Two free radical routes for the preparation of novel difluoromethylene-linked serine-*O*-glycopeptide analogues

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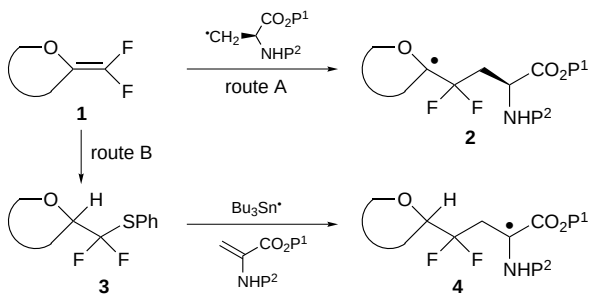
The first examples of *gem*-difluoromethylene-linked analogues of serine-derived glycopeptides have been prepared in a highly stereoselective manner using two complementary free radical chain reactions.

The importance of the carbohydrate moiety in molecular recognition processes involving glycoproteins[1,2] and the considerable potential of glycosylated peptide drugs[3] have stimulated intense current research interest in the synthesis of modified glycopeptides, where the customary *O*- or *N*-glycosidic bond linking the amino acid component to the sugar portion is replaced by a carbon-based unit of greater stability and resistance towards enzymatic deglycosylation. Thus, methods have been described, both for the synthesis of *C*-glycosyl amino acids in which the anomeric carbon is directly bound to the α-carbon of the amino acid[4–8] and for methylene-bridged glycopeptides[9–14] in which the additional methylene group can serve as a heteroatom mimic. Even the latter, however, lead to derivatives with a truncated chain when compared with the corresponding serine-*O*-glycopeptides.

Our objective in this area was to achieve site specific replacement of the exocyclic anomeric oxygen atom in a serine-derived glycopeptide fragment by a difluoromethylene group. This tetrahedral and electronegative unit has been shown to be of particular value as an oxygen atom replacement in several difluoromethylene phosphonate analogues of naturally occurring phosphates.[15]

As shown in Scheme 1, our intention was to capitalise on the chemical versatility of readily prepared carbohydrate *gem*-difluoro enol ethers[16] **1**, either as radicophiles[17] for the addition of an amino acid-derived radical to give the anomeric radical **2** (route A), or *via* their thiophenol adducts **3**,[18] as apposite precursors for difluoroalkyl radical trapping by a dehydroalanine derivative to give the carbon centred radical **4** around the amino acid unit (route B).

Thus, in a preliminary study, slow addition of tributylstannane and AIBN as initiator to a refluxing benzene solution of carbohydrate **5** and the iodoalanine reagent[19,20] **6** developed by Baldwin[21,22] afforded out first example of a difluoromethylene-linked serine analogue **7**, albeit in a disappointing 14% yield (Scheme 2). Efforts to optimise this reaction or to extend it to other *gem*-difluoro enol ether substrates were unsuccessful.



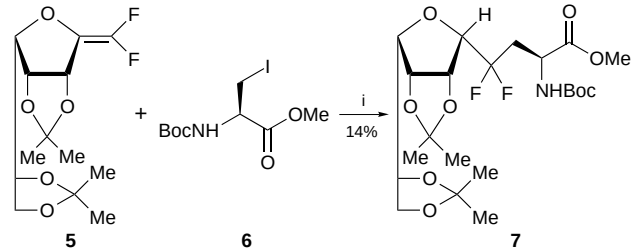
Scheme 1

We reasoned that a much more compact and conformationally restricted radical reagent was required, and elected to prepare the cyclic bis(trifluoromethyl)oxazolidinone derivative **10** which should find general use as a convenient bromoalanine reagent. Thus, as shown in Scheme 3, protection of aspartic acid **8** with gaseous hexafluoroacetone[23] was followed by conversion to the acid chloride[24] **9** which was transformed *via* the acylthiohydroxamate to the desired bromide **10** using the radical variant of the Hünsdieker reaction.[25]

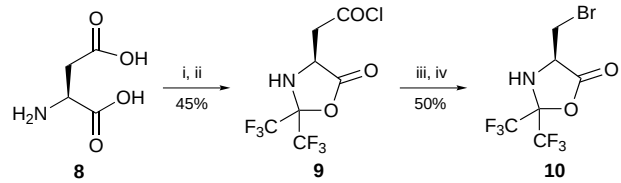
Addition of **10** to *gem*-difluoro enol ethers under tributylstannane-mediated conditions proceeded in acceptable yields with a range of substrates (Scheme 4), with abstraction of the hydrogen atom occurring exclusively from the less hindered convex face[14,26] in the case of the gulose **5** → **11** and erythrose **12** → **13** derivatives. Reaction of the ribose derivative **14** however produced an equimolar mixture of both anomers **15**, and on replacement of the methyl ether by the bulky *tert*-butyldimethylsilyl group, no addition products were observed.

The utility of the labile bis(trifluoromethyl)oxazolidinone protecting group was demonstrated by simple treatment of **11** with l-phenylalanine *tert*-butyl ester to afford the dipeptide **16** (Scheme 5).

Finally, we have also carried out a preliminary study of the alternative approach outlined in Scheme 1 route B, which effectively circumvents problems created by the steric bulk of the carbohydrate. The chiral dehydroalanine derivative (2*R*)-*N*-benzoyl-2-(*tert*-butyl)-4-methylidene-1,3-oxazolidin-5-one **17** prepared from (*S*)-alanine and used by Beckwith[13] as a radicophile, was accordingly selected to ensure diastereoselectivity at the α-carbon atom of the amino acid unit. In the final analysis, we also elected to use the phenylselanyl congeners of our previously described[18] thiophenol adducts in order to

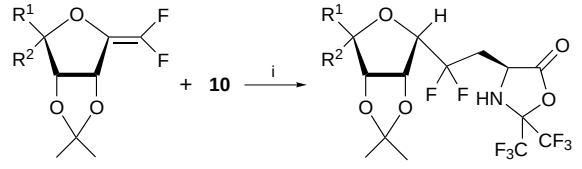


Scheme 2 *Reagents and conditions*: i, AIBN, Bu_3SnH (slow addition), benzene, reflux



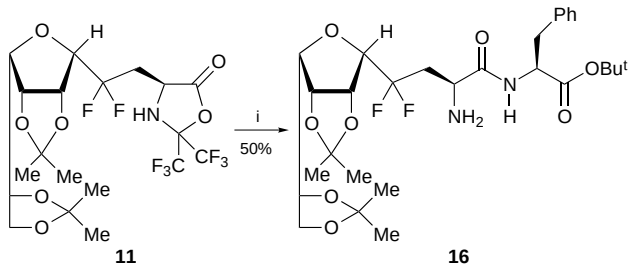
Scheme 3 *Reagents and conditions*: i, $(CF_3)_2CO$, DMSO, 50 °C; ii, $SOCl_2$, reflux; iii, 2-sulfanylpyridine 1-oxide sodium salt, THF, −15 °C; iv, $BrCCl_3$, *h*ν (tungsten)

facilitate generation of the required difluoroalkyl radicals. The results for the three carbohydrates **18**–**20** in Scheme 6 indicate that this tributylstannane-mediated coupling gives consistently higher yields than those obtained by the previous method. The successful coupling of the hindered ribose derivative **20** is particularly noteworthy since the alternative coupling strategy had been unsuccessful. From a stereochemical standpoint, the ratio of the two diastereoisomers produced in each reaction is consistent with the results obtained by Beckwith[13] with the same chiral auxiliary.



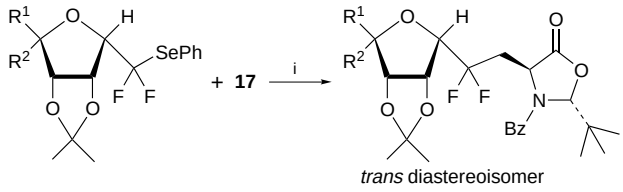
Compound	R^1	R^2	Product	Yield(%)
5	H		**11**	30
12	H	H	**13**	20
14	CH_2OMe	H	**15**	41[a]

Scheme 4 *Reagents and conditions*: i, AIBN, Bu_3SnH (slow addition), benzene, reflux. [a] Obtained as a 1 : 1 mixture of diastereoisomers at the anomeric centre.



11 **16**

Scheme 5 *Reagents and conditions*: i, l-phenylalanine *tert*-butyl ester, Et_2O, room temp., 24 h



Compound	R^1	R^2	Product	Ratio	Yield(%)
18	H		**21**	80 : 20	91
19	H	H	**22**	85 : 15	86
20	$CH_2OSiMe_2Bu^t$	H	**23**	86 : 14	71

Scheme 6 *Reagents and conditions*: i, AIBN, Bu_3SnH (slow addition), benzene, reflux

In summary, the two complementary free radical routes described herein provide a convenient approach for the synthesis of a wide range of *C*-glycosylated amino acid units in which the difluoromethylene group serves not only as a potential heteroatom mimic but also contributes to providing the correct number of atoms in the crucial linkage between the carbohydrate and amino acid components of the structures.

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