Preprint Title	Synthesis of diastereomeric pheromones: adjacent methyl-branched alcohols and ketones
Authors	VAN-DUNG LE, Chi-Hien Dang, Cong-Hao Nguyen, Van-Su Dang and Thanh-Danh Nguyen
Publication Date	09 Jul 2019
Article Type	Full Research Paper
Supporting Information File 1	Supporting information.docx; 5.3 MB
ORCID® iDs	VAN-DUNG LE - https://orcid.org/0000-0001-7977-6546; Thanh-Danh Nguyen - https://orcid.org/0000-0001-6330-8916

Synthesis of diastereomeric pheromones: adjacent methyl-branched alcohols and ketones

Van-Dung Le[1,2], Chi-Hien Dang[1,3*], Cong-Hao Nguyen[3], Van-Su Dang[4] and Thanh-Danh Nguyen[2,3]*

[1]Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam.

[2]Institute of Research and Development, Duy Tan University, Da Nang City, Vietnam

[3]Institute of Chemical Technology, Vietnam Academy of Science and Technology, 1 Mac Dinh Chi Street, District 1, Ho Chi Minh City, Vietnam.

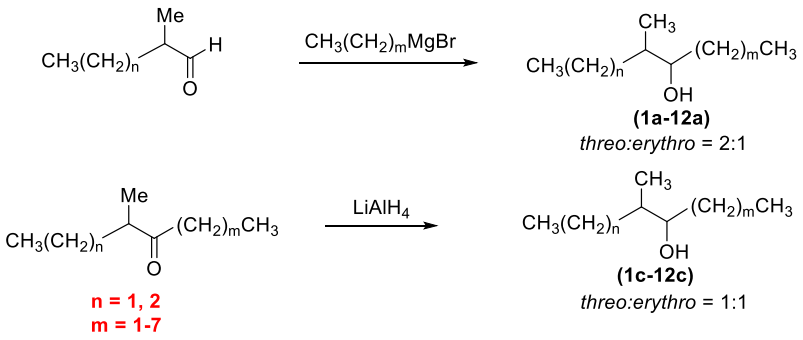
[4]Department of chemical Technology, Ho Chi Minh City University of Food industry, Ho Chi Minh City, Viet Nam.

*Correspondence: dangchihien@gmail.com (C.H. Dang), danh5463bd@yahoo.com (T.D. Nguyen)

Abstract

Racemic synthesis of adjacent methyl-branched alcohol and ketone pheromones is particularly considered for large scale trap of insects due to their similar activity to the chiral components in field trial. In this work, we presented a straightforward and effective strategy for racemic synthesis of adjacent methyl-branched alcohols to obtain the different diastereomer rates (*threo: erythreo* = 2:1 and 1:1) via Felkin-Anh model. No effect of alkyl chain length on stereoselectivity of adduct has been demonstrated. Moreover, the α-methyl ketones were effectively produced by microwave-assisted oxidation of the respective secondary alcohols using 2-iodoxybenzoic acid (IBX)

Graphic Abstract



Key words: Grignard coupling, Felkin-Anh model, pheromone, microwave irradiation, stereoselectivity.

Introduction

The use of insect pheromones as an alternative method of conventional pesticides which have negative impacts on environment and organisms are particularly considered in integrated pest management (IPM) strategies [1-3]. There are many insect pheromones possessing chiral centers with a methyl branch [4]. Among them, α-methyl alcohols and ketones bearing chiral centers were found to be pheromones of many species, especially in genius *Rhynchophorus* (Figure 1). The similar activity between absolute configuration and racemic mixture of the pheromones has been documented in insect attraction. For instants, 4-methyl-5-nonanol (**9a**) and 4-methyl-5-nonanone (**9b**) are major components of an aggregation pheromone of two Asian red palm weevils, *R. ferrugineus* and *R. vulneratus*. The absolute configuration of *R. ferrugineus* pheromone was known as (4S, 5S)-**9a**. However, attract effectiveness of both (4S,5S)-**9a** and racemic **9a** was similar in trial programs to control the red palm weevil [5-7]. Moreover, racemic mixture of **9a** was also used to manage populations of other species, *R. bilineatus* [8]. Similarly, combination of racemic mixture of 4-methyl-3-hetanol (**7a**) and other components showed the high attraction of the smaller European elm bark

beetle, *Scolytus multistriatus* [9]. Since low-cost fabrication of such pheromones is required for large-scale trapping of insects, racemic synthesis should be considered as an effective solution.

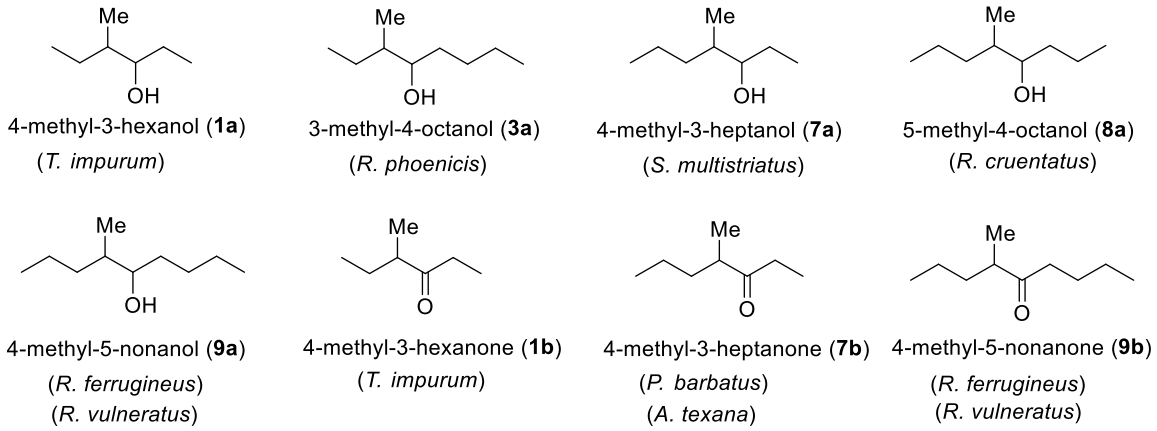


Figure 1. Examples for pheromones of adjacent methyl-branched alcohols and ketones

In diastereoselective synthesis of α-methyl alcohols, additions of an organometallic reagent or a hydride source to a ketone or an aldehyde with an existing α- chiral center respect with to the carbonyl group are known as Cram's rule or preferred Felkin-Anh model. In this model, both *syn*- and *anti*- diastereomeric adducts can be generated and predominating one of them is predictable as illustrated in Figure 2. It is well known that addition of an organometallic reagent into the carbonyl of α-methyl aldehyde forms the *syn*- isomer (FA) as major product while attack of hydride ions into the carbonyl of α-methyl ketone generates a favoured *anti*- isomer (FA). Diastereoselective synthesis of α-methyl alcohols via Felkin-Anh model is controllable based upon one of two following factors [10, 11]: (1) the steric effect of bulky groups which consist of the large group (L) and organometallic reagent (or R group). The stereoselectivity generally increases in order of alkyl group size i.e. Me < Et < *i*-Pr < *t*-

Bu. (2) Polar effects which stabilize a transition state with maximum separation between the nucleophile (Nu^-) and a large group (L). Although the stereoselective synthesis on the Felkin-Anh model has explored frequently over past decades [12-17], effect of alkyl group size on stereoselectivity is still not understood fully. To the best of our knowledge, influence of alkyl chain length has not been studied for diastereoselectivity of Felkin-Anh addition so far.

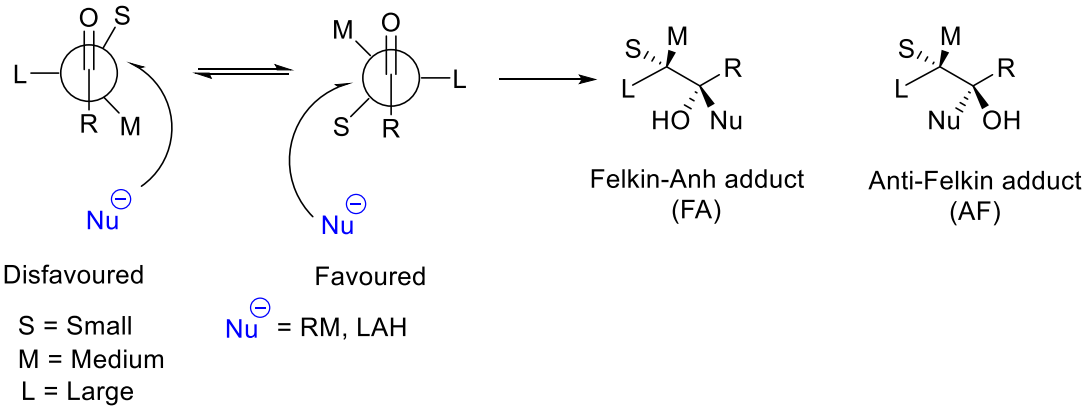


Figure 2. Felkin-Anh model for synthesis of adjacent methyl-branched alcohols

A facile synthesis of α-methyl ketone pheromones with available reagents and straightforward procedures is required. Oxidation of the respective alcohols is one of promisingly ways to fabricate pheromone products in large scale. Many reactions can be selected for such synthesis. For instants, Swern oxidation uses Dimethylchlorosulphonium ion generated *in situ* from DMSO and oxalyl chloride which allows to prepare aldehydes and ketones under mild conditions [17-20]. However, by-products such as dimethyl sulfide (Me_2S), carbon monoxide (CO) and carbon dioxide (CO_2) are toxic. The Jones Oxidation can be used to convert secondary alcohols to ketones using chromic trioxide or sodium dichromate in diluted acid.

Although the reaction occurs rapid, the reagents used are toxic [21-23]. Amongst methods, Dess-Martin oxidation using a hypervalent iodine compound (IBX) offers not only very mild conversion of alcohols to aldehydes or ketones but also a practical and environmentally friendly method [24-27]. Herein, we investigate effect of alkyl chain lengths for diastereoselective synthesis of adjacent methyl-branched alcohol pheromones through Felkin-Anh model. Oxidation of the secondary alcohols using IBX under microwave-assisted condition is also explored for synthesis of the respective α-methyl ketones.

Results and discussion

Synthetic Route of adjacent methyl-branched alcohols

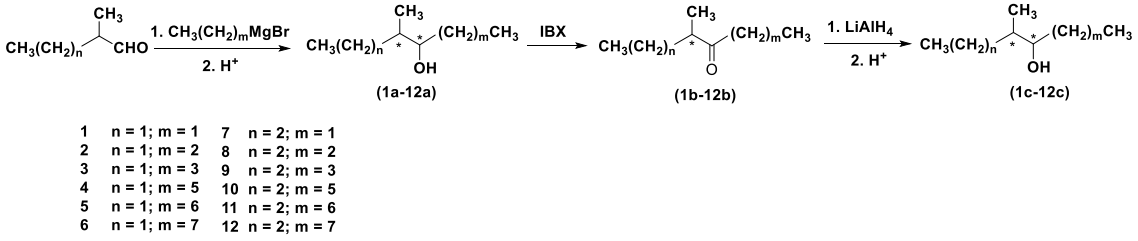
In aim to procedure and apply low-cost pheromones of methyl-adjacent alcohols, we wish to prepare alcohol pheromones (Figure 1) with dominant ratios of either *threo* or *erythro* by application of Felkin-Anh model which requires nucleophilic attack on the α-methyl carbonyl group (Scheme 1). Attack of different nucleophiles (e.g. Grignard reagent or hydride) can generate the different diastereomer mixture of the same alcohol structures. In our previous report, the racemic mixture of *R. ferrugineus* pheromone, 4-methyl-5-nonanol (**9**) has been synthesized by using Grignard coupling between 2-methylpentanal and n-butylmagnesium bromide to obtain a dominant amount of *threo* isomer [23]. Since synthesis of adjacent methyl-branched alcohol pheromones with a high amount of *erythro* isomer is required, reduction of α-methyl ketones using $LiAlH_4$ as a nucleophilic resource is expected to give pheromone with such structure. At first attempt for synthesis of these alcohol pheromones (Figure 1), the reduction of α-methyl ketones with short chain length (m = 1 and 2, entries 13-14 and 19-20, Table 1) has been carried out and unfortunately the comparatively low diastereoselectivity observed

for the addition is somewhat surprising. The similar result also observed previously for synthesis of 4-methyl-3-heptanol (**7c**) with a mixture of *threo*:*erythro* (1:1) has been found in literature [9, 28]. Therefore, we decided to study influence of alkyl straight chain length with respect to diastereoselectivity of the Felkin-Anh model as shown in Scheme 1.

In the first pathway, 1-bromoalkanes (m = 1 to 7) are utilized to prepare the Grignard reagents as nucleophile sources in reaction of the addition with racemic 2-methylalkanals (n = 1, 2) to form the secondary alcohols **1a-12a** which are expected to afford diastereomers with a dominant amount of *threo* isomer according to Felkin – Anh model. Ratios of diastereomers can be determined by NMR analysis. The peak relating to the proton at C-OH of the *threo* isomer appears a multiplet at $\delta \sim 3.50$ ($CDCl_3$) while the multiplet one corresponding to the *erythro* isomer is at $\delta \sim 3.45$ ($CDCl_3$) [7,8,23]. In fact, the generated alcohols from addition to the α-methyl aldehydes possessed a ratio of *threo*: *erythro* ≈ 2:1 (entries 1-12, Table 1). However, it is noteworthy that increase of alkyl chain length of nucleophile reagents leads to an insignificant change in rate of the obtained diastereomers. It confirms that alkyl chain length of nucleophile reagent has no effect on diastereoselectivity of Felkin – Anh adduct. Moreover, slightly increase of steric bulk in the largest group of aldehyde substrate (n = 1 and 2) also induced the poor selectivity of diastereomers. The similar observation for synthesis of other compounds has been found in the previous reports [29, 30].

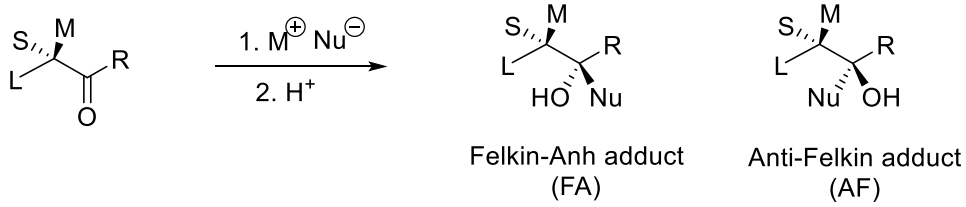
At next inspection, reduction of the corresponding α-methyl ketones using $LiAlH_4$ is carried out. The NMR analysis showed that all obtained alcohols **1c-12c** including long alkyl chains possessed mixture of *threo*:*erythro* ≈ 1:1 (entries 13-24, Table 1). It indicates independence of alkyl chain length in both sides of substrate for

stereoselectivity of Felkin-Anh adduct. In spite of no conclusion on the effect of alkyl chain length on the diastereoselectivity, the similar results have been observed for short alkyl chain (e.g. methyl and ethyl) in other substrates [10, 31]. It suggests that steric effects on adjacent carbon of two stereocenters are a prerequisite factor in diastereoselective addition of Felkin-Anh model.



Scheme 1. Synthetic route of different diastereomers of adjacent methyl-branched alcohols

Table 1. Percent of diastereomers and yields for synthesis of adjacent methyl-branched alcohols



Entry	Product	L (R_1)	M	S	R	$M^{\oplus}Nu^{\ominus}$	FA : AF[a]	Yield (%)[b]
1	**1a**	C_2H_5	CH_3	H	H	C_2H_5MgBr	1.71:1.0	84.2
2	**2a**	C_2H_5	CH_3	H	H	C_3H_7MgBr	1.86:1.0	85.6
3	**3a**	C_2H_5	CH_3	H	H	C_4H_9MgBr	2.07:1.0	83.7
4	**4a**	C_2H_5	CH_3	H	H	$C_6H_{13}MgBr$	1.74:1.0	88.8
5	**5a**	C_2H_5	CH_3	H	H	$C_7H_{15}MgBr$	1.83:1.0	95.4
6	**6a**	C_2H_5	CH_3	H	H	$C_8H_{17}MgBr$	1.92:1.0	90.9

7	**7a**	C_3H_7	CH_3	H	H	C_2H_5MgBr	1.67:1.0	87.9
8	**8a**	C_3H_7	CH_3	H	H	C_3H_7MgBr	1.82:1.0	86.5
9	**9a**[c]	C_3H_7	CH_3	H	H	C_4H_9MgBr	1.70:1.0	94.0
10	**10a**	C_3H_7	CH_3	H	H	$C_6H_{13}MgBr$	1.91:1.0	90.6
11	**11a**	C_3H_7	CH_3	H	H	$C_7H_{15}MgBr$	1.66:1.0	93.3
12	**12a**	C_3H_7	CH_3	H	H	$C_8H_{17}MgBr$	1.82:1.0	92.4
13	**1c**	C_2H_5	CH_3	H	C_2H_5	$LiAlH_4$	1.0:1.08	95.6
14	**2c**	C_2H_5	CH_3	H	C_3H_7	$LiAlH_4$	1.0:1.08	96.4
15	**3c**	C_2H_5	CH_3	H	C_4H_9	$LiAlH_4$	1.0:1.07	98.2
16	**4c**	C_2H_5	CH_3	H	C_6H_{13}	$LiAlH_4$	1.0:1.04	95.7
17	**5c**	C_2H_5	CH_3	H	C_7H_{15}	$LiAlH_4$	1.0:1.02	97.4
18	**6c**	C_2H_5	CH_3	H	C_8H_{17}	$LiAlH_4$	1.0:1.01	97.0
19	**7c**	C_3H_7	CH_3	H	C_2H_5	$LiAlH_4$	1.0:1.02	95.4
20	**8c**	C_3H_7	CH_3	H	C_3H_7	$LiAlH_4$	1.0:1.02	96.8
21	**9c**	C_3H_7	CH_3	H	C_4H_9	$LiAlH_4$	1.0:0.97	95.5
22	**10c**	C_3H_7	CH_3	H	C_6H_{13}	$LiAlH_4$	1.0:1.08	97.3
23	**11c**	C_3H_7	CH_3	H	C_7H_{15}	$LiAlH_4$	1.0:1.08	98.2
24	**12c**	C_3H_7	CH_3	H	C_8H_{17}	$LiAlH_4$	1.0:1.07	97.6

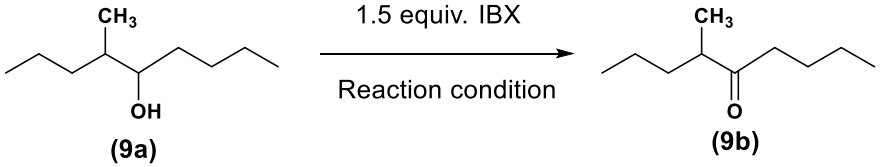
[a] Percent of diastereomers estimated by ^{1}H-NMR data. For series **a**, FA:AF = *threo:erythro*. For series **c**, FA:AF = *erythro:threo*; [b]Isolated yields of pure products; [c]reported in literature [23]

Microwave-assistant synthesis of adjacent methyl-branched ketones

Oxidation of alcohols using IBX as an oxidant on heating with or without solvents has revealed facile manners to prepare the respective aldehydes or ketones. In aim of enhancing the oxidation yields and reducing the reaction time, α-methyl ketones required for the present work were produced by microwave-assisted oxidation using IBX. In the search for a suitable procedure for oxidation, **9a** was submitted to a range of conditions with a number of different solvents. Oxidation in each solvent was carried out by both common heating coupled with stirring and microwave irradiation. At the first attempts, the oxidation of **9a** was explored in the presence of *β*-CD in water/acetone (86:14) or non-solvent [32, 33] however unfortunately the oxidation unsuccessfully employing (entries 1 and 2 in Table 2). For synthesis in common solvents including acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide, tetrahydrofuran and chloroform, microwave irradiation showed almost high yields compared with the common heating. Amongst the selected solvents, reaction in

160 acetonitrile with 1.5 molar equivalent of IBX exhibited the highest isolated yield of
161 70% under microwave irradiation in 20 min.

162 **Table 2**. Exploring conditions for the oxidation of 4-methyl-5-nonanone, **9a** using IBX



163

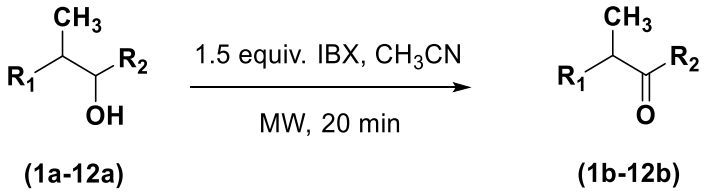
Entry	Solvent	Condition	Yield (%)[a]
1	β-CD in water/acetone	Reflux, stirred, 24h	trace
2	No solvent	MW, 20 min	15
2	Acetone	Reflux, stirred, 6h	40
3	Acetone	MW, 20 min	50
5	DMF	Reflux, stirred, 6h	30
6	DMF	MW, 20min	51
7	CH_3CN	Reflux, stirred, 6h	51
8	CH_3CN	MW, 20 min	70
9	DMSO	Reflux, stirred, 6h	35
10	DMSO	MW, 20 min	40
11	THF	Reflux, Stirred, 6h	39
11	THF	MW, 20 min	38
12	$CHCl_3$	Reflux, Stirred, 6h	41
13	$CHCl_3$	MW, 20 min	34

[a]Isolated yield of pure product

164

165 The rapid microwave-assisted oxidation was explored for substrates of the
166 secondary alcohols **1a-12a** (table 3) under the same reaction conditions. Good yields of
167 the respective ketones **1d-12d** were obtained in all cases. Substrates with low length of
168 alkyl chain (**1d, 2d, 7d** and **8d**) showed slightly lower isolated yields compared to that
169 of long chain length. It can be due to high evaporation of ketones with low molecular
170 weight.

171 Table 3. Microwave-Assisted Synthesis of adjacent methyl-branched ketones



(1a-12a) (1b-12b)

No.	Com.	R_1	R_2	Products	Yield (%)[a]
1	**1a**	C_2H_5	C_2H_5	**1b**	56
2	**2a**	C_2H_5	C_3H_7	**2b**	54
3	**3a**	C_2H_5	C_4H_9	**3b**	60
4	**4a**	C_2H_5	C_6H_{13}	**4b**	60
5	**5a**	C_2H_5	C_7H_{15}	**5b**	70
6	**6a**	C_2H_5	C_8H_{17}	**6b**	73
7	**7a**	C_3H_7	C_2H_5	**7b**	64
8	**8a**	C_3H_7	C_3H_7	**8b**	63
9	**9a**	C_3H_7	C_4H_9	**9b**	75
10	**10a**	C_3H_7	C_6H_{13}	**10b**	74
11	**11a**	C_3H_7	C_7H_{15}	**11b**	80
12	**12a**	C_3H_7	C_8H_{17}	**12b**	82

[a]Isolated yield of pure product

Conclusion

In conclusion, a straightforward, effective and low-cost synthetic strategy has been uncovered for pheromones of α-methyl alcohols which have a particular meaning for large-scale application of pheromone in IPM. The α-methyl alcohols with two different diastereomer rate (*threo: erythro* = 2:1 and 1:1) have been prepared through addition of nucleophiles into α-methyl carbonyl group. No effect of alkyl chain lenth on stereoselectivity of Felkin-Anh adduct has been demonstrated for synthesis of α-methyl alcohols. The secondary ketones were simply synthesized via oxidation of respective alcohols using IBX under microwave-assisted condition in 20 min. In a further work, these analogs will be screened to find new insect attractants.

References

1. Tewari, S., Leskey, T.C., Nielsen, A.L., Piñero, J.C., Rodriguez-Saona, C.R. Use of pheromones in insect pest management, with special attention to weevil

pheromones. *in* Ed. Abrol, D.P. *Integrated Pest Management: Current Concepts and Ecological Perspective*. California, CA, Elsevier Inc. 2014, 141–168. Doi: 10.1016/B978-0-12-398529-3.00010-5

2. Dang, C.H.; Nguyen, C.H.; Im, C.; Nguyen, T. D. Synthesis and application of pheromones for integrated pest management in Vietnam. *in* Ed. Gill, H. *Integrated Pest Management (IPM): Environmentally Sound Pest Management*, INTECH publisher, **2016**, 103-127. doi: 10.5772/63768
3. Nguyen, T.D.; Nguyen, C.H.; Im, C., Dang, CH. *Chem. Nat. Compd.*, **2016**, *52* (5), 877-879. doi: 10.1007/s10600-016-1800-7
4. Yew, J. Y.; Chung, H. *Prog. Lipid Res.*, **2015**, *59*, 88-105. Doi: 10.1016/j.plipres.2015.06.001
5. Hallett, R. H.; Gries, G.; Gries, R.; Borden, J. H.; Czyzewska, E.; Oehlscnlager, A. C.; Pierce, Jr. H. D.; Angerilli, N. P. D.; Rauf, A. *Naturwissenschaften* **1993**, *80*, 328-331. doi: 10.1007/BF01141908
6. Gunawardena, N. E.; Herath, H.M.W.K.B. *J. Natn. Sci. Coun. Sri Lanka* **1995**, *23*, 81-86.
7. Perez, A. L.; Hallett, R. H.; Gries, R.; Gries, G.; Oehlschlager, A. C.; Borden, J. H. *J. Chem. Ecol.* **1996**, *22*, 357-368. doi: 10.1007/BF02055104
8. Oehlschlager, A.C.; Prior, R.N.; Perez, AL; Gries, R; Gries, G; Pierce, HD Jr, Laup, S. *J. Chem. Ecol.* **1995**, *21*, 1619-1629. doi: 10.1007/BF02035156.
9. Pearce, G.T.; Gore, W.E.; Sivelstein, R.M.; Peacock, J.W.; Cuthbert, R.A.; Lanier, G.N.; Simeone, J.B. *J. Chem. Ecol.* **1975**, *1*, 115-124. Doi: 10.1007/BF00987724
10. Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.*, **1968**, *18*, 2199-2204. Doi: 10.1016/S0040-4039(00)89719-1

11. Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.*, **1987**, *109*, 3353-3361. Doi: 10.1021/ja00245a027
12. Pattison, G. *Beilstein J. Org. Chem.* **2017**, *13*, 2915–2921. doi:10.3762/bjoc.13.284
13. McCune, C. D.; Beio, M. L.; Friest, J. A.; Ginotra, S.; Berkowitz, D. B. *Tetrahedron Lett.*, **2015**, *56*, 3575-3579. doi: 10.1016/j.tetlet.2015.02.122
14. Othman, R. B.; Fer, M. J.; Corre, L. L.; Calvet-Vitale, S.; Gravier-Pelletier, C. *Beilstein J. Org. Chem.* **2017**, *13*, 1533–1541. Doi: 10.3762/bjoc.13.153
15. Umezu, S.; Shindo, M. *Tetrahedron Lett.*, **2013**, *54*, 6871-6873. doi: 10.1016/j.tetlet.2013.10.027
16. Piotrowska, D. G.; Glowacka, I. E.; Wroblewski, A. E.; Lubowiecka, L. Synthesis of nonracemic hydroxyglutamic acids, *Beilstein J. Org. Chem.* **2019**, *15*, 236–255. Doi: 10.3762/bjoc.15.22.
17. Omura, K.; Swern, D. *Tetrahedron*. **1978**, *34* (11), 1651–1660. doi:10.1016/0040-4020(78)80197-5
18. Carroll, A.W.; Willis, A.C.; Hoshino, M.; Kato, A.; Pyne, S.G. *J. Nat. Prod.*, **2019**, *82*, 358-367. doi: 10.1021/acs.jnatprod.8b00879
19. Guo, T.; Gao, Y.; Li, Z.; Liu, J.; Guo, K. *Synlett*, **2019**, *30* (3), 329-332. Doi: 10.1055/s-0037-1611183
20. Tanabe, S.; Kobayashi, Y. Org. Biomol. Chem., **2019**, *17*, 2393-2402. Doi: 10.1039/C8OB03196G
21. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.*, **1946**, 39-45. Doi: 10.1039/JR9460000039

22. Einterz, R. M.; Ponder, J. W.; Lenox, R. S. *J. Chem. Educ.***1977**, 54, 382-383. Doi: 10.1021/ed054p382

23. Dang, C.H.; Le, V.D.; Nguyen, C.H.; Nguyen T.D. *Arkivoc*, **2017**, *2017* (v), 187-195. Doi: 10.24820/ark.5550190.p010.271

24. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48* (22), 4155–4156. Doi: 10.1021/jo00170a070

25. Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron*, **2004**, *60*, 2131-2135. Doi: 10.1016/j.tet.2003.12.056

26. Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303-4306. Doi: 10.1021/ol048210u

27. Bartlett, S. L.; Beaudry, C. M. *J. Org. Chem.* **2011**, *76*, 9852-9855. Doi: 10.1021/jo201810c

28. Zada, A.; Ben-yehuda, S.; Dunkelblum, E.; Harel, M.; Assael, F.; Mendel, Z. *J. Chem. Ecol.*, **2004**, *30*, 631-641. Doi: 10.1023/B:JOEC.0000018634.94866.5b

29. Shumway, W.; Ham, S.; Moer, J.; Whittlesey, B. R.; Birney, D. M. *J. Org. Chem.* **2000**, *65*, 7731-7739. Doi: 10.1021/jo0002644

30. Felkin, H.; Gault Y.; Roussi, G. *Tetrahedron*, **1970**, *26*, 3761 - 3778. Doi: 10.1016/S0040-4020(01)92953-9

31. Cram, D. J.; Elhafes, F. A. A. *J. Am. Chem. Soc.* **1953**, *74*, 5828-5835. Doi: 10.1021/ja01143a007

32. Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058-2059. Doi: 10.1021/jo026751w

33. Moorthy, J. N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Lett.*, **2004**, *45*, 5419–5424. Doi: 10.1016/j.tetlet.2004.05.044

258