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COMMUNICATION

Conjugate hydrotrifluoromethylation of α,β-unsaturated acyl-oxazolidinones: synthesis of chiral fluorinated amino acids†

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A novel conjugate hydrofluoroalkylation of α,β-unsaturated acyl-oxazolidinones is described. Using this method, enantiomerically pure β-trifluoromethylated amino acids were prepared. Trifluorovaline and trifluoroisoleucine were incorporated into peptides and found to show extremely low α-helix propensities.

The chemistry of fluorine-containing organic compounds has seen a dramatic development in recent years due to the importance of these substances in both pharmaceutical applications and materials science.[1] The replacement of hydrogen by fluorine significantly alters the physical, chemical, and metabolic properties of such molecules. For example, peptides, containing non-natural fluorinated amino acids, exhibit interesting properties with respect to folding behaviour and biological activity.[2,3]

In contrast to the fluoroalkylation of aromatic substrates,[4] protocols for stereoselective trifluoromethylations forming a C_{sp_3}–CF_3-bond are more limited in number and mostly focus on nucleophilic attack on carbonyl groups[5] or electrophilic addition to electron-rich or unactivated alkenes.[6] Only a few methods have been reported for the conjugate perfluoroalkylation of α,β-unsaturated carboxylic acid derivatives and related substrates, thereby mostly focusing on iodoperfluoroalkylations of terminal C=C bonds.[7] However, reactions of R_fI with internal electron-deficient olefins are known to be difficult, due to oligomer formation, respectively.[7b,l] In 2007, Yajima and Nagano obtained optically active fluorinated α-amino acids by iodoperfluoroalkylation of acryl camphor sultams, but no example was reported in which a new stereocenter in the β-position was formed.[7e,j] We envisioned that the development of a reductive trifluoromethylation protocol of internal electron-deficient alkenes would allow for new access to optically active β-trifluoromethylated carboxylic acids and amino acids. Herein, we report the hydrofluoroalkylation of α,β-unsaturated acyl-oxazolidinones, a short synthesis of enantiomerically pure fluorinated amino acids and their incorporation into peptides.

For the stereoselective conjugate trifluoromethylation we employed the well-established chiral Evans-oxazolidinones.[8] We examined *N*-(*trans*-crotonyl)-oxazolidinone **1** as a substrate for the trifluoromethylation employing CF_3I under radical conditions. We considered Et_3B and oxygen to be added as radical initiators at low temperatures and the putatively formed enoyl radical to be quenched by Bu_3SnH.[9] The results of these optimization studies are summarized in Table 1. When CH_2Cl_2 was used as the sole solvent in the presence of $Mg(ClO_4)_2$ product **2** was formed in 33% yield but also 10% of product **3** was formed (entry 2). This became even more pronounced at elevated temperature (−40 °C, entry 3).[9c] This by-product formation could be suppressed by using a mixture of CH_2Cl_2 and THF together with ytterbium triflate hydrate. Notably, all reactions occurred with complete β-regioselectivity. Full conversion of **1** was achieved by addition of the reagents in batches (up to 3 times). It is important to note that the addition of Bu_3SnH is not necessary to obtain the desired hydrotrifluoromethylated product. In fact, comparable yields of **2** were isolated and no formation of either the α-iodo-,[7e] the α-hydroxy-,[7d,k] or the α-peroxy-substituted derivatives[7d,k] was observed (entry 7). This modified procedure generates no tin waste and greatly facilitates product purification. The reaction proceeded without diastereoselectivity but the diastereomers could be separated easily in most cases by column chromatography.[10]

Using the optimized conditions different substrates were transformed into the β-substituted carboxylic acid derivatives. Alkyl-substituted derivatives were obtained in 22–70% yield (Table 2, entries 1–7). The isolated yields largely reflect the degree of steric hindrance at the β-position. In contrast, substrates with aromatic substituents (entry 8) were unreactive. The method was further extended to the conjugate addition of other perfluoroalkyl groups. While the addition to crotonyl-oxazolidinones was slow, the corresponding acryl-oxazolidinones could be transformed in moderate yields presumably due to competing oligomerization (entries 9–12).

Although the exact mechanism for product formation is not clear at the present stage we assume that the first step is the generation of CF_3-radicals by Et_3B/O_2.[11] Following conjugate attack of the Michael system the putatively formed enoyl radical may react with free Et_3B to form the transient diethylboron

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†Electronic supplementary information (ESI) available: Syntheses, X-ray crystallographic details for **2a**, **25a**, **26a**, and additional data. CCDC 887849–887851. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26810h

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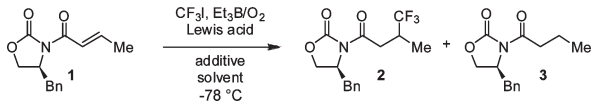
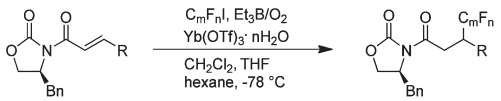
Table 1 Optimization reactions for the conjugate trifluoromethylation

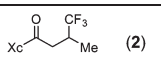
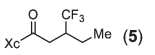
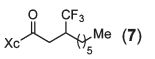
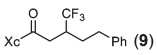
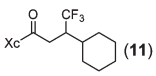
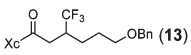
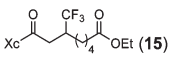
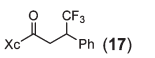
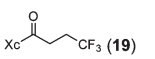
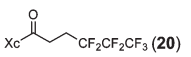
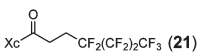
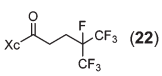


Entry	Solvent	Lewis acid	Additive	Yield **2**/%	dr	Rec. **1**/%	Yield **3**/%
1	CH_2Cl_2	—	Bu_3SnH	25	1 : 1	43	—
2	CH_2Cl_2	$Mg(ClO_4)_2$	Bu_3SnH	33	1 : 1	16	10
3[a]	CH_2Cl_2	$Mg(ClO_4)_2$	Bu_3SnH	13	1 : 1	—	57
4	CH_2Cl_2–THF 4 : 1	$Mg(ClO_4)_2$	Bu_3SnH	40	1 : 1	7	6
5	CH_2Cl_2–THF 4 : 1	$Yb(OTf)_3{\cdot}nH_2O$	Bu_3SnH	46	1 : 1	26	—
6[b]	CH_2Cl_2–THF 1 : 1	$Yb(OTf)_3{\cdot}nH_2O$	Bu_3SnH	60	1 : 1	4	—
7[b]	CH_2Cl_2–THF 1 : 1	$Yb(OTf)_3{\cdot}nH_2O$	—	70	1 : 1	—	—

[a] The reaction was performed at −40 °C. [b] The reagents were added three times.

Table 2 Radical conjugate trifluoromethylation of acyl-oxazolidinones[a]



Entry	R	C_mF_nI	Product[b]	Yield/%	dr
1	Me (**1**)	CF_3I	 (**2**)	70	1 : 1
2	Et (**4**)	CF_3I	 (**5**)	51	1 : 1
3	*n*-Hexyl (**6**)	CF_3I	 (**7**)	56	1 : 1
4	CH_2CH_2Ph (**8**)	CF_3I	 (**9**)	40	1 : 1
5	*cyclo*-Hexyl (**10**)	CF_3I	 (**11**)	22	1 : 1
6	$–(CH_2)_3OBn$ (**12**)	CF_3I	 (**13**)	38	1 : 1
7	$–(CH_2)_4COOEt$ (**14**)	CF_3I	 (**15**)	42	1 : 1
8	Ph (**16**)	CF_3I	 (**17**)	0	—
9	H (**18**)	CF_3I	 (**19**)	34	—
10	H (**18**)	$CF_3CF_2CF_2I$	 (**20**)	33	—
11	H (**18**)	$CF_3(CF_2)_3I$	 (**21**)	27	—
12	H (**18**)	CF_3CFICF_3	 (**22**)	17	—

[a] Conditions: −78 °C in THF–CH_2Cl_2 1 : 1, $Yb(OTf)_3{\cdot}nH_2O$ (2 equiv.), C_mF_nI (3 times 9 equiv.), Et_3B in hexane (3 times 5 equiv.); entries 9–12, reagents were added only once. [b] Xc = (*S*)-*N*-benzyl-oxazolidinonyl.

enolate.[11b–d] The presence of water in the reaction mixture results in rapid *in situ* hydrolysis of the intermediate enol borinate liberating the corresponding product. Hydrotrifluoromethylation in the presence of $Yb(OTf)_3$ under anhydrous conditions resulted in the incorporation of deuterium in the α-position upon workup with D_2O, whereas the use of deuterium-labeled solvents did not.

The β-trifluoromethylated carboxylic acid derivatives are very useful synthetic building blocks. This is exemplified in the synthesis of fluorinated α-amino acids *via* diastereoselective

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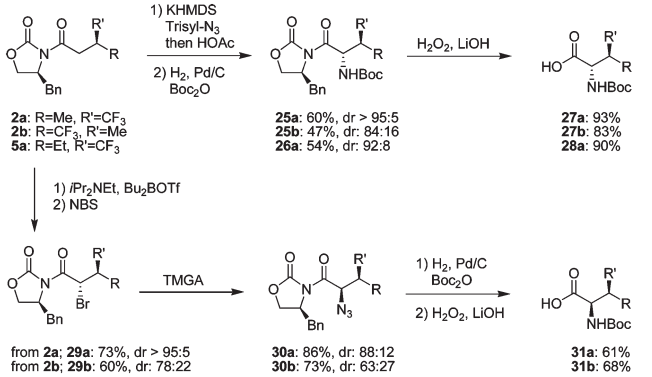

Scheme 1 Synthesis of enantiomerically pure, fluorinated amino acids.[13]

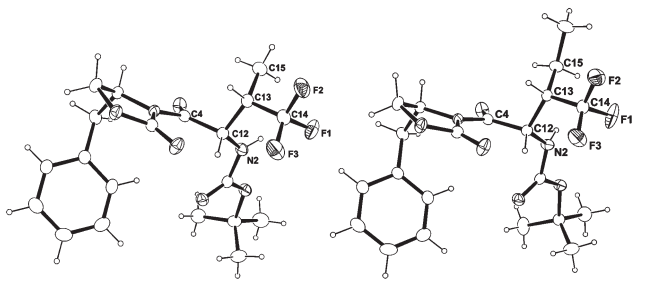

Fig. 1 Molecular structures (ORTEP[14]) of protected trifluorovaline **25a** (left) and trifluoroisoleucine **26a** (right).

amination (Scheme 1). All four diastereomers of *N*-Boc-protected trifluorovaline (TfV, 4^3F_3Val) and trifluoroisoleucine (TfI, $4'^3$-F_3Ile) were prepared in enantiomerically pure form *via* the corresponding α-azides.[8b,12] This methodology complements the fast access to β-trifluoromethylated amino acids by rhodium-catalyzed asymmetric reduction of dehydroamino acids.[12c] The absolute configuration of the amino acids was confirmed by crystal structure determination of intermediate **2a**, **25a**, and **26a** based on the known auxiliary configuration (Fig. 1).

The peptide sequence Ac-YGGKAAAAKA**X**AAKAAAAK-NH_2 (K**X**) has previously been designed as a monomeric α-helix to enable helix propensity determination of the amino acid in the guest position **X**.[15a,d] Cheng *et al.* investigated fluorinated amino acids using this model and concluded that they exhibit reduced helix propensity compared to their hydrocarbon analogues.[15a,b] TfV has mostly been incorporated as diastereomeric mixtures into peptides.[16a,b] Here, we have determined the helix propensities of each diastereomer separately. The amino acids (3*S*)-4^3-F_3Val, (3*R*)-4^3-F_3Val, and (3*S*)-$4'^3$-F_3Ile were introduced into the guest position of the model peptide and their helix propensities [*w*] were determined and compared to the values of their respective non-fluorinated analogues valine (Val) and isoleucine (Ile). The Boc-protected amino acids were converted into the Fmoc analogues by standard procedures (see ESI†). The peptides were synthesized following standard protocols for solid-phase peptide synthesis (SPPS).[17] The identity of the peptides was confirmed by high resolution mass spectroscopy (HR-ESI-ToF MS).

The CD-spectra of the referenced peptides KVal and KIle indicate helical structures as evidenced by the minima at 208 and

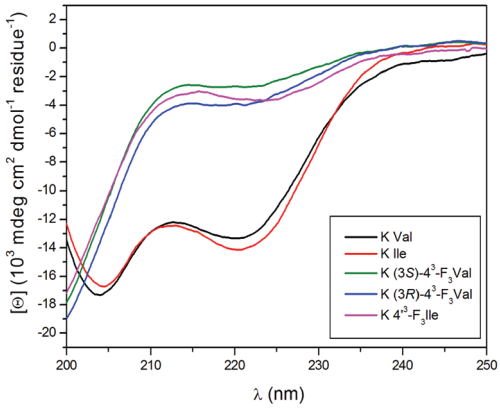

Fig. 2 Circular dichroism spectra of the peptides KVal, KIle, K(3*S*)-4^3-F_3Val, K(3*R*)-4^3-F_3Val, and K$4'^3$-F_3Ile at pH 7 (273 K) in 1 mM phosphate, borate, and citrate with 1 M NaCl.

Table 3 Ellipticity [Θ] at 222 nm was taken from normalized CD data. Fraction helix [f_{helix}] and helix propensities [*w*] were calculated from [Θ] by using modified Lifson–Roig theory

Peptide	[$\Theta_{222\ nm}$]	f_{helix}	*w*
KVal	−13 054 ± 452	0.38 ± 0.01	0.41 ± 0.04
KIle	−13 876 ± 186	0.40 ± 0.01	0.53 ± 0.05
K[(3*S*)-4^3-F_3Val]	−2685 ± 526	0.08 ± 0.02	0
K[(3*R*)-4^3-F_3Val]	−3887 ± 547	0.11 ± 0.02	0
K[(3*S*)-$4'^3$-F_3Ile]	−3602 ± 130	0.10 ± 0.01	0

222 nm, whereas the peptides containing the fluorinated analogues do not form helical structures (Fig. 2). The α-helix propensity [*w*] was calculated from CD data by using modified Lifson–Roig theory (Table 3).[15d–f] The helix propensities of Val and Ile are comparable to previously published values,[15f] but for (3*S*)-4^3-F_3Val, (3*R*)-4^3-F_3Val, and (3*S*)-$4'^3$-F_3Ile we obtained slightly negative values, which are therefore interpreted as zero.

Val and Ile are known to be better accommodated within β-sheet structures,[15c,16b,c] which is also reflected by their relatively low *w*-value. Ile with the more flexible ethyl group on the β-carbon shows a slightly higher helix propensity compared to Val. Due to its branching on the β-carbon atom the rigid side chain atoms come in close proximity to the peptide backbone,[18] thereby destabilizing α-helical structures. This effect is amplified for the two diastereomers of TfV ((3*S*)-4^3-F_3Val, (3*R*)-4^3-F_3Val) which have the larger CF_3 group on the β-carbon atom. The close proximity of this sterically demanding group to the peptide backbone strongly impedes the formation of α-helical structures. As a result these amino acids show a helix propensity of zero.

In summary, we have developed a new method for the conjugate trifluoromethylation of α,β-unsaturated acyl-oxazolidinones. The addition of iodoperfluoroalkanes utilizing triethylborane, which presumably serves as an initiator and radical terminator, occurs in a reductive fashion. All four diastereomers of trifluorovaline and L-trifluoroisoleucine were readily prepared from the corresponding products in an enantiomerically pure form. It was found that both diastereomers of L-trifluorovaline and L-trifluoroisoleucine show extremely low α-helix propensities. These findings reinforce earlier conclusions made by Cheng *et al.* that

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fluorinated amino acids should be better accommodated by β-sheet structures such as β-hairpins and amyloid-like fibrils.[15a] Since such structures bear considerable potential regarding applications as biomaterials it is conceivable that side-chain fluorination may prove to be a useful tool to modulate the properties of these structures.

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Notes and references

1 (*a*) *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, P. Kirsch (Ed.) Wiley-VCH, Weinheim, 2004; (*b*) *Fluorine in Medicinal Chemistry and Chemical Biology*, I. Ojima (Ed.), Wiley-Blackwell, Chichester, 2009; (*c*) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214; M. Shimizu and T. Hiyama, *Angew. Chem.*, 2005, **117**, 218; (*d*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.

2 (*a*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*b*) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496; (*c*) M. Salwiczek, E. K. Nyakatura, U. I. M. Gerling, S. Ye and B. Koksch, *Chem. Soc. Rev.*, 2012, **41**, 2135.

3 For recent reviews on the synthesis of fluorinated amino acids, see: (*a*) C. Czekelius and C. C. Tzschucke, *Synthesis*, 2010, 543; (*b*) X.-L. Qiu and F.-L. Qing, *Eur. J. Org. Chem.*, 2011, 3261; (*c*) K. Mikami, S. Fustero, M. Sánchez-Roselló, J. L. Aceña, V. Soloshonok and A. Sorochinsky, *Synthesis*, 2011, 3045; (*d*) R. Smits, C. D. Cadicamo, K. Burger and B. Koksch, *Chem. Soc. Rev.*, 2008, **37**, 1727.

4 For general reviews on trifluoromethylation, see: (*a*) T. Umemoto, *Chem. Rev.*, 1996, **96**, 1757; (*b*) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (*c*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*d*) K. Sato, A. Tarui, M. Omote, A. Ando and I. Kumadaki, *Synthesis*, 2010, 1865; (*e*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*f*) K. Mikami, Y. Itoh and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1; (*g*) A. Struder, *Angew. Chem., Int. Ed.*, 2012, **124**, 9082.

5 (*a*) Y. Kawano, N. Kaneko and T. Mukaiyama, *Chem. Lett.*, 2006, **35**, 304; (*b*) S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura and T. Toru, *Org. Lett.*, 2007, **9**, 3707.

6 (*a*) K. Iseki, T. Nagai and Y. Kobayashi, *Tetrahedron: Asymmetry*, 1994, **5**, 961; (*b*) Y. Itoh and K. Mikami, *Org. Lett.*, 2005, **7**, 649; (*c*) P. Eisenberger, S. Gischig and A. Togni, *Chem.–Eur. J.*, 2006, **12**, 2579; (*d*) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986; (*e*) V. Matošek, A. Togni, V. Bizet and D. Cahard, *Org. Lett.*, 2011, **13**, 5762; (*f*) A. T. Parsons and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9120; A. T. Parsons and S. L. Buchwald, *Angew. Chem.*, 2011, **123**, 9286; (*g*) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15300; (*h*) R. Shimizu, H. Egami, Y. Hamashima and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 4577; R. Shimizu, H. Egami, Y. Hamashima and M. Sodeoka, *Angew. Chem.*, 2012, **124**, 4655; (*i*) K. Mikami, Y. Tomita and Y. Itoh, *Angew. Chem., Int. Ed.*, 2010, **49**, 3819; K. Mikami, Y. Tomita and Y. Itoh, *Angew. Chem.*, 2010, **122**, 3907.

7 (*a*) C.-M. Hu and Y.-L. Qiu, *J. Org. Chem.*, 1992, **57**, 3339; (*b*) Z.-M. Qiu and D. J. Burton, *J. Org. Chem.*, 1995, **60**, 3465; (*c*) X.-T. Huang and Q.-Y. Chen, *J. Org. Chem.*, 2001, **66**, 4651; (*d*) T. Yajima, H. Nagano and C. Saito, *Tetrahedron Lett.*, 2003, **44**, 7027; (*e*) T. Yajima and H. Nagano, *Org. Lett.*, 2007, **9**, 2513; (*f*) S. Mao, X. Fang, L. Ba and F. Wu, *J. Fluorine Chem.*, 2007, **128**, 5; (*g*) S. Barata-Vallejo and A. Postigo, *Eur. J. Org. Chem.*, 2012, 1889; (*h*) X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo and G. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878; (*i*) T. Yajima, T. Tonoi, H. Nagano, Y. Tomita and K. Mikami, *Eur. J. Org. Chem.*, 2010, 2461; (*j*) T. Tonoi, A. Nishikawa, T. Yajima, H. Nagano and K. Mikami, *Eur. J. Org. Chem.*, 2008, 1331; (*k*) T. Yajima, C. Saito and H. Nagano, *Tetrahedron*, 2005, **61**, 10203; (*l*) E. Yoshioka, Kentefu, X. Wang, S. Kohtani and H. Miyabe, *Synlett*, 2011, 2085.

8 (*a*) D. A. Evans, J. V. Nelson and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1; (*b*) D. A. Evans, T. C. Britton, J. A. Ellman and R. L. Dorow, *J. Am. Chem. Soc.*, 1990, **112**, 4011.

9 (*a*) M. P. Sibi, J. Ji, J. B. Sausker and C. P. Jasperse, *J. Am. Chem. Soc.*, 1999, **121**, 7517; (*b*) T. Yajima, M. Hamano and H. Nagano, *Tetrahedron Lett.*, 2009, **50**, 1301; (*c*) S. Hirasawa, Y. Tajima, Y. Kameda and H. Nagano, *Tetrahedron*, 2007, **63**, 10930.

10 Studies varying the auxiliary structure led to a maximal dr of 1.5 : 1, but in this case the isomers were difficult to separate.

11 (*a*) C. Ollivier and P. Renaud, *Chem. Rev.*, 2001, **101**, 3415; (*b*) H. C. Brown and M. M. Midland, *Angew. Chem., Int. Ed.*, 1972, **11**, 692; H. C. Brown and M. M. Midland, *Angew. Chem.*, 1972, **84**, 702; (*c*) A. Suzuki, S. Nozawa, M. Itoh, H. C. Brown, G. W. Kabalka and G. W. Holland, *J. Am. Chem. Soc.*, 1970, **92**, 3503; (*d*) V. Beraud, Y. Gnanou, J. C. Walton and B. Maillard, *Tetrahedron Lett.*, 2000, **41**, 1195.

12 (*a*) Q. Chen, X.-L. Qiu and F.-L. Qing, *J. Org. Chem.*, 2006, **71**, 3762; (*b*) J. A. Pigza, T. Quach and T. F. Molinski, *J. Org. Chem.*, 2009, **74**, 5510; (*c*) C. Benhaim, L. Bouchard, G. Pelletier, J. Sellstedt, L. Kristofova and S. Daigneault, *Org. Lett.*, 2010, **12**, 2008.

13 (*a*) TMGA = 1,1,3,3-tetramethylguanidinium azide; trisyl-N_3 = 2,4,6-triisopropylbenzene-sulfonyl azide; (*b*) During auxiliary removal minor epimerization at C_α was observed (1–8%, see ESI†).

14 ORTEP3 for Windows – L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.

15 (*a*) H.-P. Chiu, Y. Suzuki, D. Gullickson, R. Ahmad, B. Kokona, R. Fairman and R. P. Cheng, *J. Am. Chem. Soc.*, 2006, **128**, 15556; (*b*) H.-P. Chiu and R. P. Cheng, *Org. Lett.*, 2007, **9**, 5517; (*c*) P. Y. Chou and G. D. Fasman, *Biochemistry*, 1974, **13**, 211; (*d*) A. Chakrabartty, T. Kortemme and R. L. Baldwin, *Protein Sci.*, 1994, **3**, 843; (*e*) A. J. Doig, A. Chakrabartty, T. M. Klingler and R. L. Baldwin, *Biochemistry*, 1994, **33**, 3396; (*f*) N. H. Andersen and H. Tong, *Protein Sci.*, 1997, **6**, 1920.

16 (*a*) B. Bilgiçer, A. Fichera and K. Kumar, *J. Am. Chem. Soc.*, 2001, **123**, 4393; (*b*) J.-C. Horng and D. P. Raleigh, *J. Am. Chem. Soc.*, 2003, **125**, 9286; (*c*) H.-P. Chiu, B. Kokona, R. Fairman and R. P. Cheng, *J. Am. Chem. Soc.*, 2009, **131**, 13192.

17 G. B. Fields and R. L. Noble, *Int. J. Pept. Protein Res.*, 1990, **35**, 161.

18 D. L. Minor and P. S. Kim, *Nature*, 1994, **367**, 660.

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