Journal Pre-proofs

A facile and efficient method for synthesis of β-iodocarboxylates from terminal epoxides

Ye-Fu Zhu, Bo-Le Wei, Wen-Qiong Wang, Li-Jiang Xuan

PII: S0040-4039(19)31144-X
DOI: https://doi.org/10.1016/j.tetlet.2019.151353
Reference: TETL 151353

To appear in: *Tetrahedron Letters*

Received Date: 28 August 2019
Revised Date: 17 October 2019
Accepted Date: 1 November 2019

Please cite this article as: Zhu, Y-F., Wei, B-L., Wang, W-Q., Xuan, L-J., A facile and efficient method for synthesis of β-iodocarboxylates from terminal epoxides, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151353

A facile and efficient method for synthesis of β-iodocarboxylates from terminal epoxides

Ye-Fu Zhu[a,b], Bo-Le Wei[a,b], Wen-Qiong Wang[a] and Li-Jiang Xuan[a,*]

Affiliation

[a]State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 501 Haike Road, Zhangjiang Hi-Tech Park, Shanghai 201203, PR China.

[b]University of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, PR China.

*Corresponding to: Li-Jiang Xuan; Tel: +86-21-20231968, Fax: +86-21-20231968, E-mail address: ljxuan@simm.ac.cn.

Abstract

A facile and efficient method has been developed for synthesis of β-iodocarboxylates in the presences of Ph_3P/I_2. Starting from epoxides, a series of β-iodocarboxylate compounds can be directly obtained in toluene media with excellent yields. Moreover, the method was successfully applied for the late-stage modification of natural products, such as isosteviol and vincamine derivatives, achieving the corresponding β-iodocarboxylates in good yields.

Key words: epoxides, Ph_3P, I_2, β-iodocarboxylates

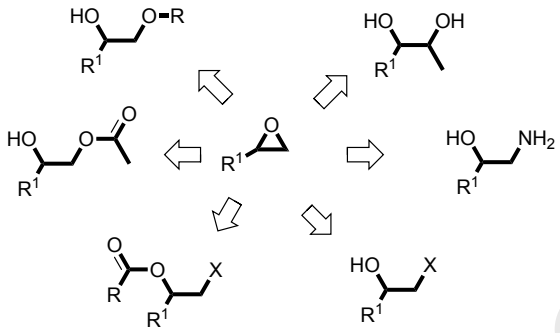
Introduction

Epoxides are a class of compounds of growing importance, which have extensive application in many fields, such as medicine [1], pesticides [2], food [3], dyestuff [4] and plastic [3b, 5]. They are used as versatile building blocks in organic synthesis due to their advantages of easy preparation, scale-up feasibility and tolerance to a broad range of conditions[6]. Thus, a wide spectrum of reactions using epoxides have been well-established, such as ring opening reaction [7], cycloaddition reaction [8], polymerzation reaction [9], oxidation reaction and reduction reaction [10].

The synthetic significance of epoxides stems largely from their facile and stereospecific nucleophilic ring opening to furnish valuable 1, 2-difunctional compounds (Scheme 1) [11]. These versatile synthetic building blocks include but are not limited to 1,2-diols [12], β-amino alcohols [7b, 11c, 13], β-alkoxy alcohols [12, 14], β-acetoxy alcohols [12, 14f, 15], β-halohydrins [16] and halohydrin esters [17].

Although numerous synthesis of chlorocarboxylates [18] and bromocarboxylate [17] esters have been reported by the nucleophilic ring opening of epoxdides, little work was focused on the selective ring opening to afford corresponding β-iodocarboxylates. The only example directly from epoxides, as far as we know, is the preparation of acyliodine, a dangerous and inconvenient reagent with low yield [19]. Considering the great importance of β-iodocarboxylates for the synthesis of

lipids [20] and biologically active compounds [21], a prompt method to this building block is extremely needed. Inspired by previous work [17,18b], we herein report an immediate epoxide ring opening reaction promoted by Ph_3P/I_2 with good yields and high selectivity.



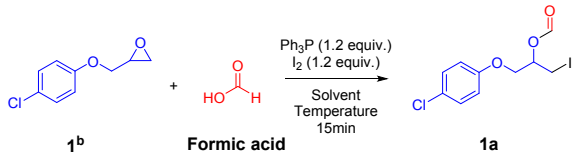
Scheme 1. Common strategies for the synthesis of difunctional products from epoxides.

Triphenylphosphine (Ph_3P) has been used as a versatile reagent in a number of functional group transformations due to its inexpensiveness, affordability, and reactivity. Considering the special properties of Ph_3P-I_2 intermediate, we assumed that phosphorous atom may have an important influence on this ring opening reaction. To validate the feasibility of this hypothesis, we have initially investigated the ring opening reaction by using compound 1 and iodine as the substrate, Ph_3P as ligand, formic acid as carbon resource. After stirring for 15 min at 80 °C in $CHCl_3$, the expected product 1a was obtained in 78% yield (Table 1, entry 1). This result clearly indicated that the synthetic route of iodo-formate was reasonable and feasible. In an attempt to improve the yield of 1a, the model reaction was carried out under various conditions (Table 1).

Preliminary experiments suggested that solvent effect had a significant impact on the yield of 1a. Hence, various solvents were applied to the ring opening reaction. According to the results, toluene gave the best isolated yield at 82% (Table 1, entries 1-9). Further adjustment of temperature exhibited dramatic drop in the yields with decrease of heat (Table 1, entries 3, 9-11). After the investigation of the other factors, including the amount of Ph_3P, iodine and formic acid (see ESI), the optimal

conditions were finally established as heating the epoxide with slightly extra amount of Ph_3P, I_2, and formic acid (105 mol%) in toluene for 15 min.

Table 1. Optimization of the reaction conditions[a]

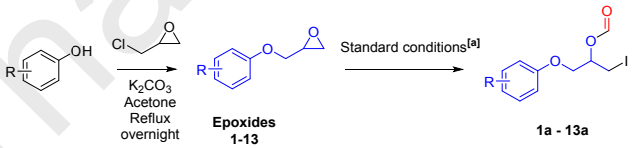


1[b] Formic acid 1a

Entry	Solvent	Temp (°C)	Yield[c] (%)
1	$CHCl_3$	80	78
2	THF	80	ND[d]
3	Toluene	80	98(82)
4	1,4-dioxane	80	91
5	Acetone	80	34
6	CH_3CN	80	93
7	DMF	80	87
8	DCM	80	95
9	Tol	60	94
10	Tol	40	71
11	Tol	20	52

[a] Reaction conditions: Epoxides 1 (1 mmol), Ph_3P (1.2 mmol), I_2 (1.2 mmol), formic acid (4 mmol), toluene (2 mL), all reactions were carried out with solvent (2 mL) in a 35 mL sealed tube (total volume 50 mL) for 15 min. [b] Substituted epoxide 1 were made by epichlorohydrin (meso), K_2CO_3 and 4-chlorophenol. [c] Yields were determined by LC-MS, the number in parentheses refers to the yield of isolated 1a. [d] Not detected.

Table 2. Reactions of substituted epoxides with formic acid.



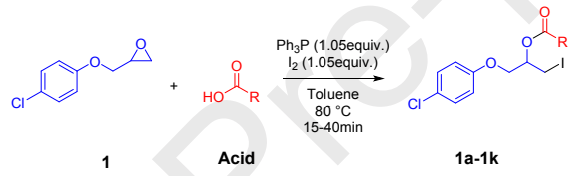
Entry	Epoxides[b](R)	Products	Yield[c](%)
1	**1**(4-Cl)	**1a**	82
2	**2**(4-H)	**2a**	81
3	**3**(4-NO_2)	**3a**	85
4	**4**(4-OMe)	**4a**	80
5	**5**(4-^{t}Bu)	**5a**	80
6	**6**(2-Cl)	**6a**	86
7	**7**(2-Me)	**7a**	85
8	**8**(3,4-OMe)	**8a**	80
9	**9**(3-OMe)	**9a**	78
10	**10**(2-^{i}Pr)	**10a**	81
11	**11**(4-Ph)	**11a**	82
12	**12** 	**12a**	75

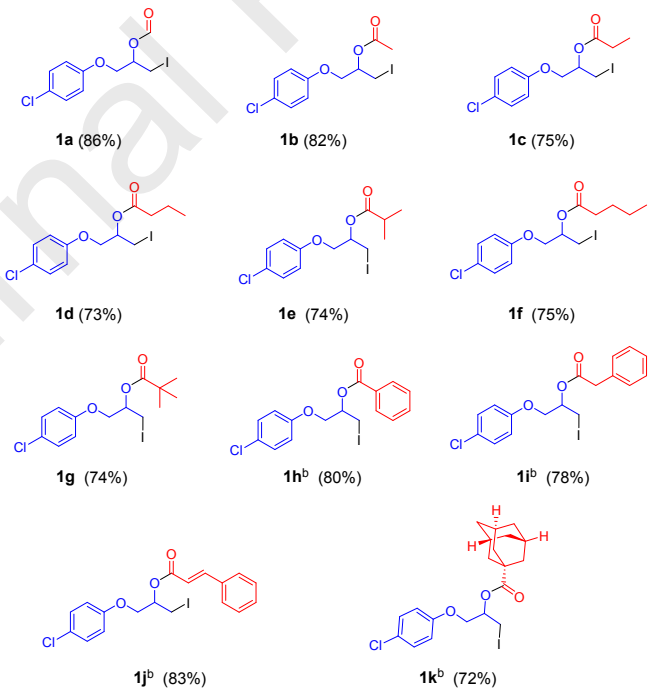
13	**13**		**13a**	77

[a] Standard conditions: Epoxides (1 mmol), Ph_3P (1.05 mmol), I_2 (1.05 mmol), formic acid (1.05 mmol), toluene (2 mL), 80 °C, 15min. [b] Substituted epoxides in this table were made by epichlorohydrin (meso), K_2CO_3 and the corresponding phenol. [c] Isolated yields.

We next studied the scope of this ring opening reaction by using a series of differently substituted epoxides under the selected conditions [22]. As shown in Table 2, ortho, meta and para substituted aromatics were chosen to further explore the steric hindrance and electronic effects. The desired products 1a-10a were obtained in good yields ranging from 78% to 86%, which indicated that these factors have low influence on the reaction. Naphthol and biphenyl derivatives were further used to extend the scope of the reaction, with yields of 75% - 82% (Table 2, entries 11-13).

Table 3. Reactions of different carbonxylic acids with 1.

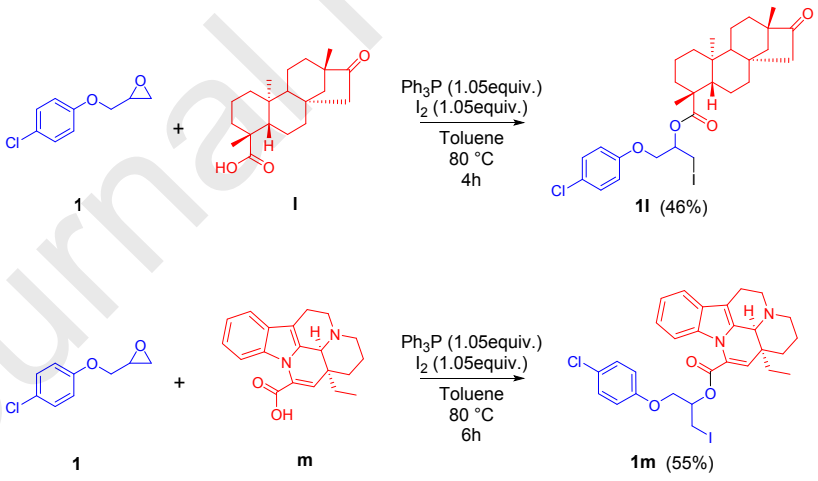




[a] Reaction conditions: Epoxides **1** (1 mmol), Ph_3P (1.05 mmol), I_2 (1.05 mmol), corresponding acid (1.05 mmol), toluene (2 mL) in sealed tube, 80 °C, 15min. [b] The reaction proceeded for 40min. [c] Isolated yields.

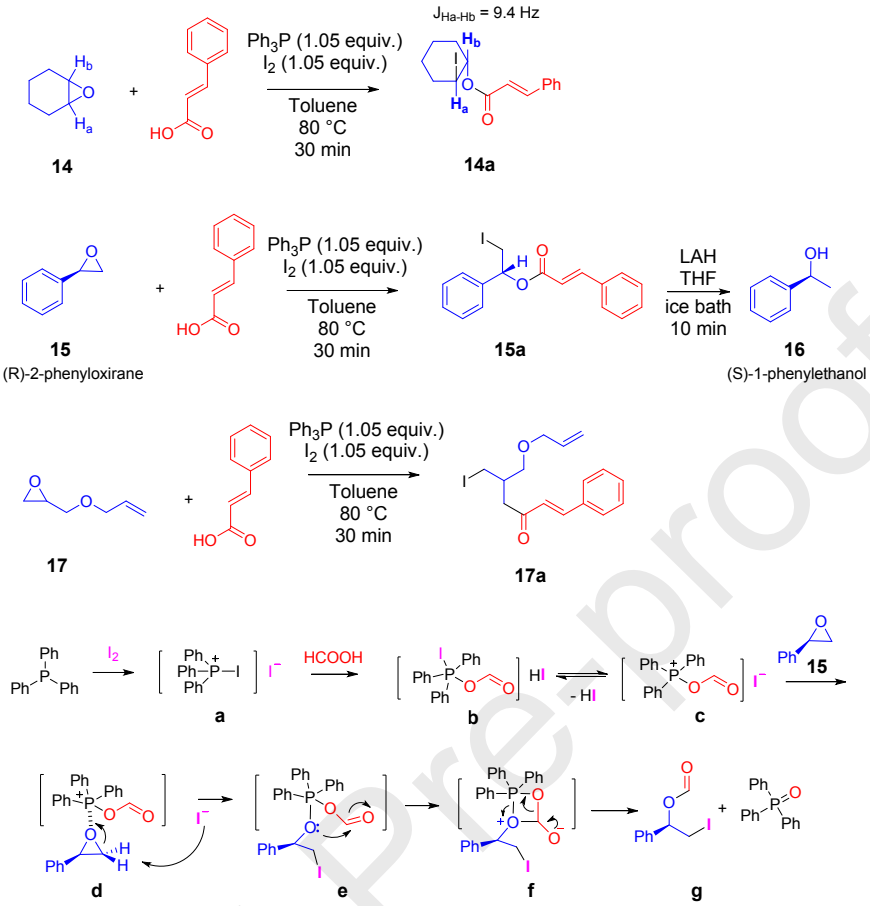
To further broaden the scope of the reaction, serials of carboxylic acids were also examined as the resource of acyl groups. Both aromatic and aliphatic acids proceeded smoothly to give the corresponding products in good to excellent yields (72% - 86%, Table 3). Even, to our delight, the steric pivalic acid and 1-adamantanecarboxylic acid also produced the β-iodocarboxylates 1g and 1k with 74% and 72% yields, respectively. Since the concept of late-stage diversification, especially on natural products, by predictable and efficient transformations is absolutely crucial for fine-tuning the biological activity [23], we therefore examined the robustness of this transformation on certain natural products. With extended reaction time, the epoxide ring opening reaction was successfully implemented on isosteviol and vincamine though with moderate yields (Scheme 2). The tolerance to several sensitive functional groups has indicated its potential application in the late-stage diversification of natural products and medicinal substrates and some drug molecules that containing carboxylic acid can be also applied in this reaction for prodrug modification.

Scheme 2. Reactions of **1** with natural products.



To reveal the stereoselectivity and mechanism of this ring opening reaction, two parallel reactions were carried out under the optimal conditions (**Scheme 3**).

Scheme 3. Reaction substrate expansion and mechanism speculation.



To be specific, **14a**, prepared from cyclohexene oxide (**14**), was determined as trans formation according to the coupling constant (*J*) between H_a and H_b and the yield of this reaction is 52%. On the other hand, **15a**, prepared from (R)-2-phenyloxirane (65% yield), was reduced by LAH to resolve (S)-1-phenylethanol (**16**), the absolute configuration of which was confirmed by optical rotational activity spectrum according to the comparison with authentic substrates in database [24]. What's more, we used compound 17 as the epoxide to get the desired product 17a with 62% yield. These results indicated the chiral center of alcohol that attached to the acyl group maintained and the iodine nucleophilic attack happened on the other side of epoxides. Based on these observations, a plausible mechanism for the formation of β-iodoformate is proposed in **Scheme 3**. An initial reaction between Ph_3P and iodine provides triphenylphosphonium iodide as reactive species. Nucleophilic displacement of these intermediates by the formic acid could afford **b**. Withdrawal of hydroiodic

acid leads to the generation of intermediate **c**, which next forms complex pair **d** between the electron-deficient phorsphorus atom and the electron-rich oxygen atom. The facial attack by iodine anion followed by trans-esterification finally delivers β-iodocarboxylate (**g**) and triphenylphosphine oxide.

Conclusions

In conclusion, we have developed a straightforward and efficient procedure for the synthesis of β-iodocarboxylates from the corresponding epoxides and acids via a ring opening process with good to excellent yields. The procedures were successfully applied in natural products isosteviol and vincamine diversificaiton to obtain corresponding products. The mild conditions, short reaction time, and generality of substrates would distinguish current transformation from the known synthesis of halohydrin esters.

Conflict of interest

All of the authors have no conflicts of interest to declare.

Acknowledgements

We gratefully acknowledge grants from the State Key Laboratory of Drug Research (SIMM1601ZZ-03), the National Natural Science Foundation of China (No. 81602995 and 21702219) and the Drug Innovation Major Project of China (Grant Nos. 2018ZX09735001-002-005).

References

[1] (a) S. K. Das, Asian. J. Org. Chem. 6 (2017) 243-256;
(b) E. A. Larin, Y. M. Atroshchenko, ARKIVOC (2016) 217-226.

[2] (a) P. Xiao, T. Mori, I. Kamei, R. Kondo, FEMS Microbiol. Lett. 314 (2011) 140-146;

(b) H. Glatt, R. Jung, F. Oesch, Mutat. Res. 111 (1983) 99-118.

[3] (a) K. Lee, A. M. Herian, T. Richardson, J. Food. Protect. 47 (1984) 340-342;
(b) M. R. Philo, A. P. Damant, L. Castle, Food Addit. Contam. 14 (1997) 75-82;
(c) J. M. do Carmo, A. A. da Silva, J. Morgan, Y. X. Wang, S. Munusamy, J. E. Hall, Nutr. Metab. Cardiovasc. Dis. 22 (2012) 598-604.

[4] (a) J. E. Klee, W. H. Meyer, Polym. Bull. 31 (1993) 659-664;
(b) D. Ross, L. E. Locascio, Anal. Chem. 75 (2003) 1218-1220.

[5] A. S. Wronski, T. V. Parry, J. Mater. Sci. 17 (1982) 2047-2055.

[6] (a) R. E. Parker, N. S. Isaacs, Chem. Rev. 59 (1959) 737-799;
(b) J. G. Smith, Synthesis-Stuttgart 8 (1984) 629-656;
(c) A. P. S. S. Murphree, ARKIVOC (2005) 6-33;
(d) H. Lin, J. Y. Liu, H. B. Wang, A. A. Q. Ahmed, Z. L. Wu, J. Mol. Catal. B-Enzym 72 (2011) 77-89.

[7] (a) I. Paterson, D. J. Berrisford, Angew. Chem. Int. Ed. 31 (1992) 1179-1180;
(b) D. M. Hodgson, A. R. Gibbs, G. P. Lee, Tetrahedron 52 (1996) 14361-14384;
(c) J. A. Ciaccio, M. Smrtka, W. A. Maio, D. Rucando, Tetrahedron Lett. 45 (2004) 7201-7204.

[8] (a) M. Tu, R. J. Davis, J. Catal. 199 (2001) 85-91;
(b) A. Decortes, A. M. Castilla, A. W. Kleij, Angew. Chem. Int. Ed. Engl. 49 (2010) 9822-9837;
(c) F. Castro-Gomez, G. Salassa, A. W. Kleij, C. Bo, Chemistry (Easton) 19 (2013) 6289-6298.

[9] (a) T. Sakai, N. Kihara, T. Endo, Macromolecules 28 (1995) 4701-4706;
(b) R. M. Thomas, P. C. Widger, S. M. Ahmed, R. C. Jeske, W. Hirahata, E. B. Lobkovsky, G. W. Coates, J. Am. Chem. Soc. 132 (2010) 16520-16525;
(c) D. J. Darensbourg, A. D. Yeung, Polym. Chem. 5 (2014) 3949-3962.

[10] (a) E. L. Eliel, M. N. Rerick, J. Am. Chem. Soc. 82 (1960) 1362-1367;

(b) T. V. Rajanbabu, W. A. Nugent, M. S. Beattie, J. Am. Chem. Soc. 112 (1990) 6408-6409.

[11] (a) E. N. Jacobsen, Acc. Chem. Res. 33 (2000) 421-431;

(b) H. Sharghi, M. A. Nasseri, K. Niknam, J. Org. Chem. 66 (2001) 7287-7293;

(c) T. Ollevier, G. Lavie-Compin, Tetrahedron Lett. 45 (2004) 49-52;

(d) Y. Sarazin, J.-F. Carpentier, *Chem. Rev.* 115 (2015) 3564-3614.

[12] M. Moghadam, S. Tangestaninejad, V. Mirkhani, I. Mohammadpoor-Baltork, S. A. Taghavi, Catal. Commun. 8 (2007) 2087-2095.

[13] (a) R. A. Slater, W. Howson, G. T. Swayne, E. M. Taylor, D. R. Reavill, J. Med. Chem. 31 (1988) 345-351;

(b) A. N. Boa, S. Clark, P. R. Hirst, R. Westwood, Tetrahedron Lett. 44 (2003) 9299-9302;

(c) K. Kopka, S. Wagner, B. Riemann, M. P. Law, C. Puke, S. K. Luthra, V. W. Pike, T. Wichter, W. Schmitz, O. Schober, Bioorg. Med. Chem. 11 (2003) 3513-3527;

(d) A. K. Chakraborti, S. Rudrawar, A. Kondaskar, Org. Biomol. Chem. 2 (2004) 1277-1280;

(e) G. Huerta, G. Contreras-Ordoñez, C. Alvarez-Toledano, V. Santes, E. Gómez, R. A. Toscano, Synth. Commun. 35 (2004) 2393-2406;

(f) F. Carree, R. Gil, J. Collin, Org. Lett. 7 (2005) 1023-1026;

(g) R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, S. Agrawal, R. V. Jasra, Tetrahedron-Asym. 17 (2006) 1638-1643;

(h) K. Tanaka, S. Oda, M. Shiro, Chem. Commun. 44 (2008) 820-822;

(i) G. Moura-Letts, J. Lizza, Synthesis 49 (2016), 1231-1242;

(j) F. A. Saddique, A. F. Zahoor, S. Faiz, S. A. R. Naqvi, M. Usman, M. Ahmad, Synth. Commun. 46 (2016) 831-868.

[14] (a) M. Lautens, K. Fagnou, M. Taylor, Org. Lett. 2 (2000), 1677-1679;

(b) J. Barluenga, H. Vazquez-Villa, A. Ballesteros, J. M. Gonzalez, Org. Lett. 4 (2002), 2817-2819;

(c) V. Mirkhani, S. Tangestaninejad, B. Yadollahi, L. Alipanah, Tetrahedron 59 (2003) 8213-8218;

(d) M. Moghadam, S. Tangestaninejad, V. Mirkhani, R. Shaibani, Tetrahedron 60 (2004), 6105-6111;

(e) R. V. Yarapathi, S. M. Reddy, S. Tammishetti, React. Funct. Polym. 64 (2005) 157-161;

(f) H. Firouzabadi, N. Iranpoor, A. A. Jafari, S. Makarem, J. Mol. Catal. A-Chem. 250 (2006) 237-242.

[15] G. Salvador, T. Mercedes, O. Natalia, W. Richard, P. Margarita, Eur. J. Org. Chem. 2004 (2010) 2160-2165.

[16] (a) G. Palumbo, C. Ferreri, R. Caputo, Tetrahedron Lett. 24 (1983), 1307-1310;

(b) R. Caputo, C. Ferreri, S. Noviello, G. Palumbo, Synthesis 17 (1986) 499-501.

[17] (a) N. Iranpoor, H. Firouzabadi, M. Chitsazi, A. Ali Jafari, Tetrahedron 58 (2002) 7037-7042;

(b) N. Iranpoor, H. Firouzabadi, A. Jamalian, Tetrahedron 62 (2006) 1823-1827.

[18] (a) N. Azizi, B. Mirmashhori, M. R. Saidi, Catal. Commun. 8 (2007) 2198-2203;

(b) L. P. Nielsen, C. P. Stevenson, D. G. Blackmond, E. N. Jacobsen, J. Am. Chem. Soc. 126 (2004) 1360-1362.

[19] K. Nakano, S. Kodama, Y. Permana, K. Nozaki, Chem. Commun. 41 (2009) 6970-6972.

[20] (a) J. D. Schmitt, A. B. Nixon, A. Emilsson, L. W. Daniel, R. L. Wykle, Chem. Phys. Lipids. 62 (1992) 263-268;

(b) J. R. Williams, J. C. Boehm, Steroids 60 (1995) 699-708.

[21] (a) K. G. Watson, Y. M. Fung, M. Gredley, G. J. Bird, W. R. Jackson, H. Gountzos, B. R. Matthews, J. Chem. Soc. Chem. Commun. 15 (1990) 1018-1019;

(b) P. J. Walsh, Y. L. Bennani, K. B. Sharpless, Tetrahedron Lett. 34 (1993) 5545-5548;

(c) M. Kapoor, N. Anand, K. Ahmad, S. Koul, S. S. Chimni, S. C. Taneja, G. N. Qazi, Tetrahedron Asymmetry 16 (2005) 717-725.

[22] (a) J. L. Wright, T. F. Gregory, T. G. Heffner, R. G. MacKenzie, T. A. Pugsley, S. V. Meulen, L. D. Wise, Bioorg. Med. Chem. Lett. 7 (1997) 1377-1380;

(b) R. W. Marquis, A. M. Lago, J. F. Callahan, R. E. L. Trout, M. Gowen, E. G. DelMar, B. C. Van Wagenen, S. Logan, S. Shimizu, J. Fox, E. F. Nemeth, Z. Yang, T. Roethke, B. R. Smith, K. W. Ward, J. Lee, R. M. Keenan, P. Bhatnagar, J. Med. Chem. 52 (2009) 3982-3993.

[23] J. Wencel-Delord, F. Glorius, Nat. Chem. 5 (2013) 369-375.

[24] (a) C. Holec, K. Neufeld, J. Pietruszka, Adv. Synth. Catal. 358 (2016) 1810-1819;

(b) V. Bodai, L. Nagy-Gyor, R. Ouml; Rkenyi, Z. Molnar, S. Kohari, B. Erdelyi, Z. Nagymate, C. Romsics, C. Paizs, L. Poppe, G. Hornyanszky, J. Mol. Catal. B-Enzym. 134 (2016) 206-214;

(c) A. Kišić, M. Stephan, B. Mohar, Adv. Synth. Catal. 357 (2015) 2540-2546.

- We developed a facile and efficient method for the synthesis of β-iodocarboxylates.
- The reaction was proceeded in the presence of Ph_3P and I_2.
- β-iodocarboxylate compounds are directly obtained with excellent yields.
- This method was applied successfully for the late-stage modification of natural products.