Use of a Heck Reaction for the Synthesis of a New α-Azido Phosphotyrosyl Mimetic Suitably Protected for Peptide Synthesis

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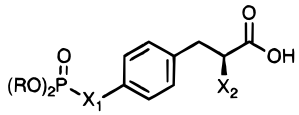
Fundamental to both solution- and solid-phase synthesis is the use of urethane-based α-amino protection, such as acid-labile Boc or base-labile Fmoc species. A little explored alternative to such carbonyl-based amino protection strategies is represented by α-azido acids, in which the azide functions as a latent amine equivalent that is both stable to a range of carboxylic acid coupling protocols and can be converted easily in situ to the free α-amino group under mild conditions.[1] Such an approach obviates the need for formal amino protection and potentially allows chain elongation in sterically limiting situations which would otherwise be difficult using bulky Boc or Fmoc groups. Recent papers describing the enzymatic and chiral HPLC resolution of α-azido acids,[2] as well as the utilization of chiral α-azido-masked acyl cyanides as synthetic equivalents of N-protected, C-activated α-amino acids,[3] have highlighted a growing interest in chiral α-azido acids as novel building blocks. Furthermore, besides having utility as masked α-amino acids for peptide synthesis, α-azido acids have also found wide use as versatile synthetic intermediates.[4−7]

In the field of cellular signal transduction, novel amino acid analogues of phosphotyrosyl residues (pTyr, **1**) have emerged as important molecular probes. Among these pTyr mimetics, phosphonomethyl phenylalanine[1] (Pmp **2**) has proven to be a particularly useful agent, due to its ability to faithfully replicate several biological interactions of native pTyr residues,[2−4] while at the same time being stable toward cellular phosphatases.[5] Since its original preparation as the racemic, free phosphonic acid,[1] enantioselective synthesis of Pmp in its N^{α}-Fmoc 4-(bis(*tert*-butyl)phosphonomethyl)-L-phenylalanine form[6,7] ((N^{α}-Fmoc-L-Pmp($^{t}Bu_2$)-OH, **3**) has allowed facile introduction of Pmp into a variety of peptides using standard Fmoc protocols. The biological importance of phosphonate-based pTyr mimetics makes the preparation of novel Pmp derivatives an important area of investigation. There is also a growing interest in α-azido acids which may serve as latent amino acid surrogates that can be introduced into peptides and subsequently reduced to the free amino compounds. Such agents may also be utilized as nonnatural amino acid replacements in their own right.[8−10] Accordingly, herein is reported protected α-azido 3-((4-phosphonomethyl)phenyl)propanoic acid analogue **4**, which is the first example of a pTyr mimetic containing an azido group at the biologically important α-center. As such, it may be considered both as a new pTyr mimetic in its own right and as a "masked" variant of L-Pmp($^{t}Bu_2$)-OH, in which the amino group is in latent form.



No	R	X_1	X_2
1	H	O	NH_2
2	H	CH_2	NH_2
3	*tert*-Butyl	CH_2	NHFmoc
4	*tert*-Butyl	CH_2	N_3
5	*tert*-Butyl	CH_2	H
6	Et	CH_2	H

Key to the synthesis of **4**, is the palladium-catalyzed Heck coupling[11] of bis(*tert*-butyl)((4-bromophenyl)methyl)phosphonate (**10**) with chiral acrylamide **9** (formed by pivaloyl mixed anhydride amidation of acrylic acid and commercially available Evans reagent, (S)-(−)-4-benzyl-2-oxazolidinone (**8**):[12] The 4-benzyl oxazolidinone was utilized rather than the 4-phenyl species, due to the former's hydrogenolytic stability under the Pd−C/H_2 conditions required later in the synthesis (Scheme 1). This coupling represents an example of a Heck reaction carried out on chiral reactants.[13,14] It provides a facile entry into the functionalized ((4-phosphonomethyl)phenyl)propenoic acid skeleton (**11**), which by analogy to work reported on tyrosine and phenylalanine analogues,[15] may serve as a versatile starting point for the preparation

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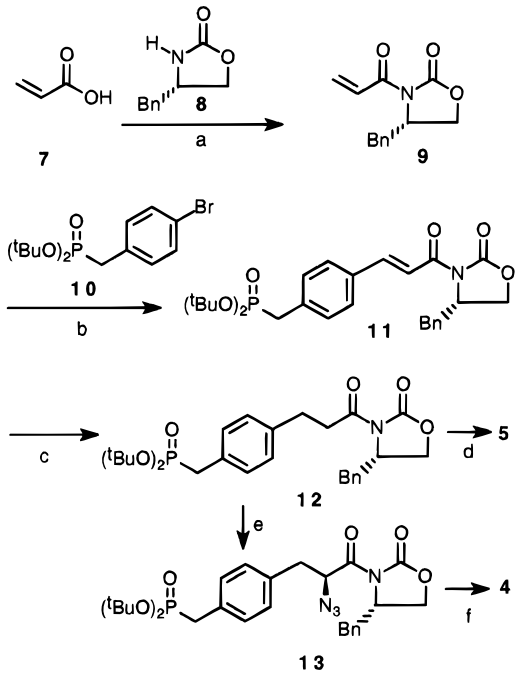
Scheme 1[a]

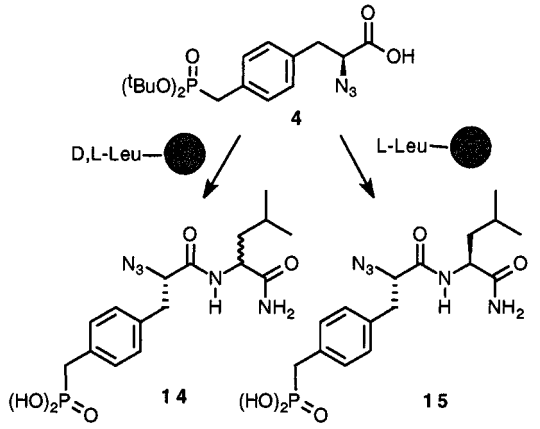


[a] (a) (1) Pivaloyl chloride, *N*-methylmorpholine, −78 °C; (2) lithim salt of **8**, −78 °C to rt (49%); (b) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, NEt_3, 85 °C (79%); (c) H_2/Pd^0 (82%); (d) LiOH, H_2O_2, THF/H_2O, 0 °C (81%); (e) KHMDS, trisyl azide (77%); (f) LiOH, H_2O_2, THF/H_2O, 0 °C (88%).

of a variety of novel β-substituted, conformationally restricted pTyr mimetics.[16]

Hydrogenation of **11** cleanly provided saturated congener **12**, which is a key branch point in the synthesis. In the first instance, **12** could be hydrolyzed directly to ((4-(bis(*tert*-butyl)phosphono)methyl)phenyl)propanoic acid (**5**) using aqueous lithium hydroxide and hydrogen peroxide.[17] Although, previously ((4-phosphonomethyl)phenyl)propanoic acid had been reported in its bis-ethyl protected phosphonate form **6**,[18] analogue **5** bears more synthetically useful *tert*-butyl phosphonate protection, and as such it represents a novel desamino pTyr mimetic suitably protected for N-terminal incorporation into signal transduction-related inhibitors using TFA cleavage protocols. Alternatively, intermediate **12** could be functionalized at the α-position, leading to desired final azido product **4**. Therefore subjecting **12** to trisyl azide-mediated electrophilic azide addition under (S)-chiral induction of the appended Evan's auxiliary,[19−23] α-azido compound **13** could be obtained enantioselectively, in greater than 94% ee (see below). To complete the synthesis, cleavage of the chiral auxiliary using aqueous lithium hydroxide in the presence of hydrogen peroxide, provided the desired final product, l-α-azido-((4-(bis(*tert*-butyl)-phosphono)methyl)phenyl)propanoic acid (**4**), in high yield without noticeable hydrolysis of *tert*-butyl phosphonate protection.

Scheme 2



To determine the enantiomeric purity of final product **4**, leucine amide dipeptides were prepared by solid-phase techniques, with HPLC separation performed on resulting azido diastereomers.[24] Racemic D,L-leucine-containing dipeptides (**14**) first served as standards which showed good separation of diastereomers (diastereomeric retention time difference of 1.0 min). Next, dipeptide **15** was prepared using enantiomerically pure L-leucine and shown to have less than 3% diastereomeric contamination resulting from the D-isomer (Scheme 2).

Conclusion

Reported herein is an application of a Heck reaction for the preparation of novel pTyr mimetics. Of particular note, analogue **4** is the first α-azido-based pTyr mimetic yet reported, and as such, it represents a new member of a growing family of α-azido acids. Finally as a unique azido variant of the widely used pTyr mimetic Pmp (**3**), compound **4** may find use as a new pTyr mimetic in the construction of novel signal transduction inhibitors.

Experimental Section

General Procedures. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross. Solvent was removed by rotary evaporation under reduced pressure, and silica gel chromatography was performed using high performance silica gel (60 Å pore, 10 μm particle size). Anhydrous solvents were obtained commercially and used without further drying. Analytical HPLC were conducted using a Vydac C_{18} column (10 mm diam × 250 mm long; solvent A = 0.1% aqueous TFA; solvent B = 0.1% TFA in acetonitrile; flow rate = 2 mL/min.).

(*S*)-4-Benzyl-3-(prop-2-enoyl)-1,3-oxazolidin-2-one (9). To a solution of acrylic acid (**7**) (8.2 mL; 120 mmol) and *N*-methylmorpholine (NMM) (13.2 mL; 120 mmol) in anhydrous THF (100 mL) at −78 °C under argon was added pivaloyl chloride (14.8 mL; 120 mmol), and the mixture was stirred at −78 °C (1 h). To a separate round-bottom flask containing Evan's reagent, (S)-(−)-4-Benzyl-2-oxazolidineone[25] (**8**) (17.7 g; 100 mmol) in anhydrous THF (200 mL) at −78 °C under argon, was added *n*-BuLi, 1.6 M in hexanes (62 mL; 100 mmol), and the solution was stirred at −78 °C (30 min). To this was then added via cannula at −78 °C the suspension of acryloyl mixed

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(25) Both (*S*)-(−)- and (*R*)-(+) 4-benzyl-2-oxazolidinone can be purchase from Aldrich Chemical Corp., St. Louis, MO.

anhydride, and the resulting mixture was stirred first at −78 °C (1.5 h) and then at room temperature (2 h). The mixture was partitioned between saturated NH_4Cl/EtOAc, and the combined organics were washed with brine, dried ($MgSO_4$), and taken to dryness to yield a syrup (27.6 g). Purification by silica gel chromatography (EtOAc in hexanes, from 0% to 50%) provided unreacted Evan's reagent (6.44 g) as well as product (**9**) as a white foam, which crystallized (7.16 g; 49% based on recovered starting material), mp 70−72 °C. ^{1}H NMR ($CDCl_3$) δ 7.61 (dd, 1H, J = 10.7, 17.1 Hz), 7.49−7.26 (m, 5H), 6.70 (dd, 1H, J = 1.7, 17.1 Hz), 6.03 (dd, 1H, J = 1.7, 10.2 Hz), 4.99−4.79 (m, 1H), 3.37−4.25 (m, 2 H), 3.44 (dd, 1H, J = 3.0, 13.2 Hz), 2.92 (dd, 1H, J = 9.8, 13.2 Hz). FABMS ($^+$VE, NBA) m/z 232 (MH^+). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.57; H, 5.82; N, 6.08.

Bis(*tert*-butyl) ((4-Bromophenyl)methyl)phosphonate (10). To a solution of di-*tert*-butyl phosphite (9.70 g; 50 mmol) in anhydrous THF (100 mL) at −78 °C under argon was added *n*-BuLi, 1.6 M in hexanes (33.2 mL; 50 mmol), over 5 min, and the solution was stirred first at −78 °C (30 min) and then at 0 °C (30 min). To this was added a solution of 4-bromobenzyl bromide (12.5 g; 50 mmol) in anhydrous THF (20 mL), and the mixture was stirred at 0 °C and then allowed to come to room temperature and stirred overnight. The mixture was partitioned between saturated aqueous NH_4Cl and EtOAc; the combined organic extracts were washed with brine, dried ($MgSO_4$), and taken to dryness, yielding a light yellow crystalline solid (18.27 g). Purification by silica gel chromatography (EtOAc in hexanes; from 0% to 100%) provided **10** as a cream-colored crystalline solid (15.21 g; 82% yield), mp 45 °C (soften), 48−56 °C. ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 2H J = 8.3 Hz), 7.16 (dd, 2H J = 2.4, 8.3 Hz), 2.99 (d, 2H J = 21.5 Hz), 1.43 (s, 18 H). HR-FABMS ($^+$VE) m/z calcd for $C_{15}H_{25}N_3O_3PBr$ (M^+): 3363.0725. Found: 3363.0735 (Δm = 2.8 ppm). Anal. Calcd for $C_{15}H_{24}BrO_3P$: C, 49.60; H, 6.66. Found: C, 50.20; H, 6.60.

3-(3-(4-((Bis(*tert*-butyl)phosphono)methyl)phenyl)prop-2-enoyl)-4(*S*)-benzyl-1,3-oxazolidin-2-one (11). A mixture of acrylamide **9** (1.48 g; 6.40 mmol), di-*tert*-butyl (4-bromobenzyl)-phosphonate (**10**) (2.36 g; 6.40 mmol), $Pd(OAc)_2$ (72 mg; 0.032 mmol), and tri-*O*-tolyl phosphine (390 mg; 1.28 mmol) in a round-bottom flask sealed with a rubber septum was alternately evacuated and flushed with argon (3×) and then to this was added NEt_3 (12 mL), and the mixture was heated with stirring at 85 °C (overnight). The resulting suspension was partitioned between ice-cold saturated NH_4Cl/EtOAc, and the combined organics were washed with brine, dried ($MgSO_4$), and taken to dryness to yield a foam (3.73 g). Purification by silica gel chromatography (EtOAc in hexanes, from 20% to 100%) provided **11** as a crystalline solid (2.58 g, 79%). Recrystallization from ether:hexanes provided an analytical sample, mp 128−129 °C. ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 2H), 7.66 (d, 2H, J = 8.1 Hz), 7.48−7.31 (m, 1H), 4.95−4.84 (m, 1H), 4.38−4.27 (m, 2H), 3.46 (dd, 1H, J = 3.0, 13.2 Hz), 3.15 (d, 2H, J = 22.2 Hz), 2.94 (dd, 1H, J = 9.4, 13.2 Hz), 1.52 (s, 18 Hz). FABMS ($^+$VE) m/z 514 (MH^+). Anal. Calcd for $C_{28}H_{36}NO_6P$: C, 65.48; H, 7.07; N, 2.73. Found: C, 65.74; H, 7.06; N, 2.81.

3-(3-(4-((Bis(*tert*-butyl)phosphono)methyl)phenyl)propanoyl)-4(*S*)-benzyl-1,3-oxazolidin-2-one (12). A solution of **11** (6.48 g; 12.7 mmol) in absolute EtOH (50 mL) was hydrogenated over Pd black (200 mg) at 40 psi H_2 in a Parr apparatus (overnight). Additional Pd black was added (200 mg) and hydrogenation cotinued (overnight). Catalyst was removed by filtration, and the filtrate was taken to dryness to yield a white crystalline solid, which was triturated with ether to provide a white solid. This was combined with additional product obtained by cooling the filtrate to −78 °C, providing **12** as a combined total of 5.37 g (82% yield), mp 114−115 °C. ^{1}H NMR ($CDCl_3$) δ 7.43−7.34 (m, 4H), 7.27 (s, 5H), 4.80−4.66 (m, 1H), 4.28−4.23 (m, 2H), 3.40−3.30 (m, 3H), 3.15−3.05 (m, 4H), 2.84 (dd, 1H, J = 9.4, 13.2 Hz), 1.53 (s, 18 Hz). FABMS ($^+$VE, NBA) m/z 516 (MH^+), 404 ($MH^+ - 2C_4H_8$). Anal. Calcd for $C_{28}H_{38}NO_6P$: C, 65.23; H, 7.43; N, 2.72. Found: C, 64.94; H, 7.34; N, 2.79.

(3-(4-((Bis(*tert*-butyl)phosphono)methyl)phenyl)propanoic Acid (5). To a solution of **12** (1.0 g; 1.95 mml) in THF (15 mL) with H_2O (5 mL) at 0 °C was added aqueous H_2O_2, 30% w/w (1.10 mL; 9.74 mmol) dropwise, followed by dropwise addition of an ice-cold solution of $LiOH\cdot H_2O$ (164 mg; 3.89 mmol) in H_2O (10 mL), and the mixture was then stirred at 0 °C (4 h). The mixture was diluted with H_2O (100 mL) and washed with CH_2Cl_2, the aqueous was cooled to ∼0 °C, ice-cold 0.1 N HCl was added (∼80 mL), and the mixture was then extracted with EtOAc. Combined organics were dried ($MgSO_4$) and taken to a syrup, which quickly crystallized to provide **5** as a white solid (563 mg; 81% yield), mp 101 (soften); 106−110 °C. ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, 2H, J = 2.1, 8.1 Hz), 7.21 (d, 2H, J = 8.1 Hz), 3.09 (d, 2H, J = 21.4 Hz), 3.02 (t, 2H, J = 7.7 Hz), 2.72 (t, 2H, J = 7.7 Hz), 1.49 (s, 18H). FABMS ($^-$VE, NBA) m/z 355 (M − H). Anal. Calcd for $C_{18}H_{29}O_5P$: C, 60.66; H, 8.20. Found: C, 60.90; H, 8.10.

3-(2-(S)-Azido-3-(4-((bis(*tert*-butyl)phosphono)methyl)-phenyl)propanoyl)-4(*S*)-benzyl-1,3-oxazolidin-2-one (13). To anhydrous THF (50 mL) at −78 °C under argon was added potassium bis(trimethylsilyl)amide, 0.5 M in toluene (29.0 mL; 14.5 mmol), followed by, via cannula, a precooled (−78 °C) solution of **12** (6.20 g; 12.1 mmol) in anhydrous THF (50 mL), and the resulting violet solution was stirred at −78 °C (30 min). To this was added rapidly, via cannula, a precooled (−78 °C) solution of (2,4,5-triisopropyl)phenylsulfonyl azide (4.50 g; 14.5 mmol). The resulting yellow solution was stirred at −78 °C (2 min) and quenched by addition of HOAc (3.8 mL; 66.6 mmol) followed by solid KOAc (4.87 g; 49. 7 mmol). The mixture was stirred at room temperature (3.5 h), partitioned between saturated $NaHCO_3$ in brine/EtOAc, washed with saturated $NaHCO_3$ in brine, dried ($MgSO_4$), and taken to dryness to yield a yellow resin (8.66 g). Purification by silica gel chromatography (50% EtOAc in hexanes) provided **13** as a white foam (5.13 g, 77%). Crystallization from ether provided an analytical sample, mp 80 °C (soften); 115−117 °C. ^{1}H NMR ($CDCl_3$) δ 7.46−7.27 (m, 9H), 5.37 (dd, 1H, J = 6.0, 9.0 Hz), 4.70−4.58 (m, 1H), 4.30−4.14 (m, 2H), 3.40 (dd, 1H, J = 3.0, 13.2 Hz), 3.28 (dd, 1H, J = 6.0, 13.2 Hz), 3.10 (d, 2H, J = 21.4 Hz), 2.90 (dd, 1H, J = 9.4, 13.2 Hz), 1.50 (s, 9H), 1.49 (s, 9H). FABMS ($^+$VE) m/z 557 (MH^+), 501 ($MH^+ - C_4H_8$), 445 ($MH^+ - 2C_4H_8$). Anal. Calcd for $C_{28}H_{37}N_4O_6P$: C, 60.42; H, 6.70; N, 10.07. Found: C, 60.53; H, 6.79; N,10.09.

3-(2(*S*)-Azido-3-(4-((bis(*tert*-butyl)phosphono)methyl)-phenyl)propanoic Acid (4). To a solution of **13** (4.77 g; 8.60 mmol) in THF (40 mL) with H_2O (10 mL) at 0 °C was added aqueous H_2O_2, 30% w/w (4.88 mL; 43.0 mmol) dropwise, followed by dropwise addition of an ice-cold solution of $LiOH\cdot H_2O$ (722 mg; 17.2 mmol) in H_2O (40 mL), and the mixture was then stirred at 0 °C (2 h). To the solution was added Na_2SO_3 (5.42 g; 43.0 mmol) in H_2O (20 mL), the mixture was diluted with brine (300 mL) and washed with CH_2Cl_2, the aqueous was cooled to ∼0 °C, ice-cold 1.0 N HCl was added until the pH ≤ 3, and the mixture was extracted with EtOAc. Combined organics were dried ($MgSO_4$), and solvent was removed to provide **6** as a highly crystalline white solid (3.00 g; 88% yield), mp 68−72 °C. ^{1}H NMR ($CDCl_3$) δ 7.29 (brs, 4H), 4.24−4.14 (m, 1H), 3.25−3.00 (m, 4H), 1.49 (s, 9H), 1.44 (s, 9H). FABMS ($^-$VE) m/z 396 (M−H). HR−FABMS ($^-$VE, MCA, Gly) m/z calcd. for $C_{18}H_{27}N_3O_3P$ (M−H): 396.1688. Found: 396.1667 (Δm = 2.1 mmu; 5.3 ppm). $[\alpha]_D$ = $^+$14.1° (c 0.95, $CHCl_3$). Anal. Calcd for $C_{18}H_{28}N_3O_5P\bullet{}^3/_4H_2O$: C, 52.61; H, 7.24; N, 10.23. Found: C, 52.63; H, 6.77; N, 10.36.

Determination of Enantiomeric Purity of Analogue 4. Dipeptides **14** and **15** were prepared from protected azido acid **4** using Rink amide resin[26] (0.4 mequiv/g, purchased from Bachem Corp., Torrance, CA) with Fmoc-protocols similar to those previously described.[27] Fmoc-D,L-Leu and Fmoc-L-Leu-Rink amide resins were prepared by coupling the appropriate Fmoc-protected amino acides to Rink resin, with the resulting Fmoc-protected resins (12.5 mg) then being washed well with several 1 mL portions of *N*-methyl-2-pyrolidoinone (NMP). Fmoc amino protection was removed by treatment with 20% piperidine in NMP (0.5 mL, 2 min followed by 0.5 mL, 20 min). Resins were washed well with NMP (10 × 1 mL) and then coupled overnight with a solution of active ester formed by reacting 12.5 μmol each of protected azido acid **4**, 1-hydroxybenzotriazole (HOBt), and 1,3-diisopropylcarbodiimide (DIPCDI) in NMP (1.0 mL, 10 min).

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Resins were first washed with NMP (10 × 1 mL) and dichloromethane (10 × 1 mL), and then dipeptides were cleaved from the resin using a mixture of trifluoroacetic acid (TFA, 1.80 mL) and H_2O (200 μl) (1h), taken to dryness, and analyzed by HPLC (linear gradient from 10% B to 90% B over 20 min). Retention times of diastereomeric peaks as determined using dipeptide **14** prepared from racemic D,L-leucine indicated diastereomers eluting at 18.6 min and 19.1 min. Enantiomeric contamination of azido acid **4** was then determined by similar analysis of dipeptide **15**, where diastereomeric contamination accounted for an area less than 3% of that observed for the major diastereomer. These results indicated greater than 94% enantiomeric purity.

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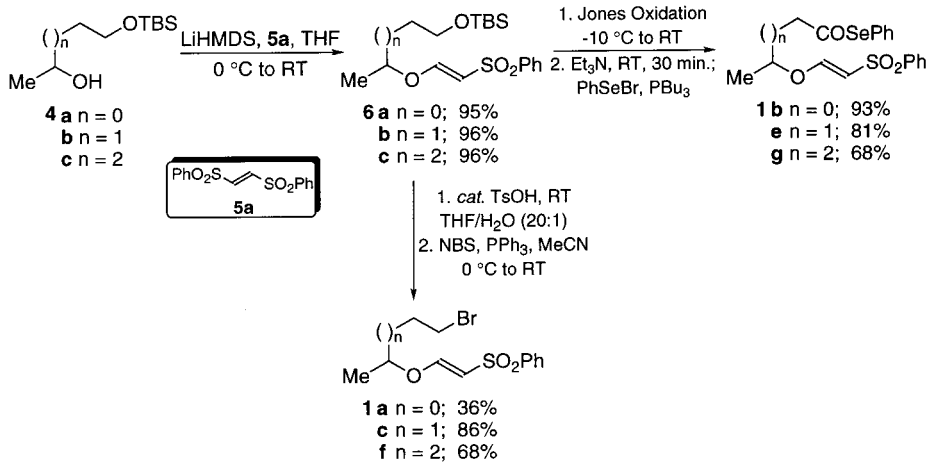
Additions and Corrections

Vol. 65, 2000

P. Andrew Evans* and Thara Manangan. Stereoselective Synthesis of Cyclic Ethers Using Vinylogous Sulfonates as Radical Acceptors: Effect of *E*/*Z* Geometry and Temperature on Diastereoselectivity.

Page 4524. The values for $(\ )_n$ in the original Scheme 1 are incorrect (for **6** and **1**). The corrected Scheme 1 is presented below.

Scheme 1



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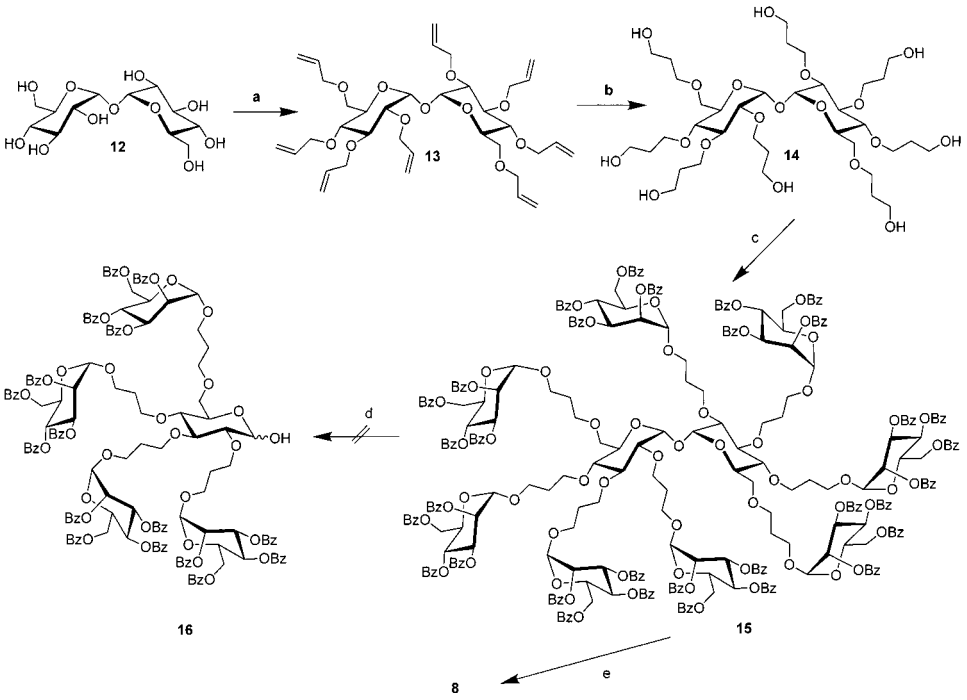
Vol. 65, 2000

Michael Dubber and Thisbe K. Lindhorst*. Synthesis of Carbohydrate-Centered Oligosaccharide Mimetics Equipped with a Functionalized Tether.

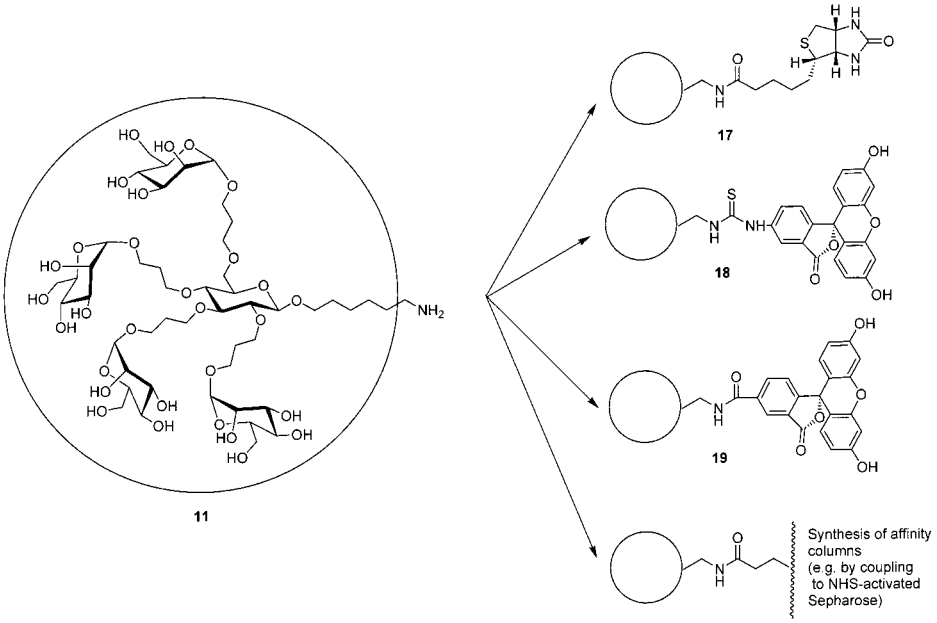
Page 5277. Corrected Schemes 2 and 3 are depicted below.

Scheme 2. Trehalose Pathway[a]



[a] Key: (a) allyl bromide, NaH, DMF; (b) 9-BBN-H, THF; (c) 7, TMS-OTf, acetonitrile; (d) aqueous TFA, THF, or acetonitrile; (e) 6-bromohexanol, $BF_3{\cdot}Et_2O$, CH_2Cl_2.

Scheme 3. Applications of 11



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