Journal of Organometallic Chemistry 695 (2010) 2354–2358

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Lithiated anions derived from (alkenyl)pentamethyl phosphoric triamides: Useful synthons for the stereoselective synthesis of 9-oxo- and 10-hydroxy-2(*E*)-decenoic acids, important components of queen substance and royal jelly of honeybee *Apis mellifera*

Tomasz K. Olszewski*, Catherine Bomont, Philippe Coutrot, Claude Grison

Centre D'Ecologie Fonctionnelle et Evolutive, Unité Mixte de Recherche 5175, Campus CNRS, 1919 Route de Mende, 34293 Montpellier cedex 5, France

ARTICLE INFO

Article history:
Received 4 June 2010
Received in revised form
21 June 2010
Accepted 22 June 2010
Available online 6 August 2010

Keywords:
Homoenolate anion
Enephosphoramide carbanion
Carbonyl protecting group
Chemical messengers
Natural compounds

ABSTRACT

Lithiated anions derived from (alkenyl)pentamethyl phosphoric triamides as homoenolate equivalents are used in the reaction with halogenated acetal and ketal giving regioselectively the γ-alkylation adducts. Chemoselective acidic hydrolysis of the enephosphoramide moiety in the presence of acetal or ketal groups leads to expected carbonyl products, key intermediates in the synthesis of natural compounds. The synthetic potential of the presented strategy is illustrated by stereoselective synthesis of two pheromones namely, 9-oxo-2(*E*)-decenoic acid **1** from queen substance and 10-hydroxy-2(*E*)-decenoic acid **2** from royal jelly of honeybee *Apis mellifera*.

1. Introduction

Carbon–carbon bond formation represents one of the most important events in organic chemistry. A large number of available protocols take advantage of the activation of methyl/methylene produced by the electron withdrawing effect of adjacent carbonyl functionality that facilitates the reaction of an electrophile at the α-carbon *via* enol/enolate intermediate. The reaction at the β-carbon is also feasible and proceeds *via* intermediacy of homoenolates. In contrast to enolate anions however, most homoenolate anions are difficult to handle, and not easy to prepare therefore, numerous efforts have been expended to understand the factors affecting the reactivity and regioselectivity of these reagents [1–6].

In this context, we have previously reported on the synthetic utility of lithium anions derived from (alkenyl)pentamethyl phosphoric triamides as an effective homoenolate synthetic equivalents for the preparation of aldehydes and ketones [7]. The value of this synthetic strategy is based on the remarkable ability of lithiated allylphosphoramide ambident anions to react exclusively at the γ position with electrophiles. Additionally, the conjugate enephosphoramide group which is stable to bases liberates the carbonyl group under mild acidic conditions [7] (Fig. 1).

Herein, we wish to demonstrate the flexibility offered with the application of lithium anions derived from (alkenyl)pentamethyl phosphoric triamides, by the stereoselective synthesis of two natural products namely 9-oxo-2(*E*)-decenoic acid (9-ODA) **1** from queen substance and 10-hydroxy-2(*E*)-decenoic acid (10-HDA) **2**, pheromones of honeybee *A. mellifera* (Fig. 2).

In addition to their role as interesting synthetic targets both pheromones represent very promising biological activity. 9-ODA was found to possess antibacterial, anti-inflammatory and antidotal activity and also can act as an accelerator of graft wound or thermal burn healing and as an immunomodulator [8]. In turn, 10-HDA has demonstrated an antitumor [9], antibacterial [10], immunomodulatory [11] and antioxidant activities [12] and was recently found to promote neurogenesis [13]. The majority of the reported syntheses rely upon the a priori most obvious concept namely, condensation of the corresponding carbonyl compound (7-oxo-octanal in the case of pheromone 1 and 8-hydroxy-octanal for 2) with either malonic acid (the Doebner reaction) or their use in selective olefination reaction (Fig. 2) [14]. The main problem related with this most straightforward approach is the preparation of the carbonyl

* Corresponding author. Tel./fax: +33 (0) 467 61 32 44.
E-mail address: tomasz.olszewski@pwr.wroc.pl (T.K. Olszewski).

0022-328X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2010.06.020

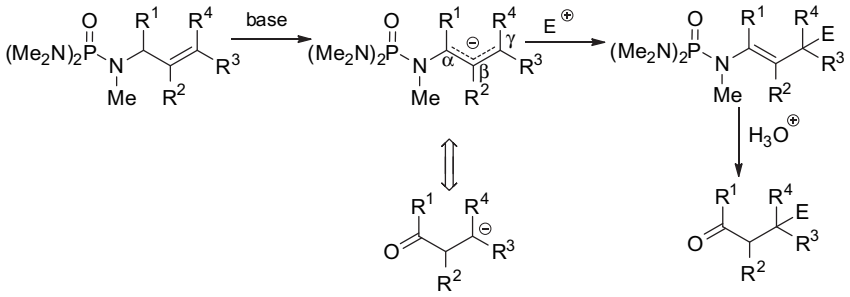


Fig. 1. Concept of (alkenyl)pentamethyl phosphoric triamides as homoenolate synthetic equivalents.

precursors which is not a trivial issue and usually requires multi-step protocols. Conceptually, 7-oxo-octanal and 8-hydroxy-octanal could be prepared by Michael reaction involving the conjugate addition of functional organometallics to acrolein. Although this strategy is limited by the instability of acrolein, the acrolein dialkylacetal approach raised the problem of competitive SN_2' allylic substitution [15]. An interesting solution is the copper catalyzed reaction to protected acrolein [16]. Most recent and effective syntheses of 7-oxo-octanal involve: a) preparation and reduction of 7-oxooctanoic acid to corresponding diol and oxidation with PCC [17]; b) preparation of 7,7-dimethoxy-heptanal followed by its methylenation, oxidation and deprotection [18] or c) the use of heptane-1,7-diol as substrate followed by its selective protection with THP group, and subsequent sequence oxidation, methylenation, oxidation and finally deprotection and again oxidation [19]. In turn, the most convenient protocols leading to 8-hydroxy-octanal require: a) the use of 8-nonenoic acid as substrate, reduction of the carboxylic acid followed by hydroxylation of the terminal C=C and oxidative cleavage of the intermediate 1,2-diol [20] or b) selective bromination of octane-1,8-diol, protection of the free hydroxyl with THP group and oxidation at the halogenated carbon atom followed by deprotection [21]. Simple and efficient preparation of 7-oxo-octanal and 8-hydroxy-octanal, their synthetic equivalents and analogues would not only facilitate the access to the pheromones 1 and 2 but also would be of great interest for the synthesis of cyclic compounds *via* intermolecular aldol reactions that use unmodified dialdehydes, ketoaldehydes and diketones [17,18,22].

2. Results and discussion

Our approach to the synthesis of pheromones **1** and **2** was based on a simple retrosynthetic pathway involving the Wittig–Horner reaction between 6-(2-methyl-1,3-dioxolan-2-yl)hexanal **4** (for the synthesis of **1**) or 7-(1,3-dioxolan-2-yl)heptanal **5** (in the case of **2**) with lithiated anion **3** used earlier in our group [23] (Scheme 1). Compounds **4** and **5** can be viewed as equivalents of 7-oxo- and 8-hydroxy-octanals respectively (Fig. 2). Both molecules **4** and **5** were easily prepared, in the key step of the synthesis, from enephosphoramides **6a**, **b** issued from the reaction of halogenated derivatives possessing a masked carbonyl function **7a**, **b** with carbanions derived from allylphosphoramide **8**.

2.1. Synthesis of queen substance, 9-oxo-2(E)-decenoic acid *1*

The starting material for the preparation of **1**, the 2-(3-iodopropyl)-2-methyl-1,3-dioxolane **7a** was prepared in a two step reaction sequence from commercially available 5-chloro-2-pentanone **9** (Scheme 2, Supplementary material).

It is noteworthy, that the choice of the protecting group for the carbonyl function present in **9** was crucial for the success of the synthesis. After several attempts, the acetal group proved to be the best option. This protecting group was found, in the further steps of the synthesis, to be stable under mild acidic conditions (pH 3.2), which were necessary to hydrolyse the enephosphoramide **6a** in order to obtain the desired aldehyde **4**, while it liberates the carbonyl function under strong acidic conditions (1 N aq. HCl, room temp., 4 h) producing the desired compound **1** (Scheme 3).

With compound **7a** in hand a series of experiments was performed to establish the best conditions for the reaction with lithiated enephosphoramide anion **11** (Supplementary material, Scheme 3).

The highest yields were obtained by using two equivalents of lithiated anion **11** with respect to the iodo derivative **7a**, and in the

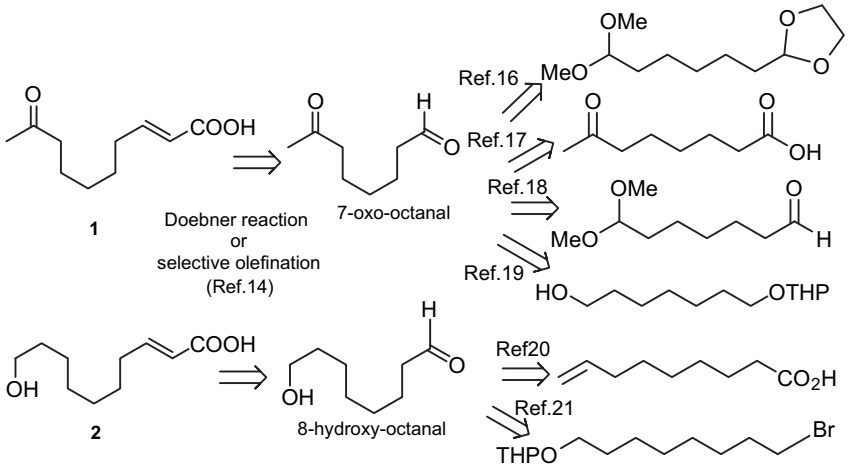
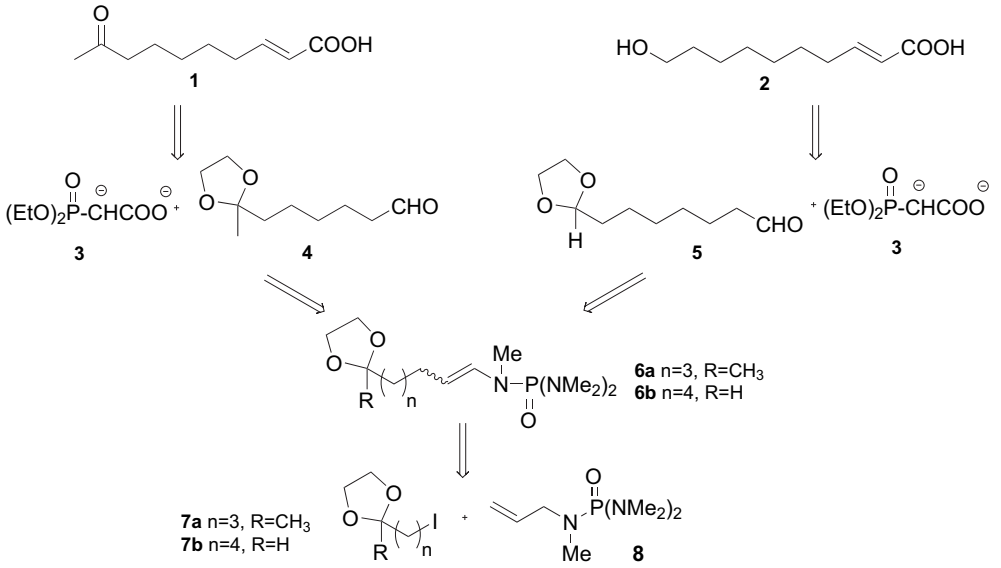
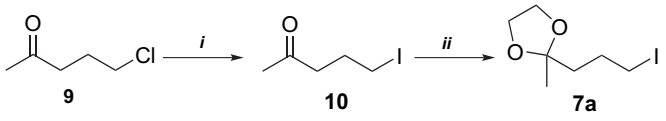


Fig. 2. Examples of synthetic strategies leading to pheromones **1** and **2**.



Scheme 1. Retrosynthetic analysis that includes application of lithium anions derived from (alkenyl)pentamethyl phosphoric triamides.

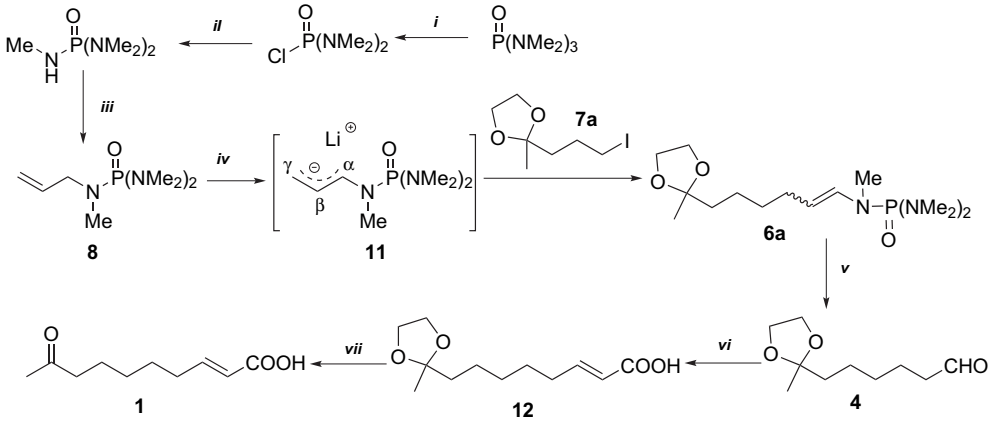


Scheme 2. Preparation of compound **7a**. *Reagents and conditions*: i) NaI, acetone, reflux, 88%; ii) ethylene glycol, cat. TsOH, toluene, reflux 1 h, 95%.

presence of one equivalent of HMPA (as a chelation agent for lithium) with respect to anion **11**. The lithiated anion **11** was prepared from corresponding enephosphoramide **8** by deprotonation with *n*-BuLi at −50 °C in THF. The addition of iodo acetal **7a** to a cooled (−50 °C) solution, followed by gentle warming to 20 °C produced, after neutral hydrolysis, the expected conjugate enephosphoramide **6a** with 89% yield (calculated on the basis of ^{31}P NMR of the crude mixture) as a mixture of two stereoisomers *E* and *Z* in a ratio 85:15. It should be noted here, that the reaction was clean and the ambident anion reacted exclusively at γ position.

The ^{1}H NMR spectrum of the crude reaction mixture was complex and difficult to assign however, ^{31}P NMR data clearly show five phosphorylated compounds: HMPA (δ = 25.68 ppm), both expected ethylenic stereoisomers **6a** (δ = 24.28 for *E* and 25.45 ppm for *Z*) and both *Z and E* transposed allyl(pentamethyl)phosphoramides derived from γ-hydrolysis of carbanion **11** (respectively 22.97 and 22.48 ppm) (Fig. 3). The assignment of **6a** *Z* and *E* was realized by analogy with ^{31}P NMR chemical shifts of other enephosphoramides described in our previous communications [7c]. The *E* stereoisomer was the more stable one, whereas the formation of *Z* stereoisomer can be explained as the result of an internal chelation of lithium with the free nitrogen orbital, in the carbanionic precursor **11**.

Treatment of **6a** with a strong acid led to the hydrolysis of both dioxalane and enephosphoramide functions, followed by direct cyclization of the dihydroxyaldehyde [7c]. Therefore here, an accurate study on the hydrolysis of **6a** was performed. It was established that treatment of **6a** with 1 N H_2SO_4 until pH 3.2 and a reaction time of 4 h, during which time the pH was readjusted every hour to its initial value by adding 1 N aqueous H_2SO_4, created optimum conditions for the chemoselective cleavage of the carbon–nitrogen bond leading to the desired aldehyde **4** with an



Scheme 3. Synthesis of **1**. *Reagents and conditions*: i) $P(O)Cl_3$, 0.5 equiv., 2 h, 160 °C, 100%; ii) CH_3NH_2 excess, Et_2O, 48 h, 20 °C, 100%; iii) NaH/THF, allyl bromide, room temp., 80%; iv) *n*-BuLi, −50 °C, HMPA then **7a**, 89%; *v)* 1 N aq. H_2SO_4 to pH 3.2, room temp., 4 h, 90%; *vi)* *n*-BuLi, −60 °C, $(EtO)_2P(O)CH_2CO_2H$, 91%; vii) 1 N aq. HCl, room temp., 4 h, 95% (47% overall yield from commercially available **9**).

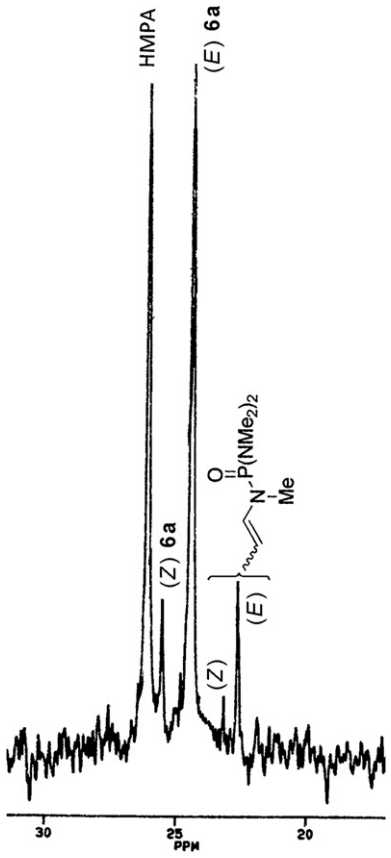
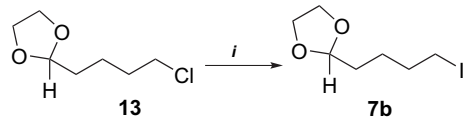


Fig. 3. ^{31}P NMR spectra ($CDCl_3$) of enephosphoramide **6a** (crude product), HMPA, transposed all(pentamethyl)phosphoramide.

excellent yield (90%) (Scheme 3). It is worth mentioning, that the presented protocol leading to aldehyde **4** is, to the best of our knowledge, the most efficient described so far (67% overall yield; 4 steps from commercially available **9**). Aldehyde **4** is a useful building block in the synthesis of natural compounds *e.g.* ketoalkenes and ketoalkenynes from *Echinacea pallida* [24].

The aldehyde was further used in the Wittig–Horner reaction with dianion **3**, prepared from diethylphosphonoacetic acid. The desired (*E*)-8-(2-methyl-1,3-dioxolan-2-yl)oct-2-enoic acid **12** was obtained with 91% yield. It is noteworthy that, the reaction was completely stereoselective and resulted in the exclusive formation of only the *E* stereoisomer.



Scheme 4. Preparation of compound **7b**. *Reagents and conditions*: i) NaI, acetone, reflux, 88%.

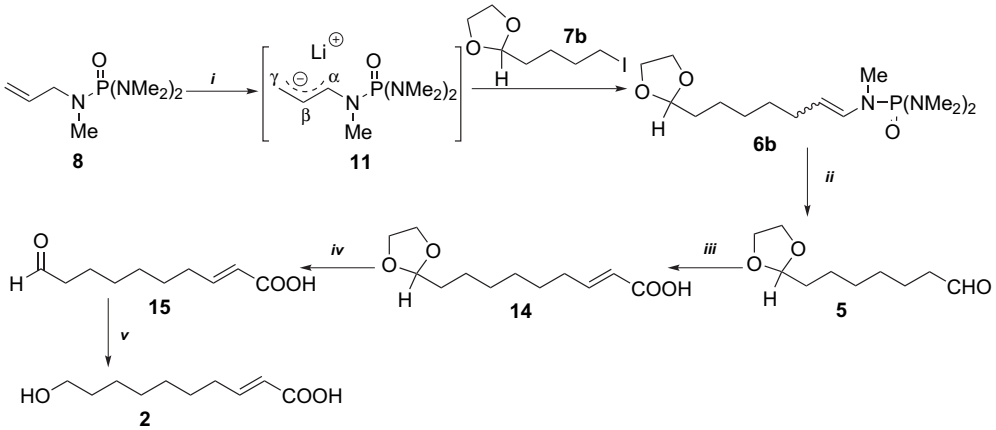
In the last step of the synthesis, the protecting group of **12** was easily removed in acidic conditions using 1 N HCl producing the desired 9-oxo-2(*E*)-decenoic acid (9-ODA) **1** with a 95% yield and with an excellent 47% overall yield from commercially available **9**. The formation of only *E* stereoisomer was unambiguously confirmed by comparison of the NMR data of the obtained sample with those previously reported in the literature (Supplementary material). The efficient preparation of **1** prompted us to extend this methodology to the synthesis of second pheromone namely 10-hydroxy-2(*E*)-decenoic acid **2** from royal jelly.

2.2. Synthesis of 10-hydroxy-2(E)-decenoic acid **2**

In the synthesis of compound **2** the already protected and commercially available starting material **13** was used rendering the desired 2-(4-iodobutyl)-1,3-dioxolane **7b** with 88% yield (Scheme 4, Supplementary material).

Next, the iodo-precursor **7b** was reacted with lithiated enephosphoramide anion **11** using analogous conditions to that described earlier for the synthesis of pheromone **1**. The expected conjugate enephosphoramide **6b** was obtained with 74% yield calculated on the basis of ^{31}P NMR as a mixture of two stereoisomers *E* and *Z* (Scheme 5). On the ^{31}P NMR spectra the *E* stereoisomer presented an upfield signal at 24.11 ppm, and the Z stereoisomer presented a downfield signal at 25.32 ppm.

Dioxolane acetal derivatives are not as robust as dioxolane ketals hence they are hydrolyzed more readily than their ketal counterparts [25]. The treatment of **6b** with 1 N H_2SO_4 until pH 3.2 and a reaction time of 4 h, during which time the pH was readjusted every hour to its initial value by adding 1 N aqueous H_2SO_4, led to the chemoselective hydrolysis of the enephosphoramide moiety and formation of the expected aldehyde **5** with a 90% yield (Scheme 5). Next, the aldehyde **5** was exposed to anion **3** in the Wittig–Horner olefination producing the desired (*E*)-9-formylnon-2-enoic acid **15**



Scheme 5. Synthesis of compound **2**. *Reagents and conditions*: i) *n*-BuLi, −50 °C, HMPA then **7b**, 74%; ii) 1 N aq. H_2SO_4 to pH 3.2, room temp., 4 h, 90%; iii) *n*-BuLi, −60 °C, $(EtO)_2P(O)CH_2CO_2H$, 85%; iv) 1 N aq. HCl, room temp., 4 h, 92%; v) MeOH, $NaBH_4$, room temp., 2 h, 83% (49% overall yield from commercially available **13**).

with 92% yield and total *E* stereoselectivity. In the last step of the synthesis, the alcohol function in the acid **15** was reduced to an aldehyde by means of $NaBH_4$ generating with 83% yield the desired 10-hydroxy-2(*E*)-decenoic acid **2** with conserved *E* geometry of the double bond. The overall yield of the entire reaction sequence, starting from the commercially available **13** was 49%.

In conclusion, a novel and versatile approach to the preparation of two known pheromones from honeybees *A. mellifera* namely, 9-oxo-2(*E*)-decenoic acid **1** from queen substance (47%, overall yield starting form commercially available substrate) and 10-hydroxy-2(*E*)-decenoic acid **2** from royal jelly (49%, overall yield starting form commercially available material) and total *E* stereoselectivity of the double bond present in both final structures was presented. The key step of the synthesis was the reaction between homoenolate anion equivalent derived from enephosphoramide and halogenated derivatives possessing a masked carbonyl function. The synthetic value of this strategy is based on the nature of the conjugate enephosphoramide group which is stable to bases but liberates the aldehydic group under mild acidic conditions. The results illustrate the benefit and interest of the enephosphoramide strategy for the construction of natural products. The potential in total synthesis of other natural compounds is currently being investigated in our laboratory and the results will be reported in due course.

Appendix. Supplementary material

Detailed experimental procedures, spectroscopic characterization of all compounds and copies of the NMR spectra for compounds **8**, **6a**, **6b**, **4**, **5**, **7a**, **12**, **14**, **15**, **1**, **2**. This information can be found, in the online version, at doi:10.1016/j.jorganchem.2010.06.020.

References

[1] A. Nickon, J.L. Lambert, J. Am. Chem. Soc. 84 (1962) 4604–4605.
[2] V. Nair, S. Vellalath, B.P. Babu, Chem. Soc. Rev. 37 (2008) 2691–2698 [and the references cited therein].
[3] D. Hoppe, Synthesis 1 (2009) 43–55 [and the references cited therein].
[4] D. Hoppe, Angew. Chem. Int. Ed. Engl. 23 (1984) 932–948.
[5] D. Enders, O. Niemeier, A. Henseler, Chem. Rev. 107 (2007) 5606–5655.
[6] B.E. Maki, E.V. Patterson, Ch. J. Cramer, K.A. Scheidt, Org. Lett. 11 (2009) 3942–3945.
[7] (a) P. Coutrot, C. Grison, C. Bômont, Phosphorus, Sulfur, and Silicon 77 (1993) 195;
(b) P. Coutrot, C. Grison, C. Bômont, Tetrahedron Lett. 35 (1994) 8381–8384;
(c) P. Coutrot, C. Grison, C. Bômont, J. Organomet. Chem. 586 (1999) 208–217;
(d) C. Grison, A. Thomas, F. Coutrot, P. Coutrot, Tetrahedron 59 (2003) 2101–2123;
(e) C. Grison, A. Thomas, F. Coutrot, P. Coutrot, J. Organomet. Chem. 689 (2003) 1530–1539.
[8] G.Yu. Ishmuratov, A.F. Ismagilova, A.A. Sharipov, O.N. Gerasyuta, R.Ya. Kharisov, N.M. Ishmuratova, G.A. Tolstikov, Pharm. Chem. J. 37 (2003) 309–313.
[9] G.F. Townsend, W.H. Brown, E.E. Felauer, B. Hazlett, Can. J. Biochem. Physiol. 39 (1961) 1765–1770.
[10] M.S. Blum, A.F. Novak, S. Taber, Science 130 (1959) 452–453.
[11] D. Vucevic, E. Melliou, S. Vasilijic, S. Gasic, P. Ivanovski, I. Chinou, M. Colic, Int. Immunopharmacol 7 (2007) 1211–1220.
[12] T. Nagai, M. Sakaia, R. Inouec, H. Inouec, N. Suzukia, Food Chem. 75 (2001) 237–240.
[13] N. Hattori, H. Nomoto, H. Fukumitsu, S. Mishama, S. Furukawa, Biomed. Res. 28 (2007) 261–266.
[14] (a) For a review see: G.Yu. Ishmuratov, R.Ya. Kharisov, N.M. Botsman, N.M. Ismuratova, G.A. Tolstikov Chem. Nat. Compounds 38 (2002) 1–23 [more recent examples include];
(b) R.Ya. Kharisov, O.V. Botsman, L.P. Botsman, N.M. Ishmuratova, G.Yu. Ishmuratov, G.A. Tolstikov, Chem. Nat. Compounds 38 (2002) 145–148;
(c) G.Yu. Ishmuratov, M.P. Yakovleva, L.P. Botsman, N.M. Ishmuratova, R.R. Muslukhov, G.V. Khambalova, G.A. Tolstikov, Chem. Nat. Comp. 39 (2003) 28–30;
(d) J. Villieras, M. Rambaud, M. Graff, Tetrahedron Lett. 26 (1985) 53–56;
(e) G.Yu. Ishmuratov, M.P. Yakovleva, K.A. Tambovtsev, Yu.V. Legostaeva, L.V. Kravchenko, N.M. Ishmuratova, G.A. Tolstikov, Chem. Nat. Compounds 44 (2008) 74–76.
[15] J.F. Normant, A. Commerçon, M. Bourgain, J. Villieras, Tetrahedron Lett. 16 (1975) 3833–3836.
[16] J. Villieras, M. Rambaud, M. Graff, Synth. Comm. 15 (1985) 569–580.
[17] C. Ghobril, C. Sabot, Ch. Mioskowski, R. Baati, Eur. J. Org. Chem. (2008) 4104–4108.
[18] F. Douelle, A.S. Capes, M.F. Greaney, Org. Lett. 9 (2007) 1931–1934.
[19] J.S. Dickschat, E. Hemke, S. Schultz, Chem. Biodiversity 2 (2005) 318–352.
[20] K. Sisido, M. Kawanisi, K. Kondo, T. Morimoto, A. Saito, N. Hukue, J. Org. Chem. 27 (1962) 4073–4076.
[21] R. Chiron, J. Chem. Ecol. 8 (1982) 709–713.
[22] S. Mukherjee, J. Woon Yang, S. Hoffmann, B. List, Chem. Rev. 107 (2007) 5471–5569.
[23] (a) P. Coutrot, C. Grison, S. Genève, C. Didierjean, A. Aubry, A. Vicherat, M. Marraud, Lett. Pept. Sci. 4 (1997) 415–422;
(b) C. Grison, P. Coutrot, S. Genève, C. Didierjean, M. Marraud, J. Org. Chem. 70 (2005) 10753–10764;
(c) C. Grison, S. Genève, E. Halbin, P. Coutrot, Tetrahedron 57 (2001) 4903–4923.
[24] M. Egger, P. Pellett, K. Nickl, S. Geiger, S. Graetz, R. Seifert, J. Heilmann, B. Konig, Chem. Eur. J. 14 (2008) 10978–10984.
[25] P.J. Kociensky, Protecting Groups. Georg Thieme Verlag Stuttgart, New York, 1994.