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Tetrahydrofuran Cα-Tetrasubstituted Amino Acids: Two Consecutive β-Turns in a Crystalline Linear Tripeptide

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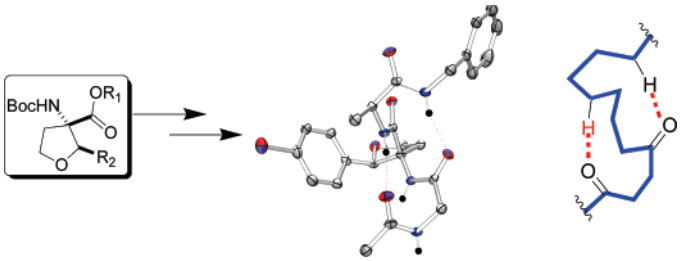

The synthesis of tetrahydrofuran Cα-tetrasubstituted amino acids (TAAs) and their effect on the conformation in small peptides are reported. The synthesis starts from the protein amino acid methionine, which is protected at the C and N terminus and converted into the corresponding sulfonium salt by alkylation. Simple base treatment in the presence of an aryl aldehyde leads to the formation of tetrahydrofuran tetrasubstituted Cα-amino acids in a highly diastereoselective (trans/cis ratio up to 97:3) reaction with moderate to good yields (35−78%) depending on the aldehyde used. Palladium-catalyzed coupling reactions allow a subsequent further functionalization of the TAA. The *R*,*S*,*S*-TAA-Ala dipeptide amide adopts a β-turn type I conformation, whereas its *S*,*R*,*S* isomer does not. The *R*,*S*,*S*-Gly-TAA-Ala tripeptide amide shows in the solid state and in solution a conformation of two consecutive β-turn type III structures, stabilized by $i + 3 \rightarrow i$ intramolecular hydrogen bonds.

Introduction

The conformation of a peptide is crucial for its biological activity.[1] Most small natural peptides are conformationally flexible, show structural dependence on the environment, and are therefore not suitable to study or control secondary peptide structures. One of the successful approaches to restrict peptide conformation is the introduction of side chain restricted amino acids.[2,3] Disubstitution by alkyl or aryl groups in the α position of an α-amino acid leads to a conformational constraint (Thorpe−Ingold effect) and a stereochemically stable quaternary carbon center.[4] Different methods to incorporate functionality in the α position of an amino acid or using α,β-unsaturated amino acids as precursors have been reported.[5] Toniolo[6] recently reviewed the effect of Cα tetrasubstitution on the structure of homooligoamides mostly resulting in stable 3_{10} or α-helices.[7] In short peptides, Cα-alkylated α-amino acids stabilize turn structures,[8] which in general have received particular attention because they play an important role in globular proteins from both structural and functional points of view.[9]

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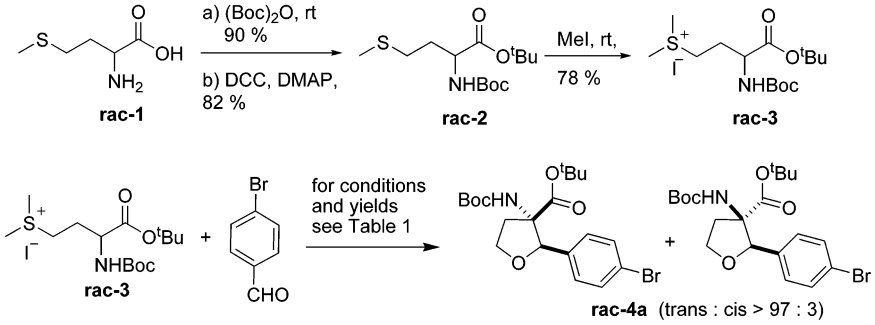
SCHEME 1. Synthesis of the Protected Methionine Sulfonium Salt *rac*-3 and Its Conversion to TAA *rac*-4



A polypeptide chain cannot fold into a compact structure without turns, which usually occur on the solvent-exposed surface of proteins and hence probably represent antigenic sites involved in molecular recognition.[10] Many naturally occurring oligopeptides have been proposed to adopt turns in their bioactive conformation.[11] Different types of bends are defined according to the number and spatial arrangement of the residues involved, and β-turns (β-bends reverse turn) are the most abundant and best characterized group of folded secondary structures.[12] Subclasses of β-turns are further distinguished on the basis of the backbone dihedral angles (φ, ψ) associated with central $i + 1$ and $i + 2$ positions. In the past years, several artificial turn inducing structures were reported by Nowick,[13] Schmuck,[14] Frigel,[15] Kelly,[16] Gellman,[17] Balaram,[18] and others. We report here the preparation and structural characterization of tetrahydrofuran Cα-tetrasubstituted amino acids (TAAs) from methionine, which induce two consecutive β-turns as part of a tripeptide of aliphatic α-amino acids.

Results and Discussion

The key step of the TAA synthesis is the aldol-type reaction of a methionine-derived sulfonium salt[19] with an aldehyde followed by a cyclization. Scheme 1 shows the preparation of the sulfonium salt **3** starting from the racemic natural amino acid methionine (***rac*-1**). Methionine sulfonium iodide ***rac*-3a** was treated with KOH. Acidic protons are found at the sulfonium moiety and at the α-carbon of the amino acids. Under the reaction conditions, the α-proton of the amino acid is removed and its stereoinformation is lost. The ester enolate reacts with the carbonyl group of the aromatic aldehyde, and the intermediate alkoxide substitutes intramolecularly dimethylsulfide[20] giving tetrahydrofuran amino acids ***rac*-4** with high diastereoselectivity of the α- and β-stereocenters. A proposed mechanism of the reaction is outlined in Figure 1.

A series of optimizations revealed that aromatic aldehydes with an electron-withdrawing substituent and a sterically

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(20) No higher oligomers were observed, even if the reaction was performed on large scale or at higher concentrations. The intramolecular substitution is significantly favored over any intermolecular substitution reaction.

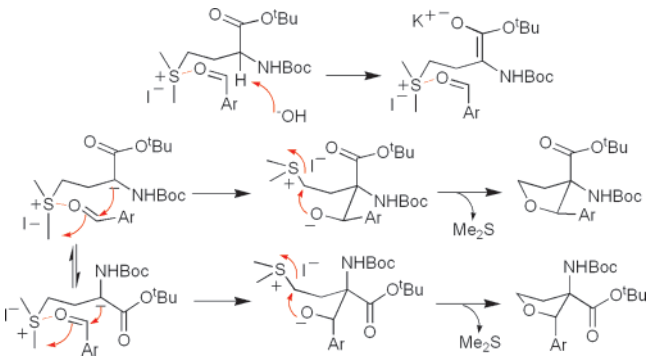


FIGURE 1. Proposed reaction mechanism of tetrahydrofuran Cα-tetrasubstituted amino acid formation.

TABLE 1. Optimization of the Reaction Conditions Converting Compound *rac*-3 to TAA *rac*-4a

solvent	base	reaction temp [°C]	reaction time [h]	yield [%]	trans/cis[b] ratio
DCM[a]	KOH	20	5	40	97:3
	KO^{t}Bu		4.5	47	
^{t}BuOH	KOH	−5	3.5	40	97:3
DMF	KOH	−5	2	55	96:4
	CsOH		1.5	54	
toluene[a]	KOH	20	4	52	96:4
	KO^{t}Bu		3	60	
CH_3CN	KOH	−5	3	78	>97:3
	KO^{t}Bu		2	60	
	CsOH		2	65	

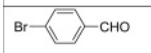
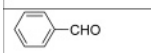
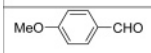
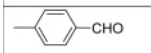
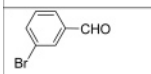
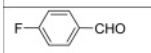
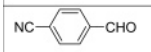
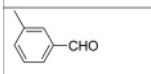
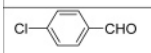
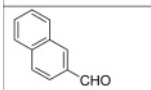
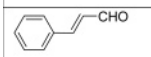
[a] Tetrabutyl ammonium bromide (10 mol %) was added as the phase transfer catalyst. [b] The trans/cis ratio was determined by HPLC.

demanding protecting group for the carboxyl function, such as ^{t}Bu, give the best reaction conversions and stereoselectivities. A decrease of the reaction temperature from room temperature to −5 °C increases product yields and selectivity. Several solvents and bases were tested. The reaction occurred smoothly in polar solvents. As KOH is not soluble in less polar solvents, such as dichloromethane and toluene, tetrabutylammonium bromide was added as a phase transfer catalyst. However, yields are moderate in these solvents. Among all solvents, CH_3CN gave the best yield of the desired product in 0.5−1 h (Table 1). Additionally, the scope of the reaction and its dependence on steric and electronic properties of the aryl aldehyde were investigated (Table 2). Electronic effects on the reaction yield are small, whereas diastereoselectivity depends on the aldehyde. The relative stereochemistry of the major diastereoisomer was confirmed by X-ray diffraction analysis of compound ***rac*-4e** (Figure 2) and compound ***rac*-4a** (as benzyl ester, see Supporting Information for data). With benzene, high selectivities (trans/cis ≥ 97:3) with moderate to good yields (45−78%; 50−95% according to aldehyde conversion) of naphthalene and cinnamic aldehyde are obtained, whereas the diastereoselectivity is poor with furfural and *p*-cyanobenzaldehyde.

Compound ***rac*-4a** was converted into the carboxylic acid ***rac*-5** (Scheme 2) by treatment with 6 M HCl in methanol affording the hydrochloride salt of the free amino acid quantitatively. N-Reprotection with Boc-anhydrid gave compound ***rac*-6**.[21] Using standard peptide coupling conditions, the racemic carboxylic acid ***rac*-6** was coupled with L-alanine methyl ester hydrochloride and L-phenylalanine methyl ester hydrochloride giving dipeptides **7**−**10** in moderate yields. The diastereomers

(21) Basic hydrolysis of the benzyl ester of compound **4a** by KOH affords the product in only 24% yield.

TABLE 2. Scope of the Reaction of Sulfonium Salt *rac*-3 with Aromatic Aldehydes

Entries	Base	Temp. (°C)	Time (h)	Product	Yield[a] (%)	*trans/cis* ratio
	KOH	-5 to rt	3	**rac-4a**	78 [95]	97/3[b]
	KOH	-5	.5	**rac-4b**	35 [50]	96/4[b]
	KOH	-5 to rt	2	**rac-4c**	70 [85]	97/3[b]
	KOH	-5	2	**rac-4d**	50 [80]	96/4[b]
	KOH	-5 to rt	2	**rac-4e**	55 [90]	96/4[b]
	KOH	-5	3	**rac-4f**	47 [70]	20/1[c]
	KOH	-5 to rt	2	**rac-4g**	63 [74]	20/1[c]
	CsOH	-5 to rt	2.5	**rac-4h**	55 [87]	9/1[c]
	CsOH	-5	3	**rac-4i**	55 [60]	20/1[c]
	CsOH	-5 to rt	2.5	**rac-4j**	55 [70]	20/1[c]
	KOH	-5 to rt	3	**rac-4k**	55 [67]	20/1[c]
	KOH	-5 to rt	2.5	**rac-4l**	58 [80]	20/1[c]

[a] The isolated yield was determined with respect to the aryl aldehyde used. The isolated yield with respect to the converted aryl aldehyde is given in brackets. [b] Selectivity was determined by HPLC on a chiral column. [c] Selectivity was determined by column chromatographic separation. [d] Determined by NMR.

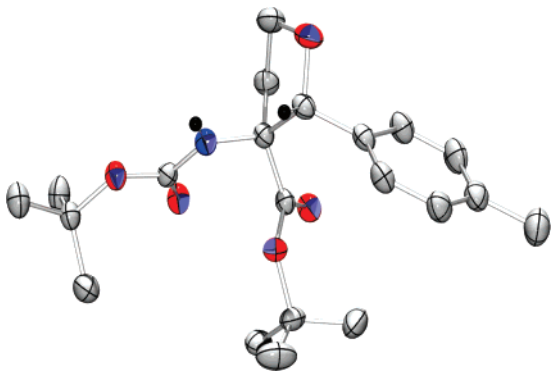
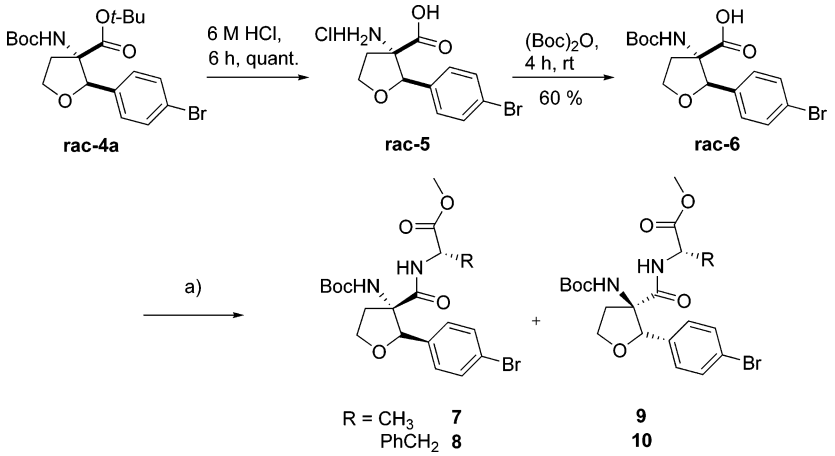


FIGURE 2. X-ray diffraction analysis of the major diastereomer of compound ***rac*-4e** confirming the trans configuration. For clarity, only one enantiomer and only the amide hydrogen atoms are shown.

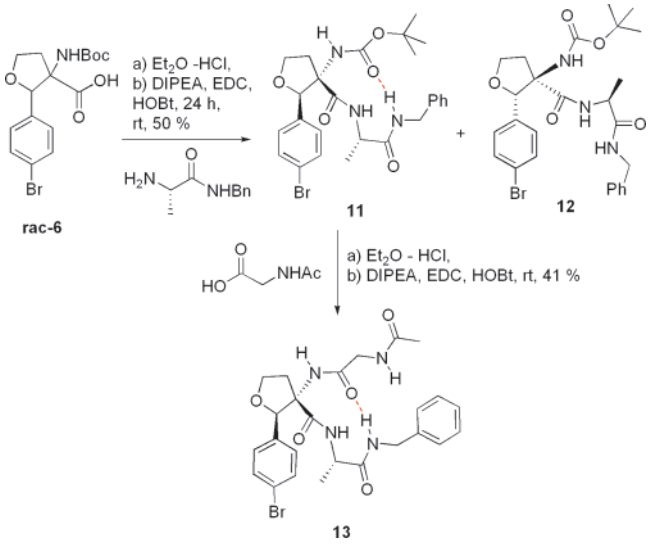
are now separable by column chromatography, and crystals suitable for X-ray diffraction analysis were obtained for the *R*,*S*,*S*-isomer **7** and *S*,*R*,*S*-isomer **9**.

SCHEME 2. Deprotection of TAA and Coupling with Chiral Amino Acids



a) DIPEA, EDC, HOBt, L-alanine methyl ester hydrochloride or L-phenylalanine methyl ester hydrochloride, DCM, 24 h, rt, 60% and 55%, respectively.

SCHEME 3. Incorporation of TAA *rac*-6 into a Short Peptide Chain



TAAs were incorporated into a short peptide chain to demonstrate their ability to induce a turn structure (Scheme 3).[22] Compound ***rac*-6** was coupled with the benzyl amide of L-alanine, and the diastereomers **11** and **12** were separated by column chromatography. The crystalline structure of dipeptide **11** confirmed the *R*,*S*,*S* configuration. The molecule adopts a β-turn type I conformation with terminal Boc-CO and benzylamide NH groups intramolecularly hydrogen bonded [N···O: 2.92 Å; N−H···O: 163°]. The torsion angles (φ, ψ) of the TAA $i + 1$ (−61.7, −25.2) and L-Ala $i + 2$ (−82.9, −2.0) residues correspond to a β-turn type I (Figure 3).[23] The X-ray diffraction analysis of the *S*,*R*,*S* diastereomer **12** (see Supporting Information) shows no intramolecular hydrogen bonds or turn structure formation.

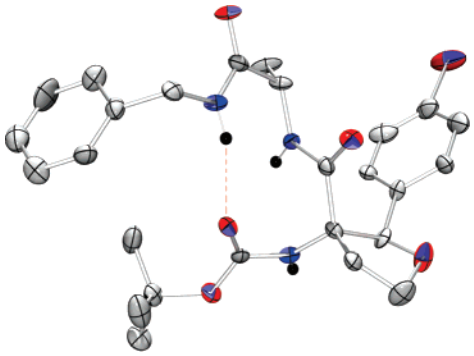


FIGURE 3. X-ray diffraction structure of compound **11** accommodating a β I turn in the crystal state. The intramolecular $i + 3 \rightarrow i$ hydrogen bond is indicated by a dashed line. Only the amide hydrogen atoms are shown.

After Boc-deprotection, isomer **11** was coupled with acetylated glycine yielding tripeptide **13**. Instead of a simple elongated β-turn structure, a conformation consisting of two consecutive β-turns type III, slightly deviating from an ideal 3_{10} helix structure, was observed in the solid state (Figure 4). The torsion angles (φ, ψ) for the left-side turn Gly $i + 1$ (−62.4°, −21.0°) and TAA $i + 2$ (−55.1°, −26.0°) and for the right-side turn TAA $i + 2$ (−55.1°, −26.0°) and L-Ala (−71.6°, −31.5°) resemble the typical values (−60°, −30° and −60°, −30°). The structure is stabilized by two intramolecular hydrogen bonds (N···O: 2.92 Å; N−H···O: 163° and N···O: 3.26 Å; N−H···O: 149°). A 2D ROESY spectrum (see Supporting Information) provides evidence for the existence of the proposed conformation in solution. Additional support comes from a variable-temperature NMR study in DMSO-d_6: Temperature coefficients of the amide protons H_d (−0.58 ppb/K) and H_c (−3.17 ppb/K) possibly indicate strong intramolecular hydrogen bonds, and temperature coefficients of H_a and H_b are significantly higher (−5.35 ppb/K and −7.20 ppb/K, respectively; see Supporting Information for data). However, temperature coefficients are only assessed as an indication because a more detailed analysis is required to unambiguously correlate their values to hydrogen bonding as shown by Andersen et al.[24]

(22) (a) Jimenerz, A. I.; Ballano, G.; Cativiela, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 396−399. (b) Jimenez, A. I.; Cativiela, C.; Aubry, A.; Marraud, M. *J. Am. Chem. Soc.* **1998**, *120*, 9452. (c) Jimenez, A. I.; Cativiela, C.; Gomez-Catalan, J.; Perez, J. J.; Aubry, A.; Paris, M.; Marraud, M. *J. Am. Chem. Soc.* **2000**, *122*, 5811. (d) Jimenez, A. I.; Cativiela, C.; Marraud, M. *Tetrahedron Lett.* **2000**, *41*, 5353. (e) Jimenez, A. I.; Marraud, M.; Cativiela, C. *Tetrahedron Lett.* **2003**, *44*, 3141.

(23) The torsion angles closely resemble the ideal values of (−60°, −30°) and (−90°, 0°).

(24) Andersen, N. H.; Neidigh, J. W.; Harris, S. M.; Lee, G. M.; Liu, Z.; Tong, H. *J. Am. Chem. Soc.* **1997**, *119*, 8547−8561.

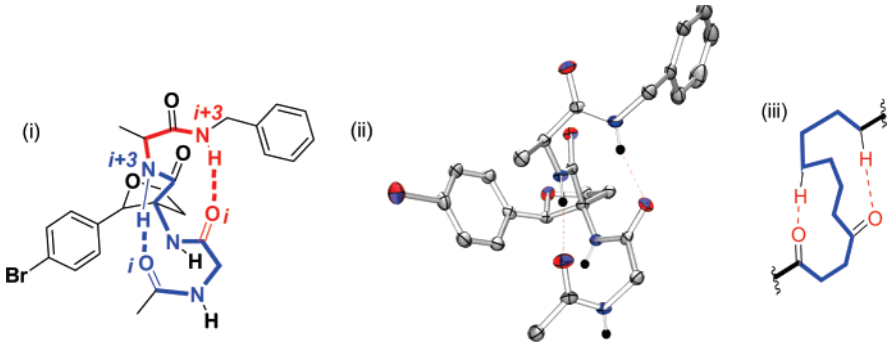
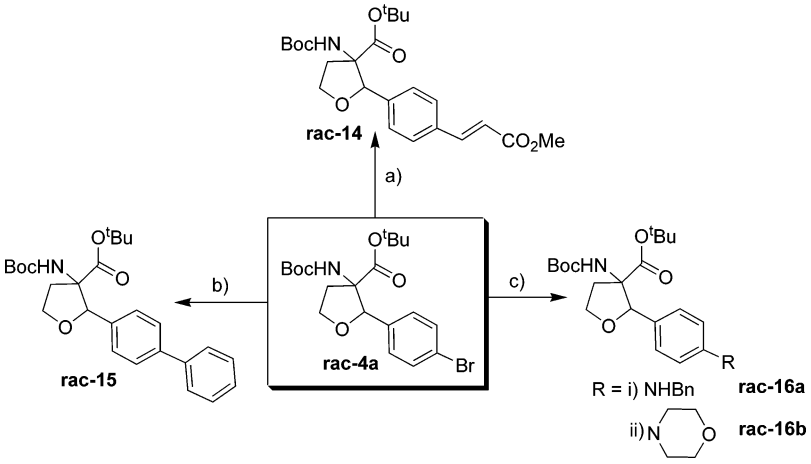


FIGURE 4. Structure (i) and X-ray diffraction analysis (ii) of compound **13** exhibiting two consecutive β-turns, each stabilized by an intramolecular $i + 3 \rightarrow i$ hydrogen bond (dashed lines). Only amide hydrogen atoms are shown. (iii) Backbone structure of the tripeptide.

SCHEME 4. Cross-Coupling Reactions



a) Methylacrylate, Et_3N, $Pd(Ac)_2$, P(*o*-tolyl)$_3$, in DMF, 14 h, 80 °C, 71%; b) phenylboronic acid, Na_2CO_3, $Pd(OAc)_2$, TBAB, in water/DME (1:1), 100 °C, 71%; c) benzylamine or morpholine, K_3PO_4, 2-isobutyryl-cyclohexanone in DMF, 100 °C, 75% or 35%.

The bromine substituent in compound ***rac*-4a** allows a subsequent functionalization of the TAA, which may be of use for specific labeling or modification of properties of the turn motif. Conventional Suzuki,[25] Heck,[26] and Buchwald[27] coupling (Scheme 4) gave derivatives ***rac*-14** to ***rac*-16**.

Conclusion

In summary, we have reported the racemic diastereoselective synthesis of tetrahydrofuran Cα-tetrasubstituted amino acids (TAA) from readily available methionine. Dipeptides of TAA and chiral amino acids yield diastereomers, which are readily separated by column chromatography. Short peptide sequences containing the *R*,*S*-isomer of TAA show a stable turn structure in the crystal state and in solution. Two consecutive β-turn type III turns, resembling a distorted 3_{10} helix structure, are found for a tripeptide amide consisting of Gly-TAA-Ala. Good accessibility and variable modification by transition-metal-catalyzed coupling reactions make TAAs a useful addition to the family of Cα-tetrasubstituted α-amino acids and artificial turn structures in peptide research.

Experimental

Sulfonium Salt Cyclization, Typical Procedure. An oven- or flame-dried flask was cooled under a stream of nitrogen and charged with sulfonium iodide ***rac*-3** (1 mmol) in acetonitrile (4 mL/mmol). The colorless solution was cooled to 0 °C. Powdered KOH or KO^{t}Bu or CsOH (1 mmol) was added, and the reaction mixture was stirred for 15 min. Then the aryl aldehyde (0.9 mmol) was added, and the mixture was stirred for another 2−4 h. After consumption of all of the starting material, the reaction mixture was quenched by adding water (3 mL/mmol). The reaction mixture was diluted with diethyl ether (4 mL/mmol) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 5 mL/mmol). Then, combined ether layers were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using 10−15% diethyl ether/PE as the eluant.

***tert*-Butyl-2-(4-bromophenyl)-3-(*tert*-butoxycarbonylamino)-tetrahydrofuran-3-carboxylate (*rac*-4a).** Yield = 60% using KO^{t}Bu as a base, 82% using KOH as a base, and 65% using CsOH as a base. R_f = 0.23 (diethyl ether/PE = 1:4), mp = 131−133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.45 (s, 9H), 2.61−2.68 (m, 2H), 4.16−4.33 (m, 2H), 5.00 (bs, 1H), 5.71 (bs, 1H), 7.20 (d, J = 8.23 Hz, 2H), 7.42 (d, J = 8.23 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.42 (+), 28.40 (+), 35.80 (−), 67.91 (−), 69.63 (+), 80.13 (C_{quat}), 82.62 (C_{quat}), 84.42 (C_{quat}), 121.75 (C_{quat}), 127.91 (+), 131.02 (+), 136.72 (C_{quat}), 154.3 (C_{quat}), 170.03 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4OAc] =

(25) de Meijere, A.; Meyer, F. E.; *Angew. Chem, Int. Ed. Engl*. **1995**, *33*, 2379−2411.
(26) Leadbeater, N. E.; Marco, M. *J. Org. Chem*. **2003**, *68*, 888−892.
(27) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2006**, *128*, 8742−8743.

442.2, 444.2 [MH^+] (80), 459.3, 461.3 [$M - NH_4^+$] (75). IR (KBr): $\tilde{\nu}$ cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd for $C_{20}H_{28}BrNO_5$ (442.34): C, 54.30; H, 6.38; N 3.17. Found: C, 54.27; H, 6.67; N, 3.16.

***tert*-Butyl-3-(*tert*-butoxycarbonylamino)-2-phenyltetrahydrofuran-3-carboxylate (*rac*-4c).** Yield = 70% using KOH as a base. R_f = 0.21 (diethyl ether/PE = 3:17), mp = 61−63 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.45 (s, 9H), 2.50−2.80 (m, 2H), 4.23 (m, 1H, -OC*H*H-), 4.33 (m, 1H, -OCH*H*-), 5.02 (bs,1H), 5.60 (bs, 1H), 7.25−7.30 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.92 (+), 28.12 (+), 35.83 (−), 67.04 (−), 82.65 (C_{quat}), 84.87 (C_{quat}), 123.44 (+), 128.08 (C_{quat}), 133.53 (+), 137.52 (+), 150.61 (+), 154.54 (+), 155.36 (C_{quat}), 170.09 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc] = 364.3 [MH^+] (100), 381 [$M - NH_4^+$] (50). IR (KBr): $\tilde{\nu}$ cm^{-1} = 3358, 2978, 2932, 2872, 1720, 1494, 1454, 1365. Anal. calcd for $C_{20}H_{29}NO_5$ (363.45): C, 66.09; H, 8.04; N, 3.85. Found: C, 65.89; H, 8.32; N, 3.32.

***tert*-Butyl-3-(*tert*-butoxycarbonylamino)-2-(4-methoxy-phenyl)-tetrahydrofuran-3-carboxylate (*rac*-4d)**. Yield = 50% using KOH as a base and 45% using KO^{t}Bu as a base. R_f = 0.25 (diethyl ether/PE = 1:4), mp = 97−99 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.13 (s, 9H), 1.49 (s, 9H), 2.52−2.65 (m, 1H, -C*H*H-), 2.68−2.82 (m, 1H, -CH*H*-), 3.78 (s, 3H), 4.11−4.23 (m, 1H, -OC*H*H-), 4.27−4.35 (m, 1H, -OCH*H*-), 4.93 (bs, 1H), 5.48 (bs, 1H), 6.80 (d, J = 7.96 Hz, 2H), 7.25 (d, J = 7.96 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.49 (+), 28.41 (+), 55.00, 67.74 (−), 69.14, 82.08 (C_{quat}), 113.00 (+), 127.57 (C_{quat}), 129.50 (+), 154.54 (C_{quat}), 159.46 (C_{quat}), 170.08 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc] 394.2 [MH^+] (60), 411.2 [$M - NH_4^+$] (20). IR (KBr): $\tilde{\nu}$ cm^{-1} = 3359, 2975, 2931, 2881, 1707, 1613, 1583, 1510. Anal. calcd for $C_{21}H_{31}NO_6$ (393.47): C, 64.10; H, 7.94; N, 3.56. Found: C, 64.33; H, 7.64; N, 3.37.

***tert*-Butyl-3-(*tert*-butoxycarbonylamino)-2-(4-methylphenyl)-tetrahydrofuran-3-carboxylate (*rac*-4e).** Yield = 55% using KOH as a base. R_f = 0.22 (diethyl ether/PE = 3:17), mp = 135−138 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.47 (s, 9H), 2.30 (s, 3H), 2.65 (m, 1H, -C*H*H-), 2.72 (m, 1H, -CH*H*-), 4.11 (m, 1H, -OC*H*H-), 4.32 (m, 1H, -OCH*H*), 5.02 (bs, 1H, CH-), 5.65 (bs, 1H), 6.92 (d, J = 7.95 Hz, 2H), 7.45 (m, J = 7.95 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.12 (+), 27.41 (+), 29.94 (+), 35.73 (−), 67.78 (−), 69.74 (+), 82.05 (C_{quat}), 82.07 (C_{quat}), 85.74 (C_{quat}), 126.21 (+), 128.61 (+), 134.38 (C_{quat}), 137.63 (C_{quat}), 154.57 (C_{quat}), 170.07 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10mmol/1 NH_4OAc] = 378.2 [MH^+] (100), 395.2 [$M - NH_4^+$] (20). IR (KBr): $\tilde{\nu}$ cm^{-1} = 3357, 2978, 2930, 2870, 2783, 2199, 1703, 1610, 1514, 1450. Anal. calcd for $C_{21}H_{31}NO_5$ (377.47): C, 66.82; H, 8.28; N, 3.71. Found: C, 66.91; H, 8.62; N, 3.58.

3-Amino-2-(4-bromo-phenyl)-tetrahydrofuran-3-carboxylic Acid Hydrochloride (*rac*-5). To a solution of compound ***rac*-4a** (2 g, 4.5 mmol) in 20 mL of methanol was added 10 mL of 6 M HCl. The reaction mixture was heated to reflux temperature for 6 h, then cooled to room temperature and stirred for another 2 h. The reaction mixture was concentrated by removal of methanol; remaining parts of the reaction mixture were lypophilized yielding quantitatively a white solid of the corresponding hydrochloride salt (1.4 g). The compound was used in the next step without further purification.

^{1}H NMR (300 MHz, MeOD) δ = 2.32 (m, 1H, -CH*H*-), 2.92 (m, 1H, -C*H*H-), 4.17 (m, 1H, -OCH*H*-), 4.56(m, 1H, -OC*H*H-), 5.00 (bs, 1H), 7.34 (d, J = 8.23 Hz, 2H), 7.53 (d, J = 8.23 Hz, 2H). ^{13}C NMR (75.5 MHz, MeOD) δ = 36.23 (−), 68.59 (−), 69.91 (+), 87.77 (C_{quat}), 123.89 (+), 129.76 (C_{quat}), 132.45 (C_{quat}), 136.24 (+), 170.39 (+). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4-OAc] = 0.286.1, 288.1 [$MH^+ - Cl$] (30), 303.2, 305.2 [$M + NH_4^+$] (100).

2-(4-Bromophenyl)-3-(*tert*-butoxycarbonylamino)-tetrahydrofuran-3-carboxylic Acid (*rac*-6). Procedure A. (Starting from compound ***rac*-5**): Compound ***rac*-5** (1 g, 3.13 mmol), 1,4-dioxan (5 mL), and 1.25 M aqueous NaOH (7 mL) were stirred and cooled to 6 °C for 10 min. Then a solution of di-*tert*-butyl-dicarbonate (0.75 g, 3.45 mmol) in 1,4-dioxan (2 mL) was added over 5 min. The cooling bath was removed, and the reaction was stirred for 3.5 h. The dioxane was removed in vacuo, and the residue was diluted with 1 M aqueous $KHSO_4$ (2 mL) and extracted with EtOAc (1 × 4, 1 × 3 mL). The combined organic layers were washed with water (2 mL) and brine (2 mL) and dried over $MgSO_4$. The solvent was removed to give pure ***rac*-6** as a white solid (0.72 g, 60%).

Procedure B. (Starting from compound ***rac*-4n**): Compound ***rac*-4n** (500 mg, 1.05 mmol) was dissolved in ethanol (5 mL). Then 150 mg of KOH was added to the solution, and the mixture was refluxed for 24 h. The reaction mixture was cooled, and ethanol was evaporated. The obtained yellow solid was dissolved in water (3 mL) and extracted with diethyl ether (2 × 2 mL) to remove all organic impurities. The aqueous solution was acidified with citric acid (10%, 2 mL) and extracted with ethyl acetate (2 × 3 mL). The combined organic layers were washed with brine (1 mL) and dried over $MgSO_4$. The solvent was removed to give pure compound ***rac*-6** (97 mg) as a white solid in 24% yield. This compound was used for next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.44 (s, 9H), 2.68−2.78 (m, 1H, CHH), 3.30 (m, 1H, CHH), 4.15−4.25 (m, 1H, -OCHH), 4.32 (m, 1H, OCHH-), 5.10 (bs, 1H), 5.61 (bs, 1H), 7.10−7.22 (m, 2H), 7.40−7.50 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 28.40 (+), 35.80 (−), 67.91 (−), 69.63 (+), 82.62 (C_{quat}), 84.42 (C_{quat}), 121.75 (C_{quat}), 127.91 (+), 131.02 (+), 136.72 (C_{quat}), 154.3 (C_{quat}), 170.03 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4OAc] = 0.442.2 [M^+H] (80), 459.3 [$M - NH_4^+$]. IR (KBr): $\tilde{\nu}$ cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392.

Dipeptide Esters 7 and 9. Compound ***rac*-6** (100 mg, 0.26 mmol) was dissolved in CH_2Cl_2 (1.5 mL), and the hydrochloride salt of alanine methylester (36 mg, 0.26 mmol), EDC (40 mg, 0.26 mmol), HOBT (35 mg, 0.26 mmol), and DIPEA (84 mg, 0.65 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and quenched with water (2 mL) and 1 M $KHSO_4$ (3 mL), diluted by adding 3 mL of diethyl ether and transferred to a separating funnel. The aqueous layer was extracted with diethyl ether (2 × 3 mL). Then combined ether layers were washed with brine solution (2 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using 30−40% diethyl ether/petrol ether as the eluant to give 73.2 mg (60%) of compounds **7** and **9** as white solids. Compound **7**: mp = 117−118 °C, $[\alpha]_D^{25°}$ = +34.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 0.90 (bs, 3H), 1.49 (s, 9H), 2.50 (m, 1H, -CH*H*-), 2.85 (m, 1H, -C*H*H-), 3.65 (s, 3H), 4.10 (qn, J = 6.79 Hz, 1H), 4.27−4.38 (m, 2H), 5.43 (bs, 1H), 6.25 (bs, 1H), 6.45 (bs, 1H), 7.20 (d, J = 8.25 Hz, 2H), 7.40 (d, J = 8.25 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.55 (+), 28.43 (+), 36.08 (−), 48.01(+), 52.47 (+), 66.62 (−), 67.11 (+), 80.07 (C_{quat}), 121.44 (C_{quat}), 126.82 (+), 131.13 (+), 136.12 (C_{quat}), 154.51 (C_{quat}), 170.79 (C_{quat}), 172.98 (C_{quat}). MS [PI-LSIMS; MeOH/Glycerine] = 0.471.3, 473.3 [MH^+] (60), 415.3, 417.3 [$M^+ - C_4H_8$] (50). IR (KBr): $\tilde{\nu}$ cm^{-1} = 3356, 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668. Anal. calcd for $C_{20}H_{27}BrN_2O_6$ (476.19): C, 50.96; H, 5.77; N, 5.94. Found: C, 50.92; H, 6.05; N, 5.87. Compound **9**: mp = 127−130 °C, $[\alpha]_D^{25°}$ = −34.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 0.92 (d, J = 6.24 Hz, 3H), 1.49 (s, 9H), 2.53 (m, 1H, -CH*H*-), 2.88 (m, 1H, -C*H*H-), 3.72 (s, 3H), 4.24 (qn, J = 7.34 Hz, 1H), 4.34 (m, 2H), 5.44 (bs, 1H), 6.28 (bs, 1H), 6.47 (d, J = 5.87 Hz, 1H), 7.22 (d, J = 8.44 Hz, 2H), 7.41 (d, J = 8.44 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 18.26 (+), 28.38 (+), 35.91 (−), 48.18 (+), 52.46 (+), 66.69 (−), 67.78 (+), 80.27 (C_{quat}), 121.65 (C_{quat}), 127.30 (+), 131.01 (+), 135.71 (C_{quat}), 154.32 (C_{quat}), 170.61 (C_{quat}), 172.66 (C_{quat}). MS [PI-LSIMS; MeOH/Glycerine] = 0.471.3, 473.3 [M^+H] (60), 415.3, 417.3 [$M^+ - C_4H_8$] (50). IR

(KBr): $\tilde{\nu}$ cm^{-1} = 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668, 1591, 1517, 1452. Anal. calcd for $C_{20}H_{27}BrN_2O_6$ (476.19): C, 50.96; H, 5.77; N, 5.94. Found: C, 51.02; H, 6.12; N, 5.86.

Dipeptide Esters 8 and 10. The compounds were prepared following the same procedure as that given for the preparation of **7** and **9**, using phenylalanine hydrochloride salt instead of alanine hydrochloride salt. The reaction gave 55% isolated product yield. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 2.79 (m, 1H, -CH*H*-), 2.97−3.10 (m, 1H, -C*H*H-), 3.60 (s, 3H), 4.02 (m, 1H), 4.15−4.31 (m, 3H), 4.41 (m, 1H), 5.38 (bs, 1H), 6.19 (bs, 1H), 6.57 (bs, 1H), 7.02−7.14 (m, 4H), 7.26−7.37 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 28.43 (+), 35.45 (−), 37.61 (−), 52.38 (+), 53.19 (+), 53.82 (+), 66.21 (−), 80.08 (C_{quat}), 121.46 (C_{quat}), 126.82 (+), 127.28 (+), 127.40 (+), 128.62 (+), 128.94 (C_{quat}), 129.13 (+), 131.19 (+), 135.77 (C_{quat}), 154.06 (C_{quat}), 171.05 (C_{quat}), 171.67 (C_{quat}). MS [PI-LSIMS; MeOH/Glycerine] = 546.14, 547.4 [MH$^+$] (60). IR (KBr): $\tilde{\nu}$ cm^{-1} = 3356, 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.49 (s, 9H), 2.81 (m, 1H, -CH*H*-), 2.95 (m, 1H, -C*H*H-), 3.65 (s, 3H), 4.04 (m, 1H), 4.20−4.34 (m, 3H), 4.43 (m, 1H), 5.40 (bs, 1H), 6.23 (bs, 1H), 6.60 (bs, 1H), 7.00−7.12 (m, 4H), 7.22−7.35 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 29.43 (+), 36.45 (−), 37.61 (−), 52.38 (+), 53.19 (+), 53.82 (+), 66.21 (−), 80.08 (C_{quat}), 121.46 (C_{quat}), 123.82 (+), 127.38 (+), 127.45 (+), 128.69 (+), 128.94 (C_{quat}), 129.13 (+), 131.19 (+), 135.77 (C_{quat}), 155.06 (C_{quat}), 171.06 (C_{quat}), 171.77 (C_{quat}).

Dipeptide Amides 11 and 12. The compounds were prepared as described above. The reaction gave an isolated yield of 50% of the two diastereomers. Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (d, J = 7.12 Hz, 3H), 1.43 (s, 9H), 2.55−2.64 (m, 1H, -CH*H*-), 2.69−2.81 (m, 1H, -C*H*H-), 4.00 (m, 1H), 4.20−4.28 (m, 2H), 4.34−4.44 (m, 3H), 5.12 (bs, 1H), 5.88 (bs, 1H), 6.24 (bd, 1H), 6.34 (t, 1H), 7.17−7.39 (m, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.98 (+), 28.29 (+), 36.08 (−), 43.34 (−), 49.20 (+), 67.16 (−), 68.42 (+), 80.91 (C_{quat}), 83.01 (C_{quat}), 122.05 (C_{quat}), 127.35 (+), 127.50 (+), 128.58 (+), 131.32 (+), 135.74 (C_{quat}), 137.99 (C_{quat}), 154.78 (C_{quat}), 170.54 (C_{quat}), 171.22 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4Ac] = 0.546.2, 548.2 [MH$^+$] (100), 490.1, 492.1 [M$^+$ − C_4H_8] (26).

Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (d, J = 6.82 Hz, 3H), 1.48 (s, 9H), 2.38−2.53 (m, 1H, -CH*H*-), 2.69−2.81 (m, 1H, -C*H*H-), 4.00−4.10 (m, 1H), 4.25−4.48 (m, 4H), 5.32 (bs, 1H), 6.12 (bs, 1H), 6.25 (bt, 1H), 6.60 (d, J = 6.60 Hz, 1H), 7.16−7.40 (m, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.76 (+), 28.42 (+), 35.82 (−), 43.53 (−), 49.02 (+), 66.75 (−), 67.70 (+), 80.35 (C_{quat}), 81.24 (C_{quat}), 121.60 (C_{quat}), 127.08 (+), 127.59 (+), 128.77 (+), 131.14 (+), 136.16 (C_{quat}), 137.81 (+), 154.20 (C_{quat}), 170.92 (C_{quat}), 171.38 (C_{quat}).

Tripeptide Amide 13. Compound **11** (100 mg, 0.26 mmol) was dissolved in 5 mL of DCM. To this solution was added 2 mL of HCl saturated diethyl ether solution, and the mixture was stirred for 20 min at room temperature. The solvent was evaporated, and the resulting white solid was dissolved in DMF (1.5 mL). DIPEA (89 mg, 0.67 mmol), Ac-Gly-OH (36 mg, 0.32 mmol), EDC (65 mg, 0.41 mmol), and HOBT (66 mg, 0.41 mmol) were added. The reaction mixture was stirred at room temperature for 3 days, quenched with water (2 mL) and 1 M $KHSO_4$ (3 mL), diluted by adding 3 mL of diethyl ether, and transferred into a separatory funnel. The aqueous layer was extracted with diethyl ether (2 × 3 mL); the combined ether layers were washed with brine solution (2 mL) and dried over $MgSO_4$; and the solvent was removed in vacuo. The crude product was purified by HPLC to give 41 mg of compound **13** (40% yield).

^{1}H NMR (600 MHz, DMSO) δ = 0.80 (d, J = 7.47 Hz, 3H, COSY, HSQC: H-24), 1.74 (s, 3H, COSY, HSQC: H-11), 1.99 (m, 1H, COSY, HSQC: H-$4_{a/b}$), 2.97 (m, 1H, COSY, HSQC: H-$4_{b/a}$), 3.50−3.7 (m, 2H, COSY, HMBC: H-14 and H-$8_{a/b}$), 3.82 (dd, 1H, J = 15.94 Hz, 5.14 Hz, COSY, HMBC: H-$8_{b/a}$), 3.87 (m, 1H, COSY, HMBC: H-$5_{a/b}$), 4.15 (m, 1H, COSY, HMBC: H-$17_{a/b}$), 4.25 (m, 2H, COSY, HMBC: H-$17_{b/c}$ and H-$5_{b/a}$), 4.98 (s, 1H, COSY, HMBC: H-2), 7.16 (m, 3H, aromatic), 7.27 (m, 4H, aromatic), 7.35 (d, J = 7.47 Hz, 1H, COSY, HMBC: H-13), 7.49 (m, 2H, aromatic), 7.58 (t, J = 6.36 Hz, 1H, COSY, HMBC: H-16), 8.20 (t, J = 5.25 Hz, COSY, HMBC: H-9), 9.00 (s, 1H, COSY, HMBC: H-6). ^{13}C NMR (151 MHz, DMSO) δ = 16.40 (+, HSQC: C-24), 22.10 (+, HSQC: C-11), 35.67 (−, HSQC: C-4), 41.82 (−, HSQC: C-8 or C-17), 43.10 (−, HSQC, C-8 or C-17), 48.61(+, HSQC: C-14), 67.31 (−, HSQC: C-5), 69.65 (+, HSQC: C-2), 84.83 (C_{quat}, HSQC, C-3), 121.00 (C_{quat}), 126.51 (+), 126.77 (+), 127.04 (+), 128.09 (+), 128.23 (+), 128.67 (+), 130.40 (+), 137.30 (C_{quat}), 139.19 (+), 168.50 (C_{quat}, HMBC: C-12), 170.45 (C_{quat}, HMBC: C-10), 171.46 (C_{quat}, HMBC: C-7), 171.70 (C_{quat}, HMBC: C-15). MS [PI-LSIMS; MeOH/glycerine] = 0.545.3, 547.3 [MH$^+$] (100).

(*E*)-*tert*-Butyl-3-(*tert*-butoxycarbonylamino)-2-[4-(3-methoxy-3-oxoprop-1-enyl)-phenyl]-tetrahydrofuran-3-carboxylate (*rac*-14). A mixture of 0.57 mmol of compound ***rac*-4a** (250 mg), 0.68 mmol of methylacrylate (58 mg), 0.68 mmol of triethyl amine, 1 mol % of palladium acetate, and 0.03 mmol of tris(*o*-tolyl)phosphine in 2 mL of DMF was heated to 100 °C under argon for 14 h. After the consumption of all of the starting material, the mixture was cooled to room temperature and 2 mL of 1 M $KHSO_4$ was added. The mixture was extracted (3 × 1 mL) with diethyl ether. The combined organic fraction was dried over $MgSO_4$, and the solvent was evaporated to give a solid crude product, which was purified by column chromatography (silica gel, 1:1 diethyl ether/petrol ether) affording 180 mg (71%) of the white solid product ***rac*-14**: mp = 146−149 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.46 (s, 9H), 2.61−2.68 (m, 2H), 3.80 (s, 3H), 4.16−4.33 (m, 2H), 5.09 (bs, 1H), 5.65 (bs, 1H), 6.41 (d, J = 15.92 Hz, 1H), 7.35 (d, J = 8.23 Hz, 2H), 7.50 (d, J = 8.23 Hz, 2H), 7.65 (d, J = 15.92 Hz, 1H). ^{13}C NMR (75.5 MHz, CDCl3) δ = 27.38 (+), 28.41 (+), 35.94 (−), 51.72 (+), 67.97 (−), 69.71 (+), 80.10 (C_{quat}), 82.50 (C_{quat}), 84.72 (C_{quat}), 117.73 (+), 126.72 (C_{quat}), 127.66 (+), 131.95 (+), 140.16 (C_{quat}), 144.47 (+), 154.3 (C_{quat}), 167.45 (C_{quat}), 170.05 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4OAc] = 0.448.2 [MH$^+$] (40), 465.3 [M − NH_4^+] (35), 409.2 [M − NH_4^+ − C_4H_8] (100). IR (KBr): cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd for $C_{24}H_{33}NO_7$ (447.34): C, 64.41; H, 7.43; N, 3.13. Found: C, 64.27; H, 7.67; N, 3.16.

***tert*-Butyl-2-(biphenyl-4-yl)-3-(*tert*-butoxycarbonylamino)-tetrahydrofuran-3-carboxylate (*rac*-15).** In a 25 mL Schlenk flask were placed compound ***rac*-4a** (250 mg, 0.567 mmol), phenylboronic acid (83 mg, 0.68 mmol), Na_2CO_3 (240 mg, 2.27 mmol), $Pd(OAc)_2$ (2 mg, 6 μmol), tetrabutylammonium bromide (183 mg, 0.567 mmol), and 2 mL of a water/DMF (1:1) mixture. The flask was sealed with a septum and placed into an oil bath preheated to 100 °C. The reaction mixture was held at this temperature for 20 h and cooled to room temperature. Water and diethyl ether (10 mL of each) were added, and organic material was removed by extraction. After further extraction of the aqueous layer with diethyl ether, the organic phases were combined and dried over $MgSO_4$, and the diethyl ether was removed in vacuo, leaving the crude product, which was purified by column chromatography (silica gel, 1:4 diethyl ether/PE) affording 250 mg (71%) of the white solid product ***rac*-15**: mp = 80−83 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12 (s, 9H), 1.50 (s, 9H), 2.57−2.85 (m, 2H), 4.18−4.41 (m, 2H), 5.09 (bs, 1H), 5.56 (bs, 1H), 7.31−7.59 (m, 9H). ^{13}C NMR (75.5 MHz, CDCl3) δ = 27.40 (+), 28.44 (+), 35.95 (−), 67.49 (−), 69.89 (+), 80.07 (C_{quat}), 82.26 (C_{quat}), 85.47 (C_{quat}), 126.73 (C_{quat}), 127.08 (+), 127.32 (+), 127.41 (+), 127.59 (+), 127.97 (+), 128.89 (+), 131.04 (+), 136.65 (C_{quat}), 140.94 (C_{quat}), 154.3 (C_{quat}), 170.10 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4OAc] = 440.3 [MH$^+$] (65), 457.3 [M − NH_4^+] (60), 401.2 [M − NH_4^+ − C_4H_8] (100). IR (KBr): cm^{-1} = 3362,

2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd for $C_{26}H_{33}NO_5$ (439.54): C, 71.05; H, 7.57; N, 3.19. Found: C, 70.82; H, 7.66; N, 3.15.

***tert*-Butyl-2-(4-(benzylamino)phenyl)-3-(*tert*-butoxycarbonylamino)-tetrahydrofuran-3-carboxylate (*rac*-16a).** An oven-dried Schlenk flask equipped with a Teflon septum was charged with a magnetic stir bar, 3 mL of DMF, compound ***rac*-4a** (250 mg, 0.567 mmol), CuI (5.5 mg, 0.028 mmol, 5 mol %), and K_3PO_4 (240 mg, 1.134 mmol). The flask was evacuated and filled with argon (this procedure was repeated three times). Under a flow of argon, the appropriate amine (91 mg, 0.851 mmol) was added by syringe. Finally, 2-isobutyryl-cyclohexanone (20 mg, 0.113 mmol, 20 mol %) was added via syringe. The mixture was heated to 100 °C for 10 h. Upon completion of the reaction, the mixture was allowed to cool to room temperature and diluted with 5 mL of water. The aqueous layer was extracted with diethyl ether (3 × 3 mL); the total organic fraction was dried over $MgSO_4$; and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, diethyl ether/PE 2:3) affording 200 mg (yield, 75%) of pure compound ***rac*-16a** as a white solid: mp = 122−125 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (s, 9H), 1.47 (s, 9H), 2.47−2.60 (m, 1H), 2.72−2.84 (s, 1H), 4.10 (q, J = 8.05 Hz, 1H), 4.25−4.30 (m, 1H), 4.32 (s, 2H), 4.80 (bs, 1H), 5.40 (bs, 1H), 6.55 (d, J = 8.50 Hz, 2H), 7.15 (d, J = 8.50 Hz, 2H), 7.27−7.35 (m, 5H). ^{13}C NMR (75.5 MHz, CDCl3) δ = 27.53 (+), 28.40 (+), 35.59 (−), 48.09 (−), 67.62 (−), 69.85 (+), 79.90 (C_{quat}), 81.81 (C_{quat}), 86.56 (C_{quat}), 112.40 (+), 126.00 (C_{quat}), 127.16 (+), 127.31 (+), 127.56 (+), 128.59 (+), 139.36 (C_{quat}), 147.97 (C_{quat}), 154.74 (C_{quat}), 170.05 (C_{quat}). MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4-OAc] = 0.469.3 [MH^+] (100), 486.3 [M − NH_4^+] (65). IR (KBr): cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd for $C_{27}H_{36}N_2O_5$ (468.58): C, 69.21; H, 7.74; N, 5.98. Found: C, 69.17; H, 7.67; N, 6.00.

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Supporting Information Available: Experimental procedures and characterization data for the synthesis of compounds ***rac*-2a**, ***rac*-2b**, ***rac*-3a**, ***rac*-3b**, ***rac*-4b**, ***rac*-4c**, ***rac*-4f**, ***rac*-4n**, and ***rac*-16b**. Copies of ^{1}H NMR spectra of all new compounds, temperature-dependent NMR spectra of compounds **11** and **13**, ROESY spectrum of **13**, and X-ray diffraction analyses of compounds ***rac*-4a**, **7**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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