.2 (*C*2‴,6‴), 125.2 (C_{ar}), 119.8 (*C*1), 99.5 (*C*2′), 73.5 (*C*4′), 64.8 (*C*6′), 55.0 (*C*5′), 54.1 (*C*2), 29.7 (*C*H$_3$-b), 18.8 (*C*H$_3$-a). ESI-HRMS (*m*/*z*): calcd for $[C_{24}H_{24}N_2O_2 + Na]^+$, 395.1735; found, 395.1731.

General Procedure for the Alkylation of Aminonitriles 4. Alkylated aminonitriles **4** were prepared according to a modified protocol by Enders et al.[45] In a flame-dried round-bottom flask, starting aminonitrile **3** was dissolved in dry THF (0.75 mL/100 mg) under an argon atmosphere. After cooling to −78 °C, a solution of KHMDS (1.3 equiv) in dry THF (1.25 mL/100 mg) was added. Shortly thereafter, the alkyl halide (1.3 equiv) was added as a solution in dry THF (1.00 mL/100 μL), and the mixture was stirred at −78 °C until TLC indicated complete conversion. The dry ice bath was removed, and after 1 h, a saturated $NaHCO_3$ solution was added. The mixture was then extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Because of their instability during chromatography, alkylated aminonitriles **4** were subjected to removal of the auxiliary without further purification.

*(2R,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-methyl-phenylacetonitrile (**4a**).* The title compound was prepared according to the general procedure from aminonitrile **3a** (300 mg, 0.93 mmol), KHMDS (241 mg, 1.21 mmol), and iodomethane (75.6 μL, 1.21 mmol) over 2 h at −78 °C. The crude product (365 mg, yellowish oil) was directly subjected to removal of the auxiliary. R_t: (*R*,*S*,*S*) = 1.24 min (eluent: H_2O/MeCN 50:50). R_f = 0.64 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\tilde{\nu}$: 3352, 2992, 2875, 1449, 1381, 1198, 845, 762, 698. ^1H NMR, COSY (300 MHz, $CDCl_3$): δ 7.34−7.27 (m, 3H, *H*-3‴,5‴,4″), 7.19−7.08 (m, 3H, *H*-2‴,6‴,4‴), 6.98 (pseudo-t, J_{app} = 7.8 Hz, 2H, *H*-3″,5″), 6.79 (dd-like, J_{app} = 8.4, 1.1 Hz, 2H, *H*-2″,6″), 4.90 (d, *J* = 1.8 Hz, 1H, *H*-4′), 4.61 (dd, *J* = 12.3, 1.7 Hz, 1H, *H*-6′$_a$), 4.06 (dd, *J* = 12.3, 1.4 Hz, 1H, *H*-6′$_b$), 2.55 (s, 1H, N*H*), 2.46 (s, 1H, *H*-5′), 1.64 (s, 3H, −CH_3), 1.58 (s, 3H, CH_3-a), 1.52 (s, 3H, CH_3-b). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ 139.7 (*C*1‴), 139.0 (*C*1″), 128.5 (*C*3″,5″), 128.0 (*C*4″), 127.9 (*C*3‴,5‴), 127.2 (*C*4‴), 126.9 (*C*2‴,6‴), 125.8 (*C*2″,6″), 123.0 (*C*1), 99.3 (*C*2′), 75.1 (*C*4′), 62.5 (*C*6′), 58.1 (*C*2), 52.2 (*C*5′), 32.7 (*C*H$_3$), 29.9 (*C*H$_3$-b), 18.6 (*C*H$_3$-a). ESI-MS (*m*/*z*): 279.1 (100%, $[M - CH_3COCH_3 + H]^+$), 337.1 (16.3%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{21}H_{24}N_2O_2 + Na]^+$, 359.1735; found, 359.1729. No diastereomer detected by HPLC/MS and 2D-NMR.

*(2R,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-ethyl-phenylacetonitrile (**4b**).* The title compound was prepared according to the general procedure from aminonitrile **3a** (200 mg, 0.62 mmol), KHMDS (161 mg, 0.81 mmol), and bromoethane (60.2 μL, 0.81 mmol) over 2 h at −78 °C. The crude product (226 mg, yellowish oil) was directly subjected to removal of the auxiliary. R_t: (*R*,*S*,*S*) = 2.02 min, (*S*,*S*,*S*) = 1.64 min (eluent: H_2O/MeCN 50:50). R_f = 0.65 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\tilde{\nu}$: 3351, 3029, 2878, 1452, 1382, 1200, 847, 760, 700. ^1H NMR, COSY (300 MHz, $CDCl_3$): δ 7.33−7.27 (m, 3H, *H*-3‴,5‴,4″), 7.18−7.09 (m, 3H, *H*-2‴,6‴,4‴), 6.97 (pseudo-t, J_{app} = 7.8 Hz, 2H, *H*-3″,5″), 6.72 (dd-like, J_{app} = 8.4, 1.1 Hz, 2H, *H*-2″,6″), 4.89 (d, *J* = 1.9 Hz, 1H, *H*-4′), 4.63 (dd, *J* = 12.3, 1.8 Hz, 1H, *H*-6′$_a$), 4.04 (dd, *J* = 12.3, 1.5 Hz, 1H, *H*-6′$_b$), 2.63 (d, *J* = 10.4 Hz, 1H, N*H*), 2.46 (dd, *J* = 10.4, 1.4 Hz, 1H, *H*-5′), 1.93 (dq, *J* = 14.8, 7.3 Hz, 1H, -CH_2CH$_3$), 1.76 (dq, *J* = 14.8, 7.5 Hz, 1H, -CH_2CH$_3$), 1.57 (s, 3H, CH_3-a), 1.52 (s, 3H, CH_3-b), 0.80 (t, *J* = 7.4 Hz, 3H, -CH$_2$CH_3). ^{13}C NMR, HSQC, HMBC

DOI: 10.1021/acs.joc.5b00868
J. Org. Chem. 2015, 80, 6864−6869

(75.5 MHz, $CDCl_3$): δ 139.8 (*C*1‴), 137.5 (*C*1″), 128.4 (*C*3″,5″), 127.9 (*C*4″), 127.9 (*C*3‴,5‴), 127.2 (*C*4‴), 127.0 (*C*2‴,6‴), 126.5 (*C*2″,6″), 122.3 (*C*1), 99.3 (*C*2′), 75.2 (*C*4′), 63.5 (*C*2), 62.5 (*C*6′), 52.0 (*C*5′), 37.8 (CH_2CH_3), 30.0 (CH_3-b), 18.6 (CH_3-a), 8.9 (CH_2CH_3). ESI-MS (*m*/*z*): 293.1 (100%, $[M - CH_3COCH_3 + H]^+$), 351.2 (30.3%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{22}H_{26}N_2O_2 + H]^+$, 351.2073; found, 351.2089. No diastereomer was detected by HPLC/MS or 2D-NMR.

*(2R,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-benzyl-phenylacetonitrile (**4c**).* The title compound was prepared according to the general procedure from aminonitrile **3a** (300 mg, 0.93 mmol), KHMDS (241 mg, 1.21 mmol), and benzyl bromide (143.7 μL, 1.21 mmol) over 2 h at −78 °C. The crude product (yellowish oil, 426 mg) was directly subjected to removal of the auxiliary. R_t: (*R*,*S*,*S*) = 4.13 min, (*S*,*S*,*S*) = 2.78 min (eluent: H_2O/MeCN 50:50). R_f = 0.67 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\bar{\nu}$: 3349, 2992, 2875, 2251, 1452, 1381, 1198, 1073, 908, 729, 697. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 7.40−7.36 (m, 3H, *H*-3‴,5‴,4‴), 7.34−7.30 (m, 3H, *H*-4^{Bn},3^{Bn},5^{Bn}), 7.25−7.22 (m, 2H, *H*-2‴,6‴), 7.19−7.12 (m, 3H, *H*-4″,2^{Bn},6^{Bn}), 6.98 (pseudo-t, J_{app} = 7.8 Hz, 2H, *H*-3″,5″), 6.73 (d-like, J_{app} = 7.3 Hz, 2H, *H*-2″,6″), 4.88 (d, *J* = 1.7 Hz, 1H, *H*-4′), 4.46 (dd, *J* = 12.2, 1.8 Hz, 1H, *H*-6′$_a$), 3.89 (dd, *J* = 12.2, 1.3 Hz, 1H, *H*-6′$_b$), 2.99 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 2.94 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 2.73 (br d, 1H, N*H*), 2.46 (br d, 1H, *H*-5′), 1.46 (s, 3H, CH_3-a), 1.40 (s, 3H, CH_3-b). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ 139.9 (*C*1‴), 137.9 (*C*1″), 133.9 (*C*1^{Bn}), 130.7 (*C*2^{Bn},6^{Bn}), 128.5 (*C*3″,5″), 128.4 (*C*3^{Bn},5^{Bn}), 128.2 (*C*4″), 127.9 (*C*3‴,5‴), 127.9 (*C*4^{Bn}), 127.3 (*C*4‴), 127.0 (*C*2‴,6‴), 126.6 (*C*2″,6″), 121.9 (*C*1), 99.1 (*C*2′), 75.3 (*C*4′), 62.7 (*C*2), 61.7 (*C*6′), 51.8 (*C*5′), 51.2 (CH_2Ph), 29.7 (CH_3-b), 18.5 (CH_3-a). ESI-MS (*m*/*z*): 355.2 (100%, $[M - CH_3COCH_3 + H]^+$), 413.2 (71.3%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{27}H_{28}N_2O_2 + Na]^+$, 435.2048; found, 435.2054. dr (*R*,*S*,*S*)/(*S*,*S*,*S*) > 19:1 (HPLC-MS).

*(2R,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-propyl-phenylacetonitrile (**4d**).* The title compound was prepared according to the general procedure from aminonitrile **3a** (300 mg, 0.93 mmol), KHMDS (241 mg, 1.21 mmol), and 1-bromopropane (110.0 μL, 1.21 mmol) over 3 h at −78 °C. The crude product (yellowish oil, 341 mg) was directly subjected to removal of the auxiliary. R_t: (*R*,*S*,*S*) = 3.29 min, (*S*,*S*,*S*) = 2.60 min (eluent: H_2O/MeCN 50:50). R_f = 0.68 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\bar{\nu}$: 3351, 3030, 2875, 1665, 1451, 1381, 1199, 1073, 846, 763, 699. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 7.33−7.27 (m, 3H, *H*-3‴,5‴,4″), 7.18−7.08 (m, 3H, *H*-2‴,6‴,4‴), 6.96 (pseudo-t, J_{app} = 7.8 Hz, 2H, *H*-3″,5″), 6.72 (dd-like, J_{app} = 8.3, 1.1 Hz, 2H, *H*-2″,6″), 4.88 (d, *J* = 1.9 Hz, 1H, *H*-4′), 4.62 (dd, *J* = 12.2, 1.7 Hz, 1H, *H*-6′$_a$), 4.03 (dd, *J* = 12.2, 1.4 Hz, 1H, *H*-6′$_b$), 2.62 (s, 1H, N*H*), 2.45 (s, 1H, *H*-5′), 1.91−1.82 (m, 1H, CH_2-CH_2-CH_3), 1.73−1.64 (m, 1H, CH_2-CH_2-CH_3), 1.57 (s, 3H, CH_3-a), 1.51 (s, 3H, CH_3-b), 1.47−1.35 (m, 1H, CH_2-CH_2-CH_3), 1.04−0.91 (m, 1H, CH_2-CH_2-CH_3), 0.82 (t, *J* = 7.3 Hz, 3H, CH_2-CH_2-CH_3). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ 139.8 (*C*1‴), 137.8 (*C*1″), 128.4 (*C*3″,5″), 180.0 (*C*4″), 128.0 (*C*3‴,5‴), 127.2 (*C*4‴), 127.0 (*C*2‴,6‴), 126.4 (*C*2″,6″), 122.5 (*C*1), 99.3 (*C*2′), 75.2 (*C*4′), 62.8 (*C*2), 62.5 (*C*6′), 51.9 (*C*5′), 46.7 (CH_2-CH_2-CH_3), 30.0 (CH_3-b), 18.6 (CH_3-a), 17.9 (CH_2-CH_2-CH_3), 13.8 (CH_2-CH_2-CH_3). ESI-MS (*m*/*z*): 307.1 (100%, $[M - CH_3COCH_3 + H]^+$), 365.2 (31.5%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{23}H_{28}N_2O_2 + H]^+$, 365.2229; found, 365.2240. dr (*R*,*S*,*S*)/(*S*,*S*,*S*) > 29:1 (HPLC-MS).

*(2R,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-(2-propyl)-phenylacetonitrile (**4e**).* The title compound was prepared according to the general procedure from aminonitrile **3a** (150 mg, 0.47 mmol), KHMDS (121 mg, 0.60 mmol), and 2-bromopropane (56.8 μL, 0.60 mmol) over 4 h at −78 °C. The crude product (yellowish oil, 181 mg) was directly subjected to removal of the auxiliary. R_t: (*R*,*S*,*S*) = 3.21 min, (*S*,*S*,*S*) = 2.00 min (eluent: H_2O/MeCN 50:50). R_f = 0.63 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\bar{\nu}$: 3378, 2990, 2875, 1665, 1451, 1381, 1200, 1096, 846, 760, 700. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 7.33−7.29 (m, 3H, *H*-3‴,5‴,4″), 7.21−7.08 (m, 3H, *H*-2‴,6‴,4‴), 6.96 (pseudo-t, J_{app} = 7.8 Hz, 2H, *H*-3″,5″), 6.69 (d-like, J_{app} = 7.3 Hz, 2H, *H*-2″,6″), 4.90 (d, *J* = 2.0 Hz, 1H, *H*-4′), 4.63 (dd, *J* = 12.3, 1.8 Hz, 1H, *H*-6′$_a$), 3.99 (dd, *J* = 12.3, 1.5 Hz, 1H, *H*-6′$_b$), 2.81 (d, *J* = 10.7 Hz, 1H, N*H*), 2.43 (d-pseudo-q, *J* = 10.7, 1.8 Hz, 1H, *H*-5′), 1.93 (sept, *J* = 6.7 Hz, 1H, C*H*(CH_3)$_2$), 1.57 (s, 3H, CH_3-a), 1.52 (s, 3H, CH_3-b), 1.15 (d, *J* = 6.7 Hz, 3H, CH(CH_3)$_2$), 0.63 (d, *J* = 6.7 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ 139.9 (*C*1‴), 137.0 (*C*1″), 128.2 (*C*3″,5″), 127.9 (*C*4″), 127.8 (*C*3‴,5‴), 127.3 (*C*4‴), 127.1 (*C*2‴,6‴), 127.0 (*C*2″,6″), 121.6 (*C*1), 99.3 (*C*2′), 75.4 (*C*4′), 67.4 (*C*2), 62.3 (*C*6′), 52.0 (*C*5′), 40.2 (*C*H(CH_3)), 30.1 (CH_3-b), 18.6 (CH_3-a), 18.0 (CH_3), 17.8 (CH_3). ESI-MS (*m*/*z*): 307.2 (100%, $[M - CH_3COCH_3 + H]^+$), 365.2 (45.2%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{23}H_{28}N_2O_2 + Na]^+$, 387.2048; found, 387.2051. dr (*R*,*S*,*S*)/(*S*,*S*,*S*) > 4.4:1 (HPLC-MS).

*(2S,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-(methoxymethylen)-phenylacetonitrile (**4f**).* The title compound was prepared according to the general procedure from aminonitrile **3a** (100 mg, 0.31 mmol), KHMDS (80 mg, 0.40 mmol), and MOMCl (30.6 μL, 0.40 mmol) over 3 h at −78 °C. The crude product (yellowish oil, 120 mg) was directly subjected to removal of the auxiliary. R_t: (*S*,*S*,*S*) = 1.31 min, (*R*,*S*,*S*) = 1.02 min (eluent: H_2O/MeCN 50:50). R_f = 0.50 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\bar{\nu}$: 3349, 2993, 2929, 1664, 1452, 1381, 1197, 1071, 973, 845, 749, 699. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 7.34−7.28 (m, 3H, *H*-3‴,5‴,4″), 7.23−7.11 (m, 3H, *H*-2‴,6‴,4‴), 6.97 (pseudo-t, J_{app} = 7.8 Hz, 2H, *H*-3″,5″), 6.76 (dd-like, J_{app} = 8.4, 1.2 Hz, 2H, *H*-2″,6″), 4.92 (d, *J* = 2.0 Hz, 1H, *H*-4′), 4.62 (dd, *J* = 12.3, 1.8 Hz, 1H, *H*-6′$_a$), 4.05 (dd, *J* = 12.3, 1.6 Hz, 1H, *H*-6′$_b$), 3.46 (s, 3H, -OCH_3), 3.34 (d, *J* = 9.3 Hz, 1H, -CH_2-OCH_3), 3.29 (d, *J* = 9.3 Hz, 1H, -CH_2-OCH_3), 2.48 (d, *J* = 5.7 Hz, 1H, *H*-5′), 1.58 (s, 3H, CH_3-a), 1.53 (s, 3H, CH_3-b). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ 139.9 (*C*1‴), 135.1 (*C*1″), 128.6 (*C*4″,3″,5″), 127.9 (*C*3‴,5‴), 127.2 (*C*4‴), 127.1 (*C*2‴,6‴), 126.8 (*C*2″,6″), 121.5 (*C*1), 99.3 (*C*2′), 80.3 (CH_2OMe), 75.2 (*C*4′), 63.1 (*C*2), 62.3 (*C*6′), 59.8 (OCH_3), 51.8 (*C*5′), 29.9 (CH_3-b), 18.6 (CH_3-a). ESI-MS (*m*/*z*): 309.1 (100%, $[M - CH_3COCH_3 + H]^+$), 367.2 (48.0%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{22}H_{26}N_2O_3 + Na]^+$, 389.1841; found, 389.1833. dr (*S*,*S*,*S*)/(*R*,*S*,*S*) > 39:1 (HPLC-MS).

*(2R,4′S,5′S)-2-Amino-N-(2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl)-2-ethyl-(2-naphthyl)-acetonitrile (**4g**).* The title compound was prepared according to the general procedure from aminonitrile **3b** (250 mg, 0.67 mmol), KHMDS (174 mg, 0.87 mmol), and bromoethane (65.1 μL, 0.87 mmol) over 3 h at −78 °C. The crude product (yellowish oil, 285 mg) was directly subjected to removal of the auxiliary. Because of the presence of impurities, the NMR spectroscopic data were not analyzed further. R_t: (*R*,*S*,*S*) = 5.39 min, (*S*,*S*,*S*) = 5.24 min (eluent: H_2O/MeCN 40:60). R_f = 0.62 (cyclohexane/ethyl acetate 5:1). IR (ATR, cm^{-1}) $\bar{\nu}$: 3351, 2991, 2876, 1662, 1500, 1452, 1381, 1198, 1096, 847, 746, 699. ESI-MS (*m*/*z*): 343.2 (100%, $[M - CH_3COCH_3 + H]^+$), 401.2 (42.9%, $[M + H]^+$). ESI-HRMS (*m*/*z*): calcd for $[C_{26}H_{28}N_2O_2 + Na]^+$, 423.2048; found, 423.2046. dr (*R*,*S*,*S*)/(*S*,*S*,*S*) > 6:1 (HPLC-MS).

General Procedure for the Removal of the Auxiliary with Raney Nickel. Lactones **5** were prepared according to a protocol by Weinges et al.[42] Concentrated hydrochloric acid was cooled to −10 °C, and aminonitrile **4** was added. The mixture was stirred for 1 h at −10 °C, for 1 h at 0 °C, for 1 h at room temperature, and for another 4 h at 55 °C. After removal of the solvent in vacuo, the crude product was washed with cold water and subjected to catalytic oxidation without further purification. Crude lactone **5** was dissolved in aq NaOH (2 M, 1.5 mL per 100 mg lactone) under warming. A suspension of Raney nickel (100 mg, 50 wt %, per 100 mg lactone) in water was added, and the mixture was stirred under reflux (120 °C oil bath temperature) while a gentle stream of air was passed through. After complete conversion (TLC), the hot mixture was filtered over kieselguhr and neutralized by the addition of hydrochloric acid. The solvent was removed in vacuo, and the remaining solid was taken up in ethanol to remove insoluble sodium chloride by filtration. Concentration in vacuo furnished the crude α-amino acid, which was purified by preparative HPLC.

DOI: 10.1021/acs.joc.5b00868
J. Org. Chem. 2015, 80, 6864−6869

Determination of Optical Purity. A sample (2.5 μmol) of amio acid **6** was dissolved in water (50 μL), and a 1% solution of Marfey's reagent (3.7 μmol, 1.4 equiv) in acetone, as well as an aqueous sodium bicarbonate solution (1 M, 50 μL), was added. The mixture was warmed to 40 °C until TLC indicated complete conversion. The mixture was quenched by the addition of hydrochloric acid (1 M), and the ratio of the produced diastereomers was determined by analytical HPLC.

*(R)-(−)-α-Methyl-α-phenylglycine (**6a**).* The title compound was prepared according to the general procedure from crude aminonitrile **4a** (260 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5a** was obtained as a colorless solid (143 mg). ESI-HRMS (*m*/*z*): calcd for $[C_{18}H_{19}NO_3 + Na]^+$, 320.1263; found, 320.1265. Catalytic oxidation of a portion of the lactone (70 mg) was performed over 25 h. A portion (40 mg) of the crude product (60 mg) was purified by preparative HPLC to yield a colorless amorphous solid (12 mg, 0.07 mmol, 33% over 3 steps from **3a**). R_t = 3.03 min (eluent: H_2O/MeCN 97:3). R_f = 0.54 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ −27.3 (*c* 0.5, H_2O), lit.[53] $[\alpha]_D$ −41.2 (*c* 0.5, H_2O); lit.[54] $[\alpha]_D^{21}$ −68.5 (*c* 1.0, H_2O). Mp 215.5−215.8 °C (lyophilized, amorphous), lit.[53] mp 260−265 °C; lit.[54] mp (enantiomer) 260−265 °C (dec). IR (ATR, cm^{-1}) $\bar{\nu}$: 2958, 2925, 2855, 1731, 1589, 1391, 1270, 695, 644. ^{1}H NMR, COSY (300 MHz, D_2O): δ 7.53−7.43 (m, 5H, H_{ar}), 1.90 (s, 3H, CH_3). ^{13}C NMR, HSQC, HMBC (75.5 MHz, D_2O): δ 176.3 (CO_2H), 137.6 (*C*1), 129.1 (C_{ar}), 129.1 (C_{ar}), 125.8 (C_{ar}), 62.9 (C_α), 21.2 (CH_3). ESI-MS (*m*/*z*): 166.0 (100%, $[M + H]^+$), 149.0 (62.4%, $[M - NH_3 + H]^+$).

(R)/(S) calcd from Marfey method: 96:4 er; 92% ee. The analytical data match those reported in the literature.[54]

*(R)-(−)-α-Ethyl-α-phenylglycine (**6b**).* The title compound was prepared according to the general procedure from crude aminonitrile **4b** (270 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5b** was obtained as a colorless solid (199 mg). ESI-HRMS (*m*/*z*): calcd for $[C_{19}H_{21}NO_3 + Na]^+$, 334.1419; found, 334.1414. Catalytic oxidation of a portion of the lactone (70 mg) was performed over 26 h. A portion (47 mg) of the crude product (66 mg) was purified by preparative HPLC to yield a colorless amorphous solid (17 mg, 0.09 mmol, 74% over 3 steps from **3a**). R_t = 3.85 min (eluent: H_2O/MeCN 97:3). R_f = 0.63 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ −17.3 (*c* 1, H_2O), lit.[53] $[\alpha]_D$ −20.8 (*c* 0.5, H_2O); lit.[54] $[\alpha]_D^{20}$ −23.7 (*c* 1.0, H_2O). Mp 204.7−205.3 °C (lyophilized, amorphous), lit.[53] mp 248−252 °C; lit.[54] (enantiomer) mp 250−255 °C (dec). IR (ATR, cm^{-1}) $\bar{\nu}$: 3360, 2956, 2924, 2854, 1732, 1600, 1372, 1287, 740, 697. ^{1}H NMR, COSY (300 MHz, D_2O): δ 7.53−7.31 (m, 5H, H_{ar}), 2.27 (m, 2H, CH_2CH_3), 0.98 (t, *J* = 7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR, HSQC, HMBC (75.5 MHz, D_2O): δ 177.1 (CO_2H), 139.5 (*C*1), 128.9 (C_{ar}), 128.5 (C_{ar}), 126.0 (C_{ar}), 66.8 (C_α), 28.5 (CH_2CH_3), 7.7 (CH_2CH_3). ESI-MS (*m*/*z*): 180.0 (100%, $[M + H]^+$), 163.0 (67.3%, $[M - NH_3 + H]^+$).

(*R*)/(*S*) calcd from Marfey method: 98.5:1.5 er; 97% ee. The analytical data match those reported in the literature.[54]

*(R)-(+)-α-Benzyl-α-phenylglycine (**6c**).* The title compound was prepared according to the general procedure from crude aminonitrile **4c** (355 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5c** was obtained as a colorless solid (227 mg). ESI-HRMS (*m*/*z*): calcd for $[C_{24}H_{23}NO_3 + Na]^+$, 396.1576; found, 396.1572. Catalytic oxidation of a portion of the lactone (81 mg) was performed over 68 h. A portion (26 mg) of the crude product (53 mg) was purified by preparative HPLC to yield a colorless amorphous solid (22 mg, 0.09 mmol, 68% over 3 steps from **3a**). R_t = 2.52 min (eluent: H_2O/MeCN 80:20). R_f = 0.76 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ +16.6 (*c* 0.5, DMSO), lit.[55] (enantiomer) $[\alpha]_D^{20}$ −28.1 (*c* 0.5, 1 N HCl). Mp 199.7−200.5 °C (lyophilized, amorphous), lit.[56] (enantiomer) mp 268−269 °C (dec). IR (ATR, cm^{-1}) $\bar{\nu}$: 2957, 2925, 2855, 1731, 1595, 1383, 1273, 699, 644. ^{1}H NMR, COSY (400 MHz, CD_3OD): δ 7.68−7.61 (m, 2H, H_{ar}), 7.4−7.31 (m, 3H, H_{ar}), 7.30−7.19 (m, 5H, H_{ar}), 3.72 (d, *J* = 14.1 Hz, 1H, CH_2Ph), 3.42 (d, *J* = 14.1 Hz, 1H, CH_2Ph). ^{13}C NMR, HSQC, HMBC (100.6 MHz, CD_3OD): δ 174.3 (CO_2H), 140.6 (*C*1′), 136.1 (*C*1), 131.7 (C_{ar}), 129.7 (C_{ar}), 129.7 (C_{ar}), 129.4 (C_{ar}), 128.6 (C_{ar}), 127.3 (C_{ar}), 68.5 (C_α), 43.4 (CH_2Ph). ESI-MS (*m*/*z*): 242.0 (100%, $[M + H]^+$), 225.0 (67.3%, $[M - NH_3 + H]^+$).

(*R*)/(*S*) calcd from alkylated α-aminonitrile: >19:1 er; >90% ee. (*R*)/(*S*) calcd from Marfey method: 95.5:4.5 er; 91% ee. The analytical data match those reported in the literature.[56]

*(R)-(−)-α-Propyl-α-phenylglycine (**6d**).* The title compound was prepared according to the general procedure from crude aminonitrile **4d** (262 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5d** was obtained as a colorless solid (203 mg). ESI-HRMS (*m*/*z*): calcd for $[C_{20}H_{23}NO_3 + Na]^+$, 348.1576; found, 348.1587. Catalytic oxidation of a portion of the lactone (60 mg) was performed over 48 h. A portion (23 mg) of the crude product (37 mg) was purified by preparative HPLC to yield a colorless amorphous solid (8 mg, 0.04 mmol, 33% over 3 steps from **3a**). R_t = 6.60 min (eluent: H_2O/MeCN 97:3). R_f = 0.68 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ −3.0 (*c* 0.4, D_2O), lit.[57] $[\alpha]_D$ −20 (*c* 0.5, H_2O). Mp 225.5−226.0 °C (lyophilized, amorphous), lit.[53] (enantiomer) mp >300 °C (dec). IR (ATR, cm^{-1}) $\bar{\nu}$: 3375, 2960, 2927, 2871, 1731, 1596, 1363, 1288, 694. ^{1}H NMR, COSY (600 MHz, CD_3OD): δ 7.56−7.49 (m, 2H, *H*-2,6), 7.39−7.33 (m, 2H, *H*-3,5), 7.33−7.26 (m, 1H, *H*-4), 2.27−2.13 (m, 2H, $CH_2CH_2CH_3$), 1.47−1.32 (m, 2H, $CH_2CH_2CH_3$), 0.98 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3OD): δ 175.1 (CO_2H), 140.8 (*C*1), 129.7 (*C*3,5), 129.2 (*C*4), 127.2 (*C*2,6), 68.0 (C_α), 39.7 ($CH_2CH_2CH_3$), 18.4 ($CH_2CH_2CH_3$), 14.6 ($CH_2CH_2CH_3$). ESI-MS (*m*/*z*): 177.0 (100%, $[M - NH_3 + H]^+$), 194.0 (49.2%, $[M + H]^+$).

(*R*)/(*S*) calcd from alkylated α-aminonitrile: >29:1 er; >93% ee. (*R*)/(*S*) calcd from Marfey method: 98:2 er; 96% ee. The analytical data match those reported in the literature.[57]

*(R)-(−)-α-(2-Propyl)-α-phenylglycine (**6e**).* The title compound was prepared according to the general procedure from crude aminonitrile **4e** (150 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5e** was obtained as a colorless solid (141 mg). ESI-HRMS (*m*/*z*): calcd for $[C_{20}H_{23}NO_3 + Na]^+$, 348.1576; found, 348.1574. Catalytic oxidation of a portion of the lactone (66 mg) was performed over 46 h. A portion (33 mg) of the crude product (50 mg) was purified by preparative HPLC to yield a colorless amorphous solid (5 mg, 0.03 mmol, 21% over 3 steps from **3a**). R_t = 8.56 min (eluent: H_2O/MeCN 97:3). R_f = 0.56 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ −20.6 (*c* 0.4, D_2O), lit.[58] ((*S*)-enantiomer) $[\alpha]_D^{20}$ +20.0 (*c* 0.7, 1 N HCl). Mp 219.8−220.4 °C (lyophilized, amorphous), lit.[58] (enantiomer) mp 242 °C. IR (ATR, cm^{-1}) $\bar{\nu}$: 3391, 2958, 2926, 2856, 1731, 1600, 1377, 1286, 1123, 740, 698. ^{1}H NMR, COSY (600 MHz, CD_3OD): δ 7.56 (d-like, J_{app} = 7.9 Hz, 2H, *H*-2,6), 7.34 (t-like, J_{app} = 7.6 Hz, 2H, *H*-3,5), 7.27 (t-like, J_{app} = 7.3 Hz, 1H, *H*-4), 2.87 (sept, *J* = 7.0 Hz, 1H, $CH(CH_3)_2$), 1.08 (d, *J* = 7.0 Hz, 3H, CH_3), 0.80 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3OD): δ 174.7 (CO_2H), 140.3 (*C*1), 129.4 (*C*3,5), 128.7 (*C*4), 126.9 (*C*2,6), 71.9 (C_α), 35.0 ($CH(CH_3)_2$), 18.2 (CH_3), 16.8 (CH_3). ESI-MS (*m*/*z*): 194.0 (100%, $[M + H]^+$), 176.9 (28.3%, $[M - NH_3 + H]^+$).

(*R*)/(*S*) calcd from alkylated α-aminonitrile: >4.4:1 er; >63% ee. (*R*)/(*S*) calcd from Marfey method: 90:10 er; 80% ee. The analytical data match those reported in the literature.[58]

*(S)-(−)-α-(Methoxymethyl)-α-phenylglycine (**6f**).* The title compound was prepared according to the general procedure from crude aminonitrile **4f** (96 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5f** was obtained as a colorless solid (100 mg). ESI-HRMS (*m*/*z*): calcd for $[C_{19}H_{21}NO_4 + Na]^+$, 350.1368; found, 350.1373. Catalytic oxidation of a portion of the lactone (55 mg) was performed over 24 h. A portion (38 mg) of the crude product (51 mg) was purified by preparative HPLC to yield a colorless amorphous solid (16 mg, 0.08 mmol, 81% over 3 steps from **3a**). R_t = 2.52 min (eluent: H_2O/MeCN 80:20). R_f = 0.53 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ −5.4 (*c* 1, D_2O). IR (ATR, cm^{-1}) $\bar{\nu}$: 3061, 2928, 1598, 1391, 1367, 1196, 1104, 737, 698. ^{1}H NMR, COSY (600 MHz, CD_3OD): δ 7.51 (d-like, J_{app} = 7.6 Hz, 2H, *H*-2,6), 7.34 (t-like, J_{app} = 7.4 Hz, 2H, *H*3,5), 7.29 (t-like, J_{app} = 7.3 Hz, 1H, *H*-4), 4.13−4.03 (m, 1H, CH_2OMe), 3.98−3.89 (m, 1H, CH_2OMe), 3.39 (s, 3H, OCH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3OD): δ 173.8

DOI: 10.1021/acs.joc.5b00868
J. Org. Chem. 2015, 80, 6864−6869

(CO_2H), 138.5 (C1), 129.7 (C3,5), 129.4 (C4), 127.2 (C2,6), 75.9 (CH_2OMe), 67.5 (C_α), 59.5 (OCH_3). ESI-HRMS (m/z): calcd for $[C_{10}H_{13}NO_3 + Na]^+$, 218.0793; found, 218.0789.

(*R*)/(*S*) calcd from alkylated α-aminonitrile: >39:1 er; >95% ee. (*R*)/(*S*) calcd from Marfey method: >99:1 er; >98% ee.

*(R)-(−)-α-Ethyl-α-(2-naphthyl)-glycine (**6g**).* The title compound was prepared according to the general procedure from crude aminonitrile **4g** (225 mg) and concentrated hydrochloric acid (30 mL). Crude lactone **5g** was obtained as a colorless solid (235 mg). ESI-HRMS (m/z): calcd for $[C_{23}H_{23}NO_3 + Na]^+$, 384.1576; found, 384.1577. Catalytic oxidation of a portion of the lactone (70 mg) was performed over 24 h. A portion (34 mg) of the crude product (49 mg) was purified by preparative HPLC to yield a colorless amorphous solid (12 mg, 0.05 mmol, 49% over 3 steps from **3b**). R_t = 2.22 min (eluent: H_2O/MeCN 80:20). R_f = 0.64 (ethyl acetate/2-butanone/H_2O/HCO_2H 5:3:1:1). $[\alpha]_D^{26}$ −3.8 (*c* 1, CD_3OD). IR (ATR, cm^{-1}) $\tilde{\nu}$: 3359, 3059, 2935, 1600, 1559, 1393, 1379, 796, 749. ^1H NMR, COSY (600 MHz, CD_3OD): δ 8.05−7.03 (m, 7H, H_{ar}), 2.56−2.18 (m, 2H, CH_2CH_3), 1.02 (s, 3H, CH_2CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3OD): δ 174.0 (CO_2H), 134.5 (C_{ar}), 132.9 (C_{ar}), 128.9 (C_{ar}), 128.6 (C_{ar}), 128.0 (C_{ar}), 127.1 (C_{ar}), 126.8 (C_{ar}), 126.4 (C_{ar}), 126.1 (C_{ar}), 125.6 (C_{ar}), 74.8 (C_α), 29.1 (CH_2CH_3), 7.4 (CH_2CH_3). ESI-HRMS (m/z): calcd for $[C_{14}H_{15}NO_2 + H]^+$, 230.1181; found, 230.1190.

(*R*)/(*S*) calcd from alkylated α-aminonitrile: >6:1 er; >71% ee. (*R*)/(*S*) calcd from Marfey method: 97:3 er; 94% ee.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of crude alkylation products **4** and amino acids **6** as well as HPLC chromatograms of Marfey derivatives. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00868.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: opatz@uni-mainz.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Professor G. Helmchen (Heidelberg) for the kind donation of auxiliary **1**.

■ REFERENCES

(1) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875.
(2) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
(3) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem.* **2007**, *11*, 801.
(4) Ager, D. J. In *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2009; p 495.
(5) Maruoka, K. *Chem. Rec.* **2010**, *10*, 254.
(6) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Pept. Sci.* **2001**, *60*, 396.
(7) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. *Synlett* **2006**, *2006*, 1295.
(8) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.
(9) Cativiela, C.; Díaz-de-Villegas, M. a. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.
(10) Cativiela, C.; Díaz-de-Villegas, M. a. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.
(11) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127.
(12) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.
(13) Undheim, K. *Amino Acids* **2008**, *34*, 357.
(14) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1.
(15) Jautze, S.; Peters, R. *Synthesis* **2010**, 365.
(16) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294.
(17) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234.
(18) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1.
(19) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(20) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.
(21) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255.
(22) Beaufort-Droal, V.; Pereira, E.; Thery, V.; Aitken, D. J. *Tetrahedron* **2006**, *62*, 11948.
(23) Enders, D.; Milovanovic, M. *Z. Naturforsch., B: J. Chem. Sci.* **2007**, *62*, 117.
(24) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
(25) Otto, N.; Opatz, T. *Chem.—Eur. J.* **2014**, *20*, 13064.
(26) Opatz, T.; Ferenc, D. *Org. Lett.* **2006**, *8*, 4473.
(27) Bergner, I.; Opatz, T. *J. Org. Chem.* **2007**, *72*, 7083.
(28) Kison, C.; Opatz, T. *Chem.—Eur. J.* **2009**, *15*, 843.
(29) Kison, C.; Meyer, N.; Opatz, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5662.
(30) Bergner, I.; Opatz, T. *Synthesis* **2007**, 918.
(31) Leete, E.; Chedekel, M. R.; Bodem, G. B. *J. Org. Chem.* **1972**, *37*, 4465.
(32) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H. P. *J. Org. Chem.* **1986**, *51*, 4475.
(33) Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 6704.
(34) Gillaizeau-Gauthier, I.; Royer, J.; Husson, H.-P. *Eur. J. Org. Chem.* **2002**, 1484.
(35) Amorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031.
(36) Werner, F.; Blank, N.; Opatz, T. *Eur. J. Org. Chem.* **2007**, 3911.
(37) Blank, N.; Opatz, T. *J. Org. Chem.* **2011**, *76*, 9777.
(38) Imbri, D.; Tauber, J.; Opatz, T. *Chem.—Eur. J.* **2013**, *19*, 15080.
(39) Geffe, M.; Opatz, T. *Org. Lett.* **2014**, *16*, 5282.
(40) Meyer, N.; Opatz, T. *Synlett* **2003**, 1427.
(41) García Ruano, J. L.; Martín-Castro, A. M.; Tato, F.; Alonso, I. *J. Org. Chem.* **2007**, *72*, 5994.
(42) Weinges, K.; Graab, G.; Nagel, D.; Stemmle, B. *Chem. Ber.* **1971**, *104*, 3594.
(43) Weinges, K.; Stemmle, B. *Chem. Ber.* **1973**, *106*, 2291.
(44) Weinges, K.; Brune, G.; Droste, H. *Liebigs Ann. Chem.* **1980**, *1980*, 212.
(45) Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 179.
(46) Enders, D.; Mannes, D.; Raabe, G. *Synlett* **1992**, 837.
(47) Enders, D.; Kirchhoff, J.; Mannes, D.; Raabe, G. *Synthesis* **1995**, 659.
(48) Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591.
(49) Fujii, K.; Ikai, Y.; Mayumi, T.; Oka, H.; Suzuki, M.; Harada, K.-i. *Anal. Chem.* **1997**, *69*, 3346.
(50) Saari, W. S.; Williams, J.; Britcher, S. F.; Wolf, D. E.; Kuehl, F. A. *J. Med. Chem.* **1967**, *10*, 1008.
(51) Trišović, N.; Timić, T.; Divljaković, J.; Rogan, J.; Poleti, D.; Savić, M.; Uščumlić, G. *Monatsh. Chem.* **2012**, *143*, 1451.
(52) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, *1998*, 63.
(53) Cativiela, C.; Diaz de Villegas, M. D.; Galvez, J. A.; Lapena, Y. *An. Quim.* **1994**, *90*, 432.
(54) Knabe, J.; Urbahn, C. *Liebigs Ann. Chem.* **1971**, *750*, 21.
(55) Hartwig, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, *1982*, 1952.
(56) Goodson, L. H.; Honigberg, I. L.; Lehman, J. J.; Burton, W. H. *J. Org. Chem.* **1960**, *25*, 1920.
(57) Cativiela, C.; Villegas, M. D. D. d.; Galvez, J. A.; Lapena, Y. *An. Quim.* **1994**, *90*, 432.
(58) Chaari, M.; Jenhi, A.; Lavergne, J.-P.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4619.

DOI: 10.1021/acs.joc.5b00868
J. Org. Chem. 2015, 80, 6864−6869