Tetrahedron Letters 51 (2010) 277–280

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and applications of a chiral-oxygenated 3-chloro-3,6-dihydro-2*H*-pyran obtained under Overman rearrangement conditions

Ana Montero [a,b], Esperanza Benito [a], Bernardo Herradón [a,*]

[a] *Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain*
[b] *The Scripps Research Institute, Department of Chemistry, La Jolla, CA 92037, USA*

ARTICLE INFO

Article history:
Received 1 October 2009
Revised 25 October 2009
Accepted 28 October 2009
Available online 3 November 2009

Keywords:
Chlorinated carbohydrate
3,6-Dihydro-2*H*-pyran
Experimental modulation of the selectivity
Overman rearrangement
Peptide–carbohydrate hybrid
Unsaturated sugar

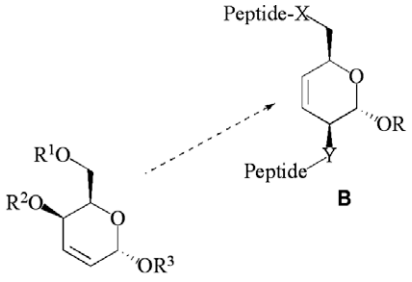
ABSTRACT

A chlorinated side product was formed under Overman rearrangement conditions from a trichloroacetimidate along with the expected allylic amide. The chlorinated product derived from a hex-2-enopyranoside was obtained in a totally stereoselective manner, and it can be a useful synthetic intermediate for chlorinated sugars. In order to improve the isolated yields of either the expected Overman rearrangement product or the chlorinated compound, we carried out a thorough study on the experimental conditions. The application of the latter for the synthesis of potential calpain inhibitors is also reported.

Functionalized chiral heterocycles are useful intermediates as well as target compounds for a variety of technological[1] and biological applications.[2] In connection with our longstanding interest on carbohydrates[3] and their synthetic applications to natural products as well as peptide–carbohydrate hybrids,[4] we surmised that sigmatropic rearrangements[5,6] from derivatives of hexenopyranosides **A** would provide suitable building blocks for the synthesis of peptide–carbohydrate hybrids **B**.[7]

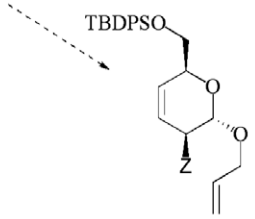
Whereas the Claisen rearrangement from **1** gave the branched chain product **2** in high yield, which in turn was used in the synthesis of peptide derivatives **B** (Y = CH_2CO);[8] the Overman rearrangement from **1** required considerable experimentation, since the yield of the expected **3** was lowered by the presence of a chlorinated side product. Finally, we could obtain the desired amide **3** in good yield that was used for the synthesis of the target molecules.[9]

On studying the reaction in-depth, we found that the chlorinated side product was **5**.[9,10] Remarkably, this side reaction took place in a totally stereoselective way, affording exclusively the 3β-chloro diastereoisomer, which is an unreported kind of chiral allylic chloride. These facts, along with the known synthetic applications of allylic chlorides[11] and their utility for the preparation of halogenated sugars (with potential applications in glycobiology[12] and in the field of nonmetabolizing sugars[13]) prompted us to perform an in-depth study of this reaction sequence (Scheme 1, Table 1). These results show that certain experimental parameters can be modulated to influence the selectivity of the reaction.[14]



A (generic structure)

1, R^1 = $tBuPh_2Si$, R^2 = H, R^3 = $CH_2CH{=}CH_2$

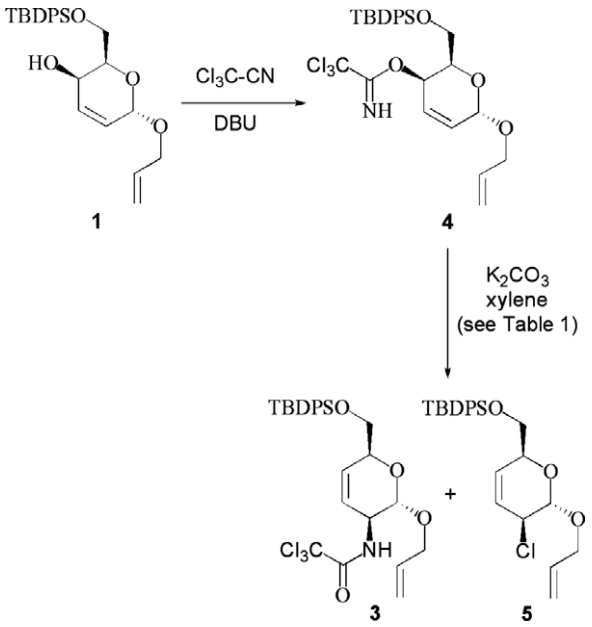


2, Z = CH_2COOR

3, Z = $NHC(O)CCl_3$

* Corresponding author. Tel.: +34 91 5615086; fax: +34 91 5644853.
E-mail address: herradon@iqog.csic.es (B. Herradón).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.136



Scheme 1. Synthesis of either amide **3** or chloride **5**.

Literature precedent guided our initial experimental set-up,[15] which involves the reaction of **1** with trichloroacetonitrile in the presence of DBU, filtration through a short path of Celite® and heating in xylene solution in the presence of K_2CO_3. However, the expected amide **3** was obtained in low yield with chloride **5** as the main product (entry 1). Since we reasoned that the chlorination reaction was radical based, we tried the reaction in the presence of hydroquinone as radical scavenger under argon atmosphere. Unexpectedly, we did not obtain amide **3** but rather obtained chloride **5** as the single product in a moderate yield (entry 2). Therefore, we followed the opposite trend using AIBN as radical initiator and obtaining a roughly 3:2 mixture of **3** and **5** in 74% overall yield (entry 3). Entries 1, 4, and 5 demonstrate the influence of the concentration on the selectivity. Under relatively dilute conditions, the selectivity was improved (up to 3:1) and the overall yield was higher; but still a considerable amount of **5** was obtained. Entries 6–9 show the effect of temperature, preheating (i.e., compound **4** was added when xylene is at the indicated temperature) and the reaction time. It was observed that a higher temperature (140 °C) and a longer reaction time were required to achieve an appropriate conversion, although the chloride was still obtained. As shown in entry 10, the reaction was sluggish when run in the absence of a solvent.

Reasoning that the formation of the chloride **5** might be due to a side product in the first step of the synthetic sequence that was not removed by filtration, we purified acetimidate **4** by chromatography. Purified **4** was submitted to Overman rearrangement conditions to give the amide **3** in 82% yield (entry 11) that was used in the previously reported synthetic applications.[9] To confirm that the formation of chloride **5** was promoted by a side product in the preparation of the acetimidate **4**, we mixed Cl_3CCN and DBU in the absence of alcohol **1** to give a brown tar **6** (with $R_f = 0$ in a variety of chromatographic mobile phases and whose structure is being studied). When the Overman reaction of purified **4** was conducted in the presence of **6**, a quantitative yield of an equimolecular mixture of **3** and **5** was obtained in a slow reaction (entry 12).

This last result undoubtedly illustrates that the side product in the formation of the trichloroacetimidate can hamper the yield and selectivity of the Overman rearrangement product. However, as commented above, the allylic chloride **5** can be a useful synthetic intermediate, and, for further synthetic applications, the experimental conditions reported in entry 2 (50% isolated yield from alcohol **1** and high scale) can be considered suitable for the synthesis of this kind of chiral allylic chloride, which is unprecedented in the literature. It is also remarkable that **5** is obtained in a totally stereoselective manner, whose relative configuration was determined by NOESY experiments and secured by X-ray diffraction analysis of a derivative.[10,16]

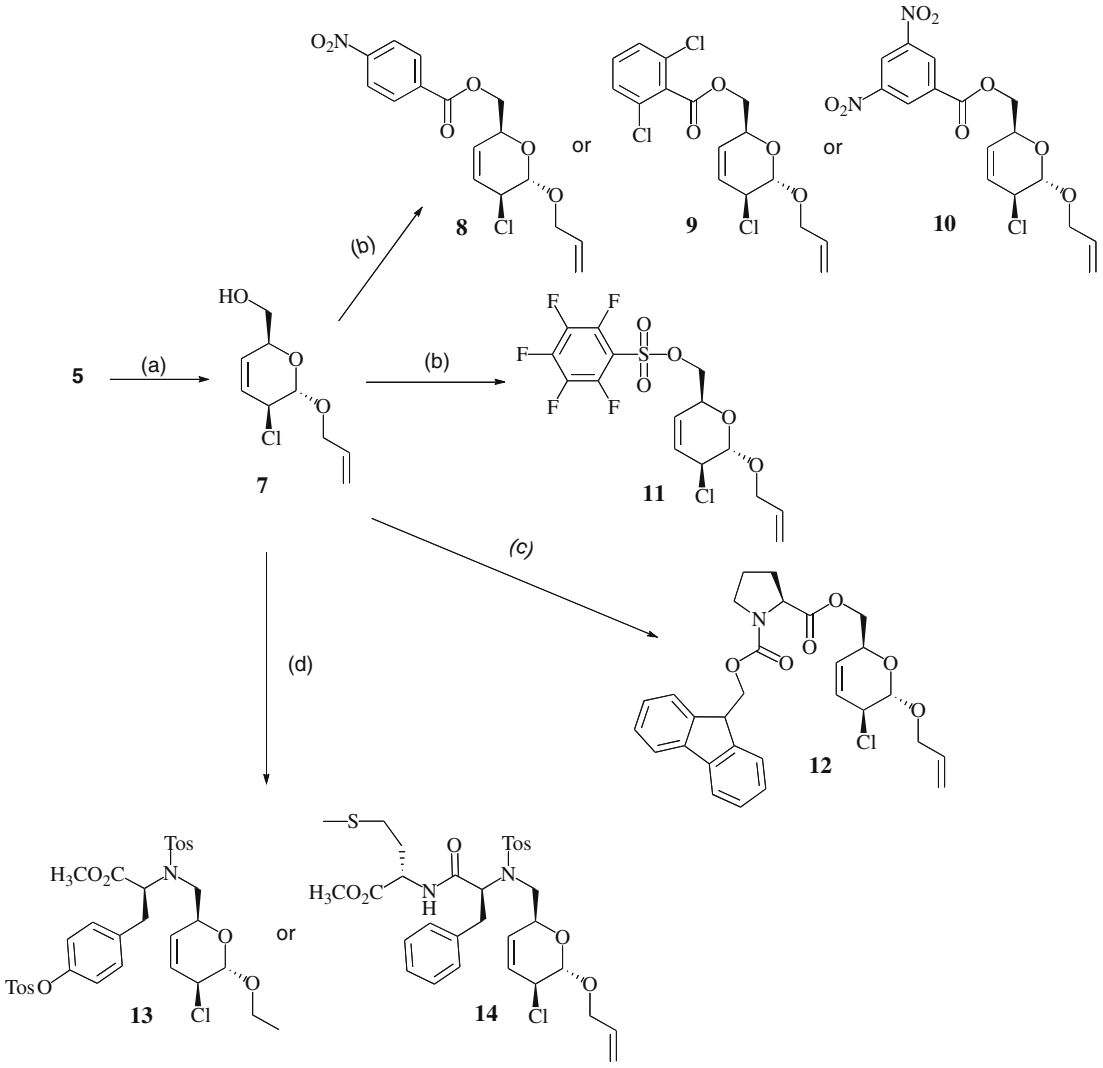
With a ready supply of **5** in hand, we performed several synthetic applications. In connection with current projects in our group, we are singularly interested on heterocycles having either peptide or aromatic substitution due to their potential applications as calpain inhibitors.[17–19] Compound **5** would be a good starting material to test the influence of chlorine substitution on biological activity. To this end, the TBDPS-protecting group of **5** was removed under standard conditions ($Bu_4NF{\cdot}3H_2O$/THF/rt) to give alcohol **7** (74% yield) that was transformed to the aromatic esters **8**–**10**, the sulfonate **11,** and the amino acid derivative **12** by acylation with the corresponding acyl chloride or sulfonyl chloride in 51–99% yields as indicated in Scheme 2. On the other hand, the amino acid derivative **13** and the peptide derivative **14** were prepared by Mitsunobu reaction[20] from the corresponding sulfonamide in 97% and 76% yields, respectively (Scheme 2).

To conclude, an 'anomalous' variant of the Overman rearrangement has been uncovered resulting from impurities present following trichloroacetimidate formation. The selectivity of this process can be controlled by proper choice of experimental conditions, providing practical access to either the amide **5** or the chloride **6**, which have proven to be useful synthetic intermediates for the synthesis of functionalized chiral heterocycles as potential calpain inhibitors. Work is in progress in order to establish the

Table 1
Experimental results obtained in the thermal treatment of the acetimidate **4**[a]

Entry	Intermediate (**4**)	Additive	T (°C)	Preheating	Time (h)	Concentration (M)	Reaction scale	Yield (**4**) (%)	Yield (**3**) (%)	Yield (**5**) (%)
1	Filtration	No	140–150	No	65	0.2	11.1 g	0	23	37
2	Filtration	Hydroquinone/Ar	140–150	No	28	0.36	6.0 g	0	0	50
3	Filtration	AIBN	140–150	No	31	0.1	100 mg	0	44	30
4	Filtration	No	140–150	No	68	0.1	100 mg	0	75	25
5	Filtration	No	140–150	No	68	0.02	100 mg	0	70	30
6	Filtration	No	80	Yes	22	0.02	20 mg	100	0	0
7	Filtration	No	110	Yes	22	0.02	20 mg	95	5	0
8	Filtration	No	140–150	Yes	22	0.02	20 mg	68	32	0
9	Filtration	No	140–150	Yes	46	0.02	3.6 g	0	57	29
10	Filtration	No	140–150	Yes	48	Neat	20 mg	31	69	Trace
11	Chromatography	No	140–150	Yes	74	0.02	4.1 g	0	82	0
12	Chromatography	**6**	140–150	Yes	99	0.02	12 mg	0	50	50

[a] All the reactions (except that indicated in entry 10) were carried out in xylene in the presence of a catalytic amount of K_2CO_3. When crude **4** was used, the isolated yield refers to overall yield from alcohol **1** (two steps).



Scheme 2. Reagents and conditions: (a) $Bu_4NF{\cdot}3H_2O$, THF, rt (74%); (b) Et_3N, CH_2Cl_2, 0 °C to rt; for **8**: $(4\text{-}NO_2)C_6H_4$–COCl (99%); for **9**: $(2,6\text{-}Cl_2)C_6H_3$–COCl (51%); for **10**: $[(3,5\text{-}(NO_2)_2]C_6H_3$–COCl (93%); for **11**: C_6F_5–SO_2–Cl, Et_3N, CH_2Cl_2, 0 °C to rt (75%). (c) Fmoc-L-Pro-Cl, Et_3N, CH_2Cl_2, 0 °C to rt (84%) (d) PPh_3, DIAD, THF, rt; for **13**: Ts-L-Tyr-(Ts)-OMe (97%); for **14**: Ts-L-Phe-L-Met-OMe (76%).

scope of the method, the reaction mechanism (including the precise origin of the chlorine atom), synthetic applications, and biological activity.[21,22]

Acknowledgment

This work was financially supported by Spanish Ministry of Science and Innovation (Grant CTQ2007-64891).

Supplementary data

Experimental details of the synthesis of **6** and spectroscopic and analytical data for new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.136.

References and notes

1. (a) de Siilva, A. P.; McCliean, C. D.; Moody, T. S. In *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: NY, 2004; pp 572–578; (b) Harmata, M. In *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: NY, 2004; pp 887–892; (c) Steed, J. W.; Turner, D. R.; Wallace, K. J. *Core Concepts in Supramolecular Chemistry and Nanochemistry*; John Wiley and Sons: Chichester, 2007.
2. (a) Eguchi, E. Bioactive Heterocycles II. In *Topics in Heterocyclic Chemistry*; Gupta, R. R., Ed.; Springer: Berlin, 2007; Vol. 8, (b) Sugawara, K.; Hashiyama, T. *Tetrahedron Lett.* **2007**, *48*, 3723–3726; (c) Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952–2963.
3. For selected examples on the reactivity, synthesis, and applications of carbohydrates, see: (a) Valverde, S.; Herradon, B.; Rabanal, R. M.; Martin-Lomas, M. *Can. J. Chem.* **1987**, *65*, 339–342; (b) Valverde, S.; Martin-Lomas, M.; Herradon, B.; Garcia-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895–1901; (c) Morcuende, A.; Valverde, S.; Herradon, B. *Synlett* **1994**, 89–91; (d) Herradón, B.; Valverde, S. *Synlett* **1995**, 599–602; (e) Valverde, S.; Gomez, A. M.; Hernandez, A.; Herradon, B.; Lopez, J. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2005–2006; (f) Herradón, B.; Fenude, E.; Bao, R.; Valverde, S. *J. Org. Chem.* **1996**, *61*, 1143–1147.
4. Mann, E. Ph.D. Thesis, Universidad Autónoma de Madrid, 2002.
5. For a review on Claisen rearrangement in carbohydrate chemistry, see: Werschkun, B.; Thiem, J. *Top. Curr. Chem.* **2001**, *215*, 293–325.
6. (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597–599; For a review, see: (b) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117–2142; For applications of Overman rearrangement in carbohydrate chemistry, see: (c) Takeda, K.; Kaji, E.; Konda, Y.; Sato, N.; Nakamura, H.; Miya, N.; Morizane, A.; Yanagisawa, Y.; Akiyama, A.; Zen, S.; Harigaya, Y. *Tetrahedron Lett.* **1992**, *33*, 7145–7148; (d) Yang, J.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 4231–4234; (e) Gupta, P.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 1925–1933.
7. For overviews on peptide–carbohydrate hybrids and sugar amino acids, see: (a) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253; (b) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514; (c) Chakraborti, T. K.; Srinivasu, P.; Tadapar, S.; Mohan, B. K. *J. Chem. Sci.* **2004**, *116*, 187–207; (d) Chakraborti, T. K.; Srinivasu, P.; Tadapar, S.; Mohan, B. K. *Glycoconjugate J.* **2005**,

22, 83–93; (e) Murphy, P. V.; Dunne, J. L. *Curr. Org. Synth.* **2006**, *3*, 403–437; (f) Murphy, P. V. *Eur. J. Org. Chem.* **2007**, 4177–4187; For recent developments, see: (g) Jockusch, R. A.; Talbot, F. O.; Rogers, P. S.; Simone, M. I.; Fleet, G. W. J.; Simons, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 16771–16777; (h) Sharma, G. V. M.; Jadhav, V. B.; Ramakrishna, K. V. S.; Jayaprakash, P.; Narsimulu, K.; Subash, V.; Kunwar, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 14657–14668; (i) Paloumbis, G.; Petrou, C.; Nock, B.; Maina, T.; Pairas, G.; Tsoungas, P.; Cordopatis, P. *Synthesis* **2007**, 845–852; (j) Chakraborty, T. K.; Kumar, S. U.; Mohan, B. K.; Sarma, G. D.; Kiran, M. U.; Jagadeesh, B. *Tetrahedron Lett.* **2007**, *48*, 6945–6950; (k) Maity, P.; Zabel, M.; Konig, B. *J. Org. Chem.* **2007**, *72*, 8046–8053; (l) Risseeuw, M. D. P.; Mazurek, J.; van Langenvelde, A.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Org. Biomol. Chem.* **2007**, *5*, 2311–2314; (m) Bughin, C.; Masson, G.; Zhu, J. *J. Org. Chem.* **2007**, *72*, 1826–1829; (n) Chandrasekhar, S.; Saritha, B.; Naresh, P.; Udayakiran, M.; Reddy, C. R.; Jagadeesh, B. *Helv. Chim. Acta* **2008**, *91*, 1267–1276; (o) Tuin, A. W.; Palachanis, D. K.; Buizert, A.; Grotenbreg, G. M.; Spalburg, E.; de Neeling, A. J.; Mars-Groenendijk, R. H.; Noort, D.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Eur. J. Org. Chem.* **2009**, 4231–4241.

8. Montero, A.; Mann, E.; Herradon, B. *Eur. J. Org. Chem.* **2004**, 3063–3073.
9. Montero, A.; Mann, E.; Herradon, B. *Tetrahedron Lett.* **2005**, *46*, 401–405.
10. A. Montero, Ph.D. Thesis, Universidad Autónoma de Madrid, 2004.
11. (a) Lubineau, A.; Canac, Y.; Le Goff, N. *Adv. Synth. Catal.* **2002**, *344*, 319–327; (b) Krohn, K.; Flörke, U.; Huele, D. *J. Carbohydr. Chem.* **2002**, *21*, 431–443; The current importance of chiral halogenated chlorides can be exemplified by the recent synthesis of a chlorosulfolipid cytotoxin, see: (c) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573–577.
12. (a) *Carbohydrate in Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Marcel Dekker: NY, 2004; (b) Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Disc.* **2009**, *8*, 661–677.
13. Ager, D. J.; Pantaleone, D. P.; Henderson, S. A.; Katritzky, A. R.; Prakash, I.; Walters, D. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 1802–1817.
14. (a) Herradon, B.; Valverde, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1479–1500; (b) Herradón, B.; Morcuende, A.; Valverde, S. *Synlett* **1995**, 455–458.
15. Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192.
16. All the new compounds have been fully characterized by spectroscopic and analytical methods (see Supplementary data).
17. For selected publications on calpain and its inhibitors, see: (a) Goll, D. E.; Thompson, V. F.; Li, H.; Wei, W.; Cong, J. *Physiol. Rev.* **2003**, *83*, 731–801; (b) Tompa, P.; Buzder-Lantos, P.; Tantos, A.; Farkas, A.; Szilagyi, A.; Banoczi, Z.; Hudecz, F.; Friedrich, P. *J. Biol. Chem.* **2004**, *279*, 20775–20785; (c) Zatz, M.; Starling, A. *N. Eng. J. Med.* **2005**, *352*, 2413–2423; (d) Neffe, A. T.; Abell, A. D. *Curr. Opin. Drug Disc. Devel.* **2005**, *8*, 684–700; (e) Carragher, N. *Curr. Pharm. Des.* **2006**, *12*, 615–638; (f) Croall, D. E.; Ersfeld, K. *Genome Biol.* **2007**, *8*, 218.
18. Our previous work has shown the importance of aromatic substitution on calpain inhibition, see: Montero, A.; Albericio, F.; Royo, M.; Herradon, B. *Org. Lett.* **2004**, *6*, 4089–4092. and references cited therein.
19. For recent examples of biologically active carbohydrates with aromatic substitution, see: (a) Jacobsson, M.; Ellervik, U.; Belting, M.; Mani, K. *J. Med. Chem.* **2006**, *49*, 1932–1936; (b) Lee, K. Y.; Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2006**, 679–681; (c) Saquib, M.; Gupta, M. K.; Sagar, R.; Prabhakar, Y. S.; Shaw, A. K.; Kumar, R.; Maulik, P. R.; Gaikwad, A. N.; Sinha, S.; Srivastana, A. K.; Chaturvedi, V.; Srivastana, R.; Srivastana, B. S. *J. Med. Chem.* **2007**, *50*, 2942–2950.
20. (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935–939; (b) Mitsunobu, N. *Synthesis* **1981**, 1–28; (c) Wisniewski, K.; Koldziejczyk, A. S.; Falkiewicz, B. *J. Peptide Sci.* **1998**, *4*, 1–14; (d) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
21. After our initial disclosure (see footnote no. 10 in Ref. 9), two articles reporting chlorinated by-products in Overman rearrangement have been published (both of them missed to cite our former article), see: (a) Pietruszka, J.; Schone, N.; Frey, W.; Grundl, L. *Chem. Eur. J.* **2008**, *14*, 5178–5197; (b) Matveenko, M.; Willis, A. C.; Banwell, M. G. *Aust. J. Chem.* **2009**, *62*, 64–68; (c) A minor mistake has been detected in the structures drawn in Ref. 9: the protecting group is TBDPS instead of TBDMS, we apologize for the error.
22. A thorough mechanistic study is underway (de Miguel, I.; Mann, E.; Herradon, B.). Our preliminary results seem to indicate that the reaction is a S_N2' although the trichloroacetimidate group is essential to achieve the total selectivity (regio- and stereo-). On the other hand, DBU and trichloroacetonitrile yield a putative 2:1 DBU-Cl ate complex which is a chlorinating agent, although its structure has not been yet clarified.