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The Overman rearrangement in carbohydrate chemistry: stereoselective synthesis of functionalized 3-amino-3,6-dihydro-2*H*-pyrans and incorporation in peptide derivatives☆

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Abstract—A stereocontrolled synthesis of an unsaturated sugar bearing two amino groups (one of them masked as an azide), using an Overman rearrangement as key step, is described. This scaffold is used to prepare two peptides having aromatic fragments, which have shown activity as calpain inhibitors.

1. Introduction

Although many peptides are biologically active, they frequently suffer from inadequate in vivo efficacy as a result of poor absorption, lack of transportation, rapid metabolic degradation, and inability to achieve the biologically active conformation. To overcome these inconveniences, many peptide analogues have been prepared.[1] An important step in the development of drug candidates is the use of molecular scaffolds that are designed to induce conformational restraints as well as to improve the pharmacological profile.[2,3] In connection with ongoing projects on the synthesis, structure, and biological activity of peptidic compounds,[4] we have been interested in the preparation of new peptide derivatives employing unsaturated carbohydrate as scaffolds (*peptide–carbohydrate hybrids*). The generic target compound **A** (Fig. 1) has peptide or amino acid residues tethered to the positions 3 and 6 of an unsaturated pyranose. Since the relative stereochemistry and the distance (by changes in the nature of the groups X and Y) of the two peptide chains can be readily controlled, the potential structural variety of compounds of type **A** is high. Additionally, the substituent on the anomeric position offers a site for further molecular diversity and the endocyclic olefinic bond provides a conformational bias to the molecule. The target molecule **A** can be synthesized from hexenopyranosides of type **B**, which in turn can be prepared from readily available glycals using standard transformations in carbohydrate chemistry. Recently, we have reported the synthesis of compounds of type **C**, using a Claisen rearrangement as key step, where the two peptide chains have the same orientation.[5] The synthetic utility of the scaffold **B** may be expanded by reversing the sense of the peptide chains (*retro-peptides*),[6] provided that a 3,6-diamino-substituted-3,6-dihydro-2*H*-pyran (**D**) is available. In this letter, we report the synthesis of the 3,6-dihydro-*2H*-pyran **1** as well as its application to peptide derivatives of type **E** as well as their activity as inhibitor of the protease calpain.

2. Results and discussion

The synthesis of the target amine **1** is indicated in Scheme 1. The allylic alcohol **3** was prepared in five steps (66% overall yield) from commercial available 3,4,6-tri-*O*-triacetyl-D-glucal (**2**) as previously reported.[5] Treatment of **3** with trichloroacetonitrile in presence of DBU furnished the trichloroacetimidate **4** (95% yield),[7] which, after purification, was submitted to the Overman rearrangement[8] by refluxing in xylene in the presence of potassium carbonate,[9,10] giving the corresponding

Keywords: Amino sugar; Calpain inhibitor; Enkephalin; Overman rearrangement; Peptidomimetic.

☆ Taken in part from the Ph.D. thesis of AM.

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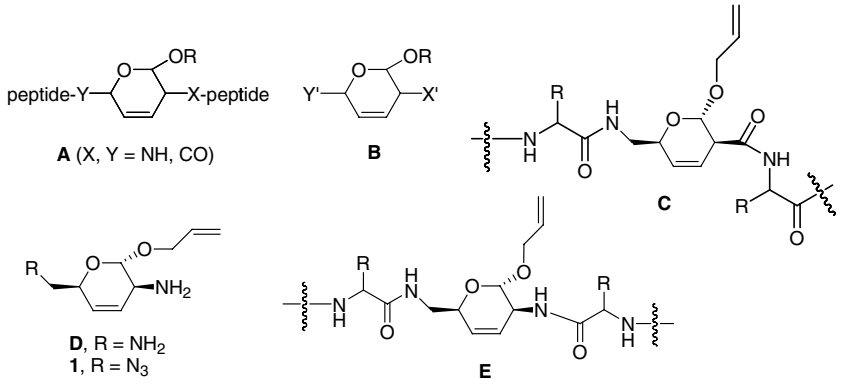
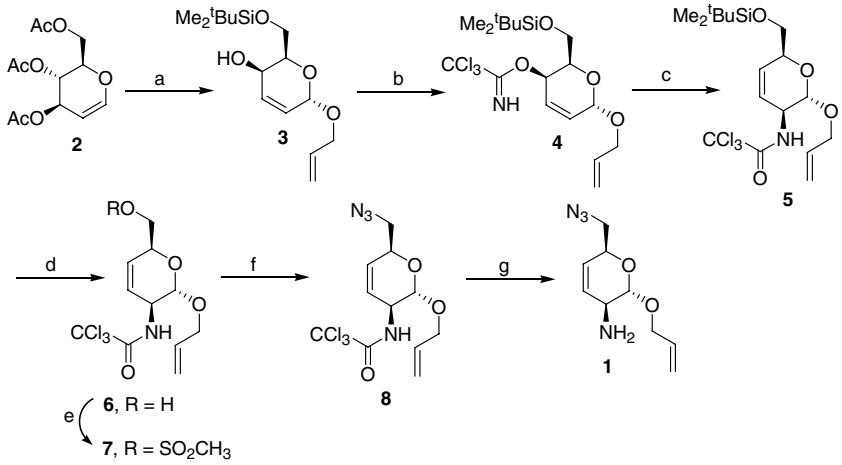


Figure 1. Structures of peptide–carbohydrate hybrids (**A**, **C**, **E**) and 3,6-dihydro-2*H*-pyran derivatives (**B**, **D**, **1**).



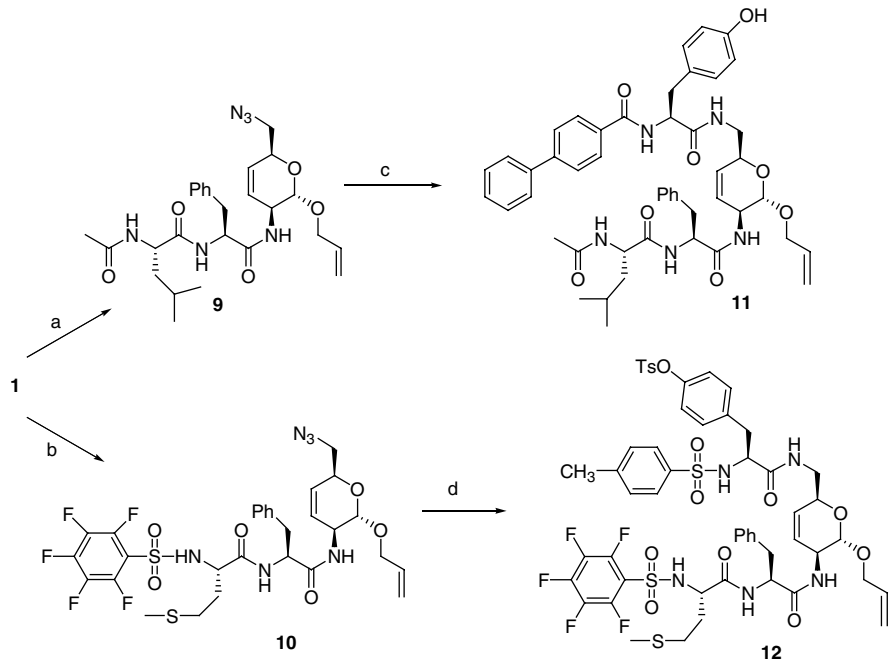
Scheme 1. Reagents and conditions: (a) five steps (66% yield), Ref. 5; (b) Cl_3CCN, DBU, CH_2Cl_2, 0 °C to rt, 95%; (c) K_2CO_3, xylene, reflux, 77%, (d) TBAF·$3H_2O$, THF, 80%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C; (f) NaN_3, Et_3N, DMF, 60 °C, 56% (two steps); (g) NaOH, EtOH, H_2O, reflux, 64%.

trichloroacetamide **5** in good yield (77%) and with total stereoselectivity.[11] Compound **5** was desylilated (TBAF, 80% yield) to the alcohol **6**, which, in turn, was sequentially transformed to the sulfonate **7** and the azide **8** (56% yield for the combined two steps). Finally, hydrolysis of the trichloroacetamide **8** under basic conditions afforded the unsaturated amino azide **1** (64% yield), that has been used for the synthesis of peptide–carbohydrate hybrids.

Our recent research on calpain,[4a,12] a cysteine protease involved in a variety of degenerative diseases,[13] has shown that peptide derivatives having hydrophobic and aromatic amino acids are inhibitors of this enzyme. Therefore, we chose as target the peptides **11** and **12**, which, in turn, can be considered as analogues of the natural penta-peptides Leu-enkephalin (Leu-Phe-Gly-Gly-Tyr) and Met-enkephalin (Leu-Phe-Gly-Gly-Tyr), respectively, where the dihydro-2*H*-pyran scaffold replaces the Gly-Gly fragment of the natural peptides.[14] Although the enkephalins are potent analgesic natural peptides acting on the opioid receptor, their pharmacological utility is limited, what makes the search for enkephalin analogues an active research field.[15]

The synthesis of **11** and **12** is indicated in Scheme 2. All the peptide bonds were formed by standard solution methods using 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents, triethyl amine as base, 4-(dimethylamino)pyridine (DMAP) as catalysts, and dimethylformamide as solvent.[16] Reaction of amino azide **1** with dipeptides Ac-Leu-Phe-OH and $C_6F_5SO_2$-Met-Phe-OH gave intermediates **9** (50%) and **10** (52%), respectively. Reduction of the azido group was achieved by reaction with triphenylphosphine and water in refluxing benzene. The resulting amines, which were used without any purification, were coupled to 4-Biph-Tyr-OH and Ts-Tyr(Ts)-OH employing the peptide coupling procedure described above to furnish compounds **11** (74%) and **12** (76%), respectively.[17]

Although a detailed conformational analysis on peptides **11**, **12**, and related compounds is underway, we have observed concentration-independent strong ν (N–H) bands at 3287 cm^{-1} in the IR spectra (CH_2Cl_2) of **11** and **12**, which are indicative of the presence of intramolecular H-bond. On the other hand, although the biological activity of **11** and **12** as enkephalin analogues has not



Scheme 2. Reagents and conditions: (a) Ac-L-Leu-L-Phe-OH, EDC, HOBt, Et_3N, DMAP, DMF, rt, 50%; (b) $C_6F_5SO_2$-Met-Phe-OH, EDC, HOBt, Et_3N, DMAP, DMF, rt, 55%, (c) (i) Ph_3P, H_2O, benzene, reflux, (ii) 4-Biph-Tyr-OH, EDC, HOBt, Et_3N, DMAP, DMF, 74% (two steps); (d) Ts-Tyr(Ts)-OH, EDC, HOBt, Et_3N, DMAP, DMF, 76% (two steps).

been determined yet, we have determined their activities as calpain inhibitors, finding that compounds **11** and **12** are moderate calpain inhibitors, with IC_{50} values of 17 and 78 μM, respectively.[18]

3. Conclusion

We have developed a totally stereoselective route for the synthesis of the densely functionalized 3,6-dihydro-2*H*-pyran **1**, which presents a *cis* stereochemistry between the side chains containing the nitrogenated functionalities. This scaffold was incorporated in peptidomimetics that can be considered modified retro-analogues of enkephalins, and that have shown activity as calpain inhibitors. Work is in progress in order to determine, by solution and computational techniques, the conformational preferences induced by template **1** when introduced into a peptidic chain as well as the biological activity of the resulting enkephalin analogues.

Acknowledgements

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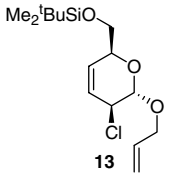
10. Interestingly, when trichloroacetimidate **4** was subjected *without any purification* to the Overman rearrangement conditions, the allylic chloride **13** was isolated as sole product in 50% yield instead of the expected trichloroacetamide **4**. Remarkably, the reaction took place in a total stereoselective way, affording exclusively the 3β-chloro diastereoisomer; its configuration was firmly established on the basis of NOESY experiments and the X-ray crystal structure of a *p*-nitrobenzoyl derivative. As other allylic chlorides [Jeganmohan, M.; Shanmugasundaram, M.; Cheng, C. *Org. Lett.* **2003**, *5*, 881–884], compound **13** can be a valuable synthetic intermediate. In addition, this compound has proved useful for the synthesis of halogenated sugars and peptide–carbohydrate hybrids, [Montero, A.; Benito, E.; Herradón, B., in preparation].



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17. The analytical and spectroscopic data for **11** and **12** are indicated below. To identify the signal assignations (that have been done by a combination of mono- and bi-dimensional NMR experiments), we have numbered the atoms in the following manner: unprimed number refer to the pyrane ring and the dipeptide fragment (including the side chains of the amino acids), starting from the pyranosidic oxygen; the primed number (′) indicate the carbon and hydrogen atoms in the allyloxy fragment; and the double-primed (″) numbers denote atoms in the tyrosine derivative fragment (including the side chain). Peptide **11**: Mp: 128–130 °C; $[\alpha]_D$ +7 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, 40 °C, DMSO-d_6) δ 9.06 (s, 1H, OH), 8.51 (d, 1H, $J_{11,9}$ = 8.5, NH-11), 8.12 (t, 1H, $J_{1'',7}$ = 5.6, NH-1″), 7.91 (m, 2H, H$_{arom}$; 1H, NH-8; 1H, NH-16), 7.80 (d, 1H, $J_{4'',2''}$ = 8.0, NH-4″), 7.72 (m, 4H, H$_{arom}$), 7.46 (m, 3H, H$_{arom}$), 7.20 (m, 5H, H$_{arom}$), 7.12 (d, 2H, J_{ortho} = 8.3, H$_{arom}$-Tyr), 6.62 (d, 2H, J_{ortho} = 8.5, H$_{arom}$-Tyr), 5.91 (d, 1H, $J_{5,4}$ = 10.5, H-5), 5.85 (C of ABCXY, 1H, H-2′), 5.66 (dd, 1H, $J_{4,5}$ = 10.5, $J_{4,3}$ = 3.9, H-4), 5.24 (A of ABCXY, 1H, $J_{4',2'}$ = 17.1, H-4′), 5.12 (B of ABCXY, 1H, $J_{3',2'}$ = 10.5, H-3′), 4.66 (m, 1H, H-9), 4.54 (m, 1H, H-2″), 4.53 (s, 1H, H-2), 4.19 (m, 1H, H-12), 4.07 (X de ABCXY, 1H, $J_{1'\alpha,1'\beta}$ = 13.2, $J_{1'\alpha,2'}$ = 6.0, H-1′α), 4.11 (X′ of A′B′X′, 1H, H-6), 4.00 (m, 1H, H-3), 3.97 (Y of ABCXY, 1H, $J_{1'\beta,1'\alpha}$ = 13.2, $J_{1'\alpha,2'}$ = 5.6, H-1′β), 3.39 (A′ of A′B′X′, 1H, $J_{7\alpha,7\beta}$ = 12.9, $J_{7\alpha,6}$ = 6.1, H-7α), 3.20 (B′ of A′B′X′, 1H, $J_{7\beta,7\alpha}$ = 12.9, $J_{7\beta,6}$ = 3.7, H-7β), 2.89 (m, 4H, H-10, H-3″), 1.82 (s, 3H, COCH$_3$), 1.48 (m, 1H, H-14), 1.31 (m, 2H, H-13), 0.83 (d, 3H, *J* = 6.6, H-15), 0.78 (d, *J* = 6.6, H-15); ^{13}C NMR (75 MHz, 40 °C, DMSO-d_6) δ 171.9 (s, CO), 171.8 (CO), 170.5 (s, CO), 169.3 (s, CO), 165.8 (s, CO), 155.7 (s, C$_{arom}$), 142.8 (s, C$_{arom}$), 139.1 (s, C$_{arom}$), 137.5 (s, C$_{arom}$), 134.4 (d, C-2′), 132.8 (s, C$_{arom}$), 130.0(d, 2C, C$_{arom}$), 129.2 (d, 2C, C$_{arom}$), 129.0 (d, 2C, C$_{arom}$), 128.6 (d, C-5), 128.4 (d, C$_{arom}$), 128.1 (d, 2C, C$_{arom}$), 127.9 (d, 2C, C$_{arom}$), 126.8 (d, 2C, C$_{arom}$), 123.2 (d, 2C, C$_{arom}$), 122.6 (d, C$_{arom}$), 122.5 (d, C-4), 116.8 (t, CH=*C*H$_2$), 114.8 (d, 2C, C$_{arom}$), 97.5 (d, C-2), 67.5 (t, C-1′), 66.2 (d, C-6), 55.4 (d, C-9), 53.4 (d, C-2″), 51.1 (d, C-12), 45.1 (d, C-3), 42.1 (t, C-13), 37.5 (t, C-7), 36.5 (t, C-10 or C-3″), 36.4 (t, C-3″ or C-10), 24.1 (d, C-14), 22.8 (q, C-15), 23.4 (q, C-15), 21.6 (q, CO*C*H$_3$); IR (KBr) ν 3430, 3287, 3061, 2956, 2920, 2861, 1640, 1541, 1384, 1276, 1115, 700; MS (ES$^+$) *m*/*z* = 830 ([M−H]$^+$, 100%); Anal. Calcd for $C_{48}H_{55}N_8O_8$: C, 69.46; H, 6.68; N, 8.44. Found: C, 69.46; H, 6.58; N, 8.35. Peptide **12**: Mp: 150–152 °C; $[\alpha]_D$ +28 (*c* 0.25, MeOH); ^{1}H NMR (300 MHz, 40 °C, DMSO-d_6) δ 9.42 (d, 1H, $J_{15,12}$ = 7.7, NH-15), 8.14 (d, 1H, $J_{11,9}$ = 7.9, NH-11), 8.06 (d, 1H, $J_{8,3}$ = 8.2, NH-8), 8.01 (t, 1H, $J_{1'',7}$ = 5.5, NH-1″), 7.96 (d, 1H, $J_{4'',2''}$ = 9.1, NH-4″), 7.69 (d, 2H, J_{ortho} = 8.4, H$_{arom}$-tolyl), 7.63 (d, 2H, J_{ortho} = 8.6, H$_{arom}$-tolyl), 7.45 (d, 2H, J_{ortho} = 8.6, H$_{arom}$-tolyl), 7.42 (d, 2H, J_{ortho} = 8.4, H$_{arom}$-tolyl), 7.20 (m, 5H, H$_{arom}$-Phe), 7.08 (d, 2H, J_{ortho} = 8.6, H$_{arom}$-Tyr), 6.79 (d, 2H, J_{ortho} = 8.4, H$_{arom}$-tolyl), 5.89 (C of ABCXY, 1H, H-2′), 5.70 (d, 1H, $J_{5,4}$ = 10.2, H-5), 5.61 (dd, 1H, $J_{4,5}$ = 10.2, $J_{4,3}$ = 4.4, H-4), 5.28 (A of ABCXY, 1H, $J_{4',2'}$ = 17.2, H-4′), 5.16 (B of ABCXY, 1H, $J_{3',2'}$ = 10.2, H-3′), 4.56 (m, 1H, H-9), 4.50 (s, 1H, H-2), 4.39 (m, 1H, H-12), 4.13 (X of ABCXY, 1H, $J_{1'\alpha,1'\beta}$ = 13.3, $J_{1'\alpha,2'}$ = 5.9, H-1′α), 4.00 (m, 2H, H-3, H-1′β), 3.96 (m, 1H, H-2″), 3.90 (m, 1H, H-6), 3.18 (m, 1H, H-7α), 3.98 (m, 2H, H-7β, H-10α), 2.80 (m, 2H, H-10″β, H-3″α), 2.62 (m, 1H, H-3″β), 2.41 (s, 3H, C*H*$_3$-tolyl), 2.39 (m, 2H, H-14), 2.33 (s, 3H, C*H*$_3$-tolyl), 2.03 (s, 3H, COC*H*$_3$), 1.91 (m, 2H, H-13); ^{13}C NMR (75 MHz, 40 °C, DMSO-d_6) δ 170.4 (s, 2C, CO), 169.4 (s, CO), 147.6 (s, C$_{arom}$), 145.4 (m, 2C, *C*–F), 145.6 (s, C$_{arom}$), 142.2 (s, C$_{arom}$), 141.9 (m, 2C, *C*–F), 139.0

(m, 1C, *C*–F), 138.1 (s, C_{arom}), 137.3 (s, C_{arom}), 136.4 (s, C_{arom}), 134.4 (d, C-2′), 133.7 (s, C_{arom}), 132.0 (C_{arom}), 131.6 (d, 2C, C_{arom}), 131.4 (d, 2C, C_{arom}), 130.6 (d, C-5), 130.2 (C_{arom}), 129.2 (C_{arom}), 128.9 (d, 2C, C_{arom}), 128.6 (d, 2C, C_{arom}), 128.1 (C_{arom}), 126.2 (C_{arom}), 122.3 (d, C-4), 121.4 (d, 2C, C_{arom}), 116.8 (t, CH=*C*H_2), 115.0 (m, *C-ipso* de C_6F_5), 97.5 (d, C-2), 67.5 (t, C-1′), 66.2 (d, C-6), 57.5 (d, C-2″), 53.6 (d, C-10), 52.6 (d, C-12), 45.1 (d, C-3), 37.6 (t, C-7), 36.5 (t, C-10; t, C-3″), 30.8 (t, C-13), 29.5 (t, C-14), 21.1 (q, *C*H_3-tolyl), 20.9 (q, *C*H_3-tolyl), 14.6 (q, *C*H_3S); IR (KBr) *v* 3429, 3288, 3063, 2956, 2923, 2868, 1639, 1545, 1454, 1384, 1276, 1115, 700; MS (ES^+) *m*/*z* = 1030 ($[(M-OAllyl)Na]^+$, 100%); Anal. Calcd for $C_{52}H_{54}F_5N_5O_{12}S_4$: C, 53.64; H, 4.67; N, 6.02; S, 11.02. Found: C, 53.76; H, 4.40; N, 6.31; S, 10.98.

18. Other peptide-scaffold hybrids (with other scaffolds than carbohydrate) with sequence similarities to enkephalins are also calpain inhibitors (Montero, A. Ph.D. Thesis, Autónoma University, Madrid, July 2004).