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Chemoselective bromination of dienoates

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Abstract: A variety of tetra-, di- and monobromo derivatives of dienoates were prepared from parent polyunsaturated esters under mild conditions. According to proposed protocol the target bromoesters were easily obtained as a rule in good yields and high selectivity.

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Keywords: dienoates • halogenation • selectivity

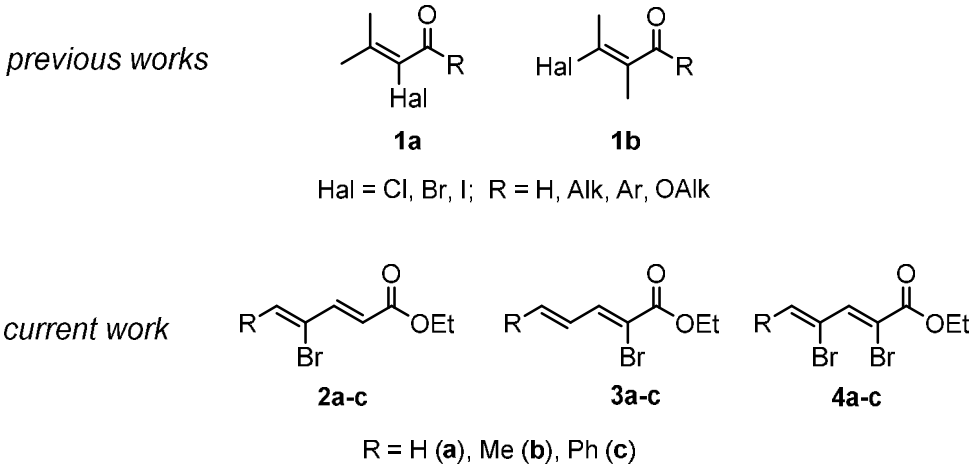
Introduction

The development of efficient and selective methods for the construction of complex molecules is a major challenge to organic chemists and is one of the principal goals of modern organic chemistry. The aim is no only to build the target molecule but to build it well. As is known, a synthetic chemist having no required reagents is like an artist without paints.[1] Therefore, it is an important task for chemists to find readily available and highly functionalized starting materials that can be easily transformed into target derivatives. Although these compounds look often structurally quite simple, their selective synthesis sometimes remains a serious problem.

Halogenated α,β-unsaturated carbonyl bearing compounds are versatile building blocks.[2-4] Being polyfunctional substrates these compounds have found a wide range of applications in organic synthesis. It is not surprising that very often they use as initial reagents in a one-pot fashion cascade assembly of bioactive and pharmaceutical compounds as well as analogs of natural substances. For example, the recently demonstrated reactivity of α-bromoenoates and fluorinated α-bromoenones has open unusual and often unpredictable transformations. These compounds were successfully employed as a starting material in the assembly of carbo- (condensed and spiro) and heterocycles which are difficult or even impossible to obtain in another way.[5-8]

To date the considerable attention has been focused on the α- or β-halo-α,β-unsaturated carbonyl derivatives **1a,b** – haloenals, haloenones, and haloenoates bearing only one conjugated double bond (Scheme 1). However, the development of efficient and highly selective method for the preparation of mono- or polyhalogenated 1,3-dienes bearing a conjugated carbonyl group **2-4** is more intriguing, and perhaps, more fundamental challenge. These conjugated 1,3-diene patterns are regarded as principal structural units which were found in molecules of numerous natural products and derivatives having various biological activities as well as in macrocyclic polyenes.[9,10] The behavior of simple dienes towards bromine has been extensively studied and now this reaction has become a classical process which is discussed in University textbooks on organic chemistry. Motivated by polyelectrophilic character of dienic systems having electron-withdrawing group, we became interested in the development of general procedure for their preparation. In fact, the simultaneous presence in their molecules several functional groups – two conjugated double bonds, halogen atom and carbonyl moiety – make them attractive and useful tools in organic synthesis. Really, they can *a priori* react as Michael acceptors or dienes, dienophiles and dipolarophiles. This feature of these compounds increases their application in synthetic and medicinal chemistry and consequently stimulates the development of efficient methods for their selective preparation.

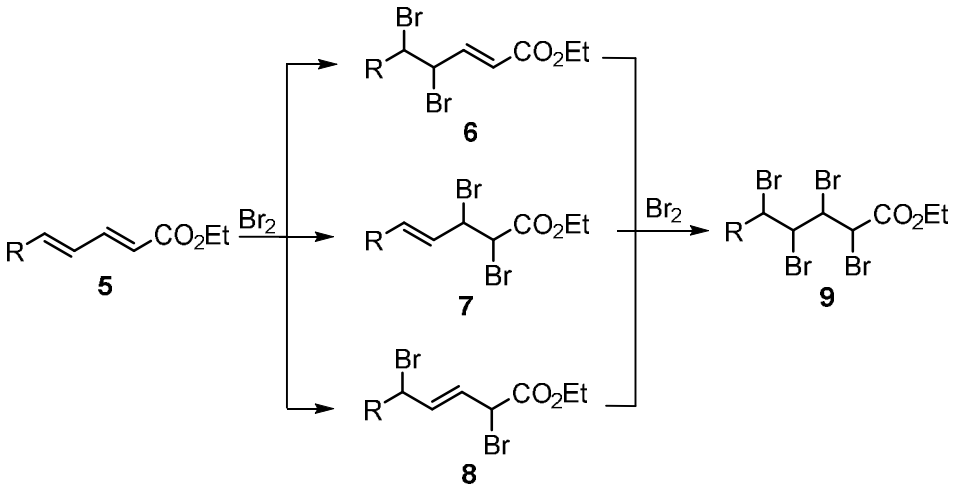
The syntheses of bromoenoates described so far are based on the commonly used methods, namely bromination – dehydrobromination of parent compounds by molecular bromine or different organobromine compounds as halogenating reagents.[11] As a continuation of our research in this field,[12] here we report an efficient synthetic procedure for the bromination of dienoates. Depending on the reaction conditions, we prepared mono- and dibromodienoates and their precursors in good to excellent chemo- and stereoselectivity.



Scheme 1. Halogenated unsaturated carbonyl-bearing compounds: previous and current work.

Results and discussion

Dienoates **5** can react with bromine *via* three different pathways: 4,5-, 2,3- or 2,5-addition modes leading to three chemoisomers **6**, **7** and **8**, correspondingly (Scheme 2). The addition of the second equivalent of bromine to enoates **6**-**8** must afford tetrabromoderivatives **9**. It is reasonable to assume that the result of bromination depends strongly on the nature of substituent R as well as the reaction conditions.



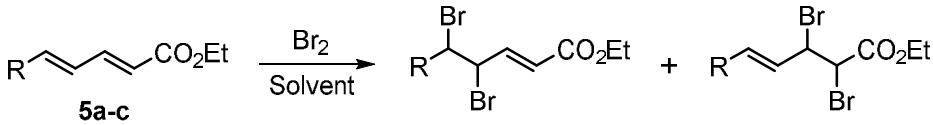
Scheme 2. Possible reaction pathways.

We first focused on the transformation of 2,4-dienoates **5** into dibromo derivatives. To evaluate the generality of this procedure and determine the influence of the structure of starting esters on the chemo- and stereoselectivity of bromination, non-substituted (**5a**), alkyl (**5b**) and aryl (**5c**) substituted dienoates were examined. We have found that the addition of bromine to selected dienoates is a rapid reaction taking place under mild reaction conditions. Thus, when

ethyl pentadienoate **5a** was treated with one equivalent of bromine in chloroform at room temperature, the dibromoenoate **6a** was only isolated in good yield (Table 1). The structure of synthesized dibromoester **6a** was assigned based on multinuclear 1D (^{1}H, ^{13}C) and 2D NMR, IR spectroscopy, mass-spectrometry and elemental analyses. Thus, both ^{1}H and ^{13}C NMR spectra revealed the presence of signals of only one double bond. For example, the doublet at 5.94 ppm (J = 15.4 Hz) and doublet of doublets at 6.75 ppm (J = 15.4, 9.4 Hz) are characteristic for *trans*-conjugate double bond. The new signals at 3.66 (dd), 3.84 (dd), and 4.61 (ddd) ppm in the ^{1}H NMR spectra confirm the presence of a pair of the moiety CH_2Br-CHBr. In the ^{13}C NMR spectrum only two signals in the field of olefinic carbons at 125.6 and 143.5 ppm were observed.

This result is in good agreement with the theoretical study. To understand the cause of high chemoselectivity of bromine addition and regarding this reaction as an electrophilic process, we carried out quantum chemical calculations of the Fukui index[13,14] for pentadienoate **5a**. Previous results on structurally related electron deficient olefins have shown that, in general, these parameters correlate well with the reactivity of similar systems.[15] According to these calculations, olefinic carbon C-2 and C-4 are the most probable centres of bromine electrophilic attack. In an effort to explain the preferential formation of 4,5-dibromoenoate **6a**, we determined the thermodynamic characteristics of all possible chemoisomers **6a**, **7a**, and **8a**. It was found that the 4,5-dibromoenoate **6a** is the thermodynamically most stable isomer. It is more stable than isomeric 2,3-dibromo penten-4-oate **7a** and 2,5-dibromoester **8a** for 11.7 kcal/mol and 11.0 kcal/mol, correspondingly (see, SI). Taking into account that the formation of the ionic intermediates was shown to be reversible, we concluded that the final formation of ester **6** is the most expected process. These results clearly explain the exclusive formation of adduct **6a** and absence of its isomers **7a** and **8a**.

Table 1 Bromination of **5a-c**.



R = H (**a**), Me (**b**), Ph (**c**)

entry	dienoate	brominating reagent	solvent	conditions	products, (yield, %)[a]	**6** (**7**), dr
1	**5a**	Br_2	$CHCl_3$	rt	**6a** (59)	-
2	**5b**	Br_2	$CHCl_3$	rt	**6b** (76) + **7b** (11)	23:77
3	**5b**	Br_2	$CHCl_3$	53°C	**6b** (67) + **7b** (8)	23:77
4	**5b**	Br_2	$CHCl_3$	-40°C	**6b** (72)	24:76
5	**5b**	Br_2	DCM	rt	**6b** (80)	33:67
6	**5b**	Br_2	CCl_4	rt	**6b** (87)	33:67
7	**5b**	Br_2	dioxane	10°C	**6b** (80)	40:60
8	**5b**	Br_2	AcOH	rt	**6b** (83)	0:100
9	**5b**	Br_2	TFA	rt	**6b** (62)	0:100
10	**5b**	Br_2	TFE	rt	**6b** (51)	11:89
11	**5b**	DPTBE	MeCN	rt	**6b** (20) + **7b** (11)	0:100
12	**5b**	HBr/oxone	AcOH	rt	**6b** (24) + **7b** (7)	0:100
13	**5c**	Br_2	$CHCl_3$	-60°C	**7c** (quant)	(33:67)
14	**5c**	Br_2	dioxane	rt	**7c** (quant)	(33:67)

[a] Isolated yield.

Having unambiguously established that the dibromo derivative **6a** has the structure of a 4,5-addition product with *E*-configuration of the residual double bond (as in the starting molecule **5a**), we assumed that dienoates **5b,c** react with bromine by the same pathway. However, in contrast with non-substituted dienoate **5a**, ethyl sorbate **5b** reacts with an equimolar quantity of bromine under the same conditions to give a (7:1) mixture of isomers **6b** and **7b** which can be easily separated by column chromatography (Table 1, entry 2). The structure of both isomers was undoubtedly established by 1D and 2D NMR spectra. Thus, olefinic proton C^5H= resonated as a doublet of quartets (J = 15.0 and 6.6 Hz) in the most low-frequency magnetic field (δ = 5.89 ppm). In contrast, the methine proton C^5H for isomeric derivative **6b** resonated at 4.17 – 4.38 ppm. The assignments of the configuration of the double bond and additional arguments on stereochemistry were easily achieved by the analysis of the coupling constants and ^1H – ^1H 2D homonuclear NOESY experiment (Fig. 1).

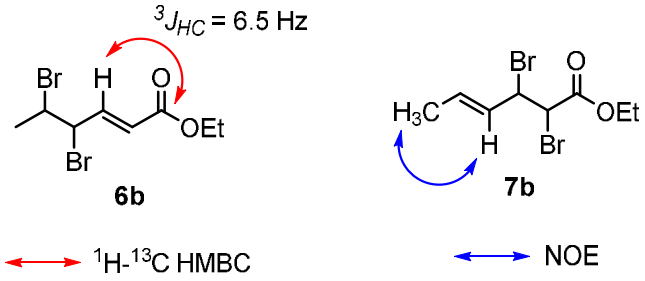
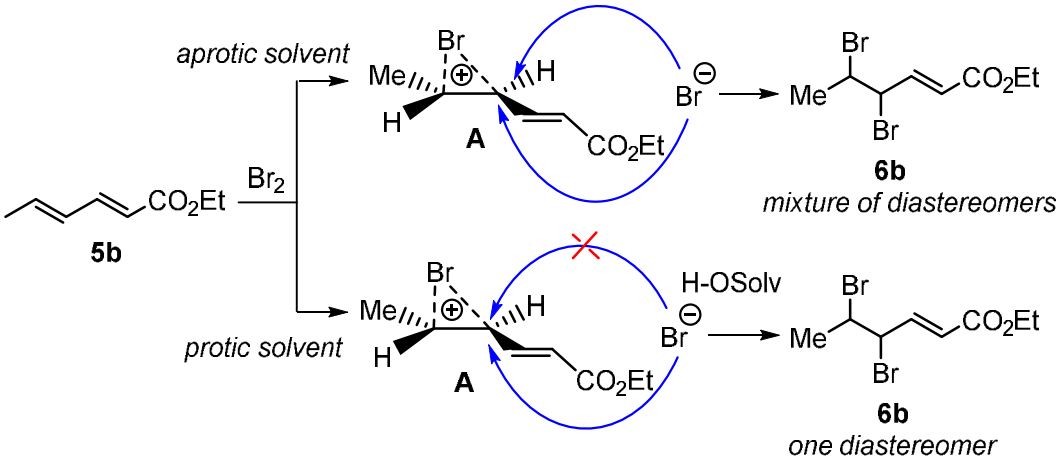


Figure 1. Main 2D correlations for compounds **6b** and **7b**.

The result obtained is not consistent with the previously described: the formation of dibromo derivatives **6b** and **8b** was reported when ethyl sorbate **5b** was treated with bromine in CCl_4 at 0°C.[16] However, authors were unable to isolate adduct **8b** and its structure seems to be wrongly deduced from its dehydrobromination reaction. Moreover, the structure of 2,3-dibromo-4-hexenoate was incorrectly determined.

When the reaction was performed at heating up to 53°C the mixture of both isomers **6b** and **7b** was also obtained. The lightly decreased yields of both reaction products can be explained by polymerization of either initial dienoate **5b** or dibromoenoates **6b** and **7b** (Table 1, entry 3). At the same time, when ethyl sorbate **5b** was treated with bromine under low temperature, the reaction proceeded chemoselectively and the isomer **6b** was isolated only in good yield (Table 1, entry 4). Generally, the nature of the solvent did not influence the direction of bromine addition: in both protic and aprotic solvents bromoester **6b** was the principle or even sole product for this reaction (Table 1, entries 5-10). But it should be noted that solvent-dependent stereochemistry of bromine addition was observed in this reaction. Thus, the reaction of ester **5b** with bromine in aprotic solvents such as DCM, chloroform, tetrachlorometane or dioxane is not stereoselective: in these cases dibromoenoate **6b** isolated as a mixture of two diastereomers in the ratio from 23:77 to 40:60. Surprisingly, when the same reaction was performed in acetic or trifluoroacetic acids as well as in fluorinated alcohol (such as TFE), the dibromo derivative **6b** was formed with high diastereoselectivity (up to 100%). This result can be explained in the term of the mechanism of bromination. Though relatively few data on the halogenation of conjugated dienes have been reported, the 1,2-addition of halogen is usually nonstereoselective[17] and strongly depend on the solvent nature.[18] Taking into account that electrophilic bromination of the double bond proceeds near exclusively as trans-addition via a bridged-ion, we hypothesized that the charge distribution in the bromonium ion **A** is not symmetric: the positive charge is preferentially located at the allylic carbon because the conjugate enoate moiety effectively stabilizes the partial positive charge on a neighboring carbon. This implies that the intermediate **A** is open to *syn* and *anti*-addition. In such cases a solvent-dependent stereochemistry should be expected. In non-protic solvents both directions of

nucleophilic attack of bromide anion are possible and the formation of the mixture of diastereomers should be expected. In contrast, in organic acids and fluorinated alcohol the bromide anion is hydrogen-bonded to the solvent. Therefore, it became less sterically accessible and less active: as a result, the increasing of selectivity toward electrophilic center and the anti-addition of bromine were only observed (Scheme 3). Interestingly to note that diastereomer formed in protic solvents is slightly dominated in the mixture of diastereomers isolated in experiments with aprotic solvents.



Scheme 3. Bromination in aprotic and protic solvents.

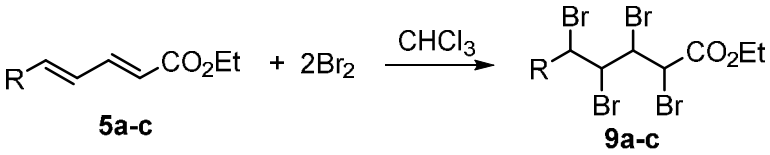
Other convenient brominating reagents such as 1,2-dipyridiniumditribromide-ethane (DPTBE) or HBr in the presence of oxone were tested with ethyl sorbate. In contrast to the experiments using molecular bromine, in these cases the formation of ethyl 4,5-dibromohexenoate **6b** as a principal reaction product was accompanied by the significant formation of isomeric 2,3-dibromoenoate **7b**: its amounts were reached by 33% (Table 1, entries 11, 12).

The preferable or exclusive bromine addition in 5,6-positions of starting dienoates **5a,b** seems to be the result of the preservation of conjugated moiety C=C-C=O. We hypothesized that the introduction of substituent conjugated with the γ,δ-double bond should change the reaction course. To test this hypothesis, the phenyl group was incorporated into the molecule of ethyl corbate **5b** instead of methyl one, and ethyl 2*E*,4*E*-5-phenylpenta-2,4-dienoate **5c** was reacted with equimolar quantity of bromine. We performed the reaction under conditions that give a higher chance to obtain both isomeric dibromoderivatives. To our delight, the steric bulk of the aryl substituent at the remaining double bond did not prevent to the reaction. It turned out that our hypothesis was correct: the bromine addition reaction proceeded chemoselectively in chloroform at low temperature to give the target dibromoderivatives **7c** in quantitative yield. This result is in excellent agreement with the thermodynamic characteristics of all chemoisomers: while non-substituted or methyl-substituted esters **6a,b** are the most stable isomers for 11.7 and 4.1 kcal/mol correspondingly, the phenyl-substituted enoates **7c** is slightly more stable (for 0.9 kcal/mol) than its isomer **6c** (See SI, S.47). The same result was obtained when the reaction was performed in dioxane as a solvent at room temperature (Table 1, entries 13, 14).

Next, we shift our focus to the preparation of tetrabromo-substituted esters **9a-c**. We were pleased to observe that the reaction of dienoates **5a-c** with twofold excess of bromine was found to be general, and tetrabromo derivatives **9a-c** were obtained in all cases in good yields. The presence or absence of any substituent at the δ-position has no significant effect on the reaction result (Table 2). Evidently, in these reactions ethyl dienoates **5** initially provide dibromoesters **6** which subsequently transformed into tetrabromo derivatives **9** by reaction with a second equivalent of bromine.

It is very important to note that the bromination of dienoates **5** is highly stereoselective: though in the molecules tetrabromoesters there are three (for **9a**) or four (for **9b,c**) asymmetric centers, in the NMR spectra of the products **9a-c** only one set of signals is observed. Therefore, the bromination of each double bond occurs through the bromonium ion ensuring *anti*-stereoselectivity.

Table 2. Synthesis of tetrabromoesters **9a-c**.



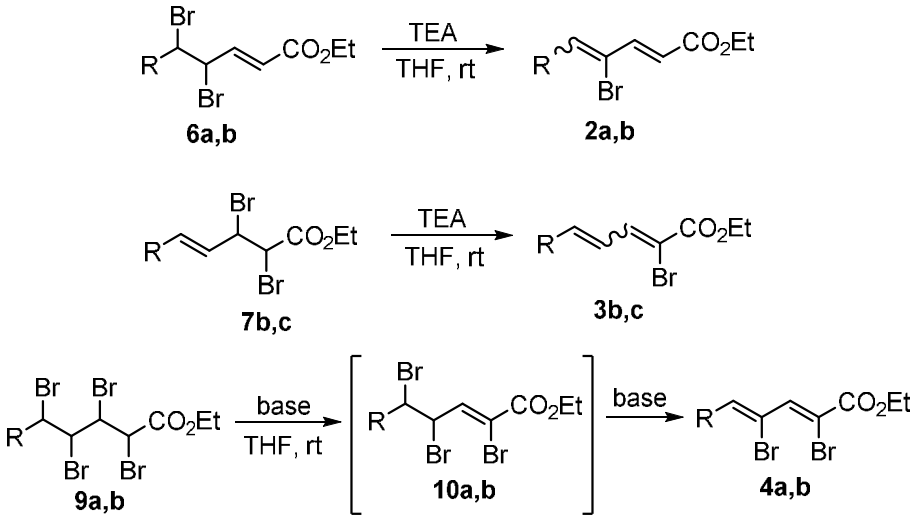
5a-c **9a-c**

entry	dienoate	Br_2 (equiv.)	conditions	products, (yield, %)[a]
1	**5a**	2.2	rt, 3 h	**9a** (48)[b]
2	**5b**	2.2	50°C, 6 h	**9b** (64)[c]
3	**5b**	2.5	50°C, 6 h	**9b** (77)
4	*2E,4E*-**5c**	2.5	rt, 16 h	**9c** (30)

[a] Isolated yield.
[b] Dibromoenoate **6a** was also isolated in 25% yield.
[c] Dibromoenoate **6b** was also isolated in 17% yield.

To obtain mono- or dibromodienoates, di- or tetrabromoesters **6**, **7** and **9** were reacted with the organic base (TEA, DABCO or DBU). The best results were obtained with triethylamine (for dibromo derivatives **6a,b** and **7b,c**) and anhydrous DABCO (for tetrabromo derivatives **9a-c**) as dehydrobromination reagent.

Thus, when dibromoenoate **6b** was treated with TEA at room temperature for 2 h, the target ethyl-4-bromosorbate **2b** was isolated in excellent yield (Scheme 4). Similarly, the treatment of ester **7b** with the same base leads to the isomeric ethyl-2-bromosorbate **3b** in moderate yield. Unfortunately, the bromodienoate **3b** is not quite stable and could not be isolated in pure form. Even recording of its NMR spectra is accompanied by decomposition: the color of the $CDCl_3$ solution rapidly changed from light-yellow to brown and new signals appeared in the ^{13}C NMR spectrum after the sample has been standing at room temperature for several hours.



Scheme 4. Dehydrobromination of di- and tetrabromoesters.

Finally, we showed that tetrabromoesters **9a-c** were direct precursors of tri- (**10a-c**) and dibromodienoates **4a-c**. Thus, when saturated ester **9b** was treated with one equivalent of TEA, tribromoester **10b** was isolated in low yield. At the same time, when the same ester reacted with 2.2 equivalents of DABCO at room temperature for only one hour, the target dibromodienoate **4b** was isolated in 44% yield. Note that according to the NMR spectra of the reaction mixture, the esters **10b** and **4b** are really formed in high yields. Unfortunately, during their purification by column chromatography on silica gel a particular decomposition or polymarization seems to take place.

Interestingly, dehydrobromination leading to 2-bromoenoate **10b** proceeds more rapidly than second elimination of HBr. Most probably, the α-hydrogen in **9b** is more acidic and can be easily removed as a proton under the basic conditions leading the enoate **10b** bearing a double bond conjugated with etoxycarbonyl group. In contrast, the elimination of the proton from C-4 atom is more difficult. Thus, by the separate experiment we showed that after standing of the solution of **6b** with DABCO in THF for 2 h at room temperature, the conversion of starting ester achieved only 20%.

Conclusion

In conclusion, we have reported an efficient method for selective bromination of alkyl dienoates. In contrast to previously described bromination of ethyl sorbate **5b**, the reaction proceeds with the formation 4,5-dibromo enoate **6b** as a principal reaction product and 2,3-dibromoenoats (not 2,5-dibromo derivative) as a minor one. The proposed protocol is suitable for substrates bearing terminal or internal (alkyl- and aryl-substituted) double bond, giving the corresponding mono-, di- or tetrabrominated esters as a rule in moderate or excellent yields (up to quantitative). Moreover, this procedure allows us to prepare the target bromine-bearing mono- and dienic systems in a highly chemo- and stereoselective manner.

Further study addressing the extension of range of bromoderivatives of carbonyl-bearing dienes and their utility to the synthesis of different heterocyclic systems will be explored by our research team in the near future.

Experimental part

General Remarks.

^{1}H (400.1 MHz), and ^{13}C (100.6 MHz) NMR spectra were recorded on Bruker AVANCE 400 MHz spectrometer. Chemical shifts (δ) are given in *ppm*; the coupling constants (*J*) are given in Hertz. The assignment of signals in the ^{1}H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC experiments. The IR spectra were recorded with an ATR/FT-IR spectrometer. The GC/MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). HRMS were recorded on HR-TOF-ESI-MS Agilent 6210 for solution in acetonitrile with electrospray ionization in the positive mode. The silica gel used for column chromatography was 230-400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and distilled prior to use. The initial ethyl sorbate **5b** is a commercial product. Ethyl dienoates **5a,c** were prepared according to reported procedures ([19] for **5a** and [20] for **5c**).

General procedure for synthesis of dibromoester 6a-c and 7.

Bromine (1 equiv.) in $CHCl_3$ (5 mL for 1 mmol) was added dropwise into a stirred solution of the enoates **5a-c** (1 equiv.) in $CHCl_3$ (2 mL for 1 mmol). During the addition the temperature was kept at 0 ÷ 10^{o}C. The mixture was then stirred at room temperature until disappearance of the deep bromine coloration. The solvent was evaporated. The dibromoderivatives **6a-c** and **7b,c** were isolated in pure form by column chromatography on Silica gel.

Ethyl (*E*)-4,5-Dibromopent-2-enoate (6a). Yield: 169 mg (59%) (from 1 mmol of **5a**); colorless oil; TLC: R_f = 0.60 (5:1 hexane: diethyl ether). IR (KBr, ν, cm^{-1}): 1656 (C=C), 1722 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 7.1, 3H), 3.66 (dd, *J* = 10.4, 10,4, 1H), 3.84 (dd, *J* = 10.4, 4.3, 1H), 4.22 (q, *J* = 7.1, 2H), 4.61 (ddd, *J* = 10.4, 9.4, 4.5, 1H), 5.94 (d, *J* = 15.4, 1H), 6.75 (dd, *J* = 15.4, 9.4, 1H). ^{13}C NMR ($CDCl_3$): δ 14.7 (CH_3), 33.8 (CH_2Br), 47.2 (CHBr), 61.5 (OCH_2), 125.6 (=CH), 143.5 (CH=), 165.7 (C=O). MS (EI) *m/z* (relative intensity): 286 (M^+, <1), 241 (9), 179 (25), 177 (25), 81 (64), 53 (100). Calcd. For $C_7H_{10}Br_2O_2$: C 29.40, H 3.52; found C 29.55, H 3.61.

Ethyl (*E*)-4,5-Dibromohex-2-enoate (6b). Yield: 539 mg (72%) (from 2.5 mmol of **5b**); light yellow oil; **TLC**: R_f = 0.43 (10:1 hexane : diethyl ether). ^{1}H NMR ($CDCl_3$): *major diastereomer*: δ 1.31 (t, *J* = 7.1, 3H), 1.89 (d, *J* = 6.6, 3H), 4.17-4.23 (m, 3H), 4.63 (dd, *J* = 9.4, 9.4, 1H), 5.99 (d, *J* = 15.4, 1H), 6.93 (dd, *J* = 15.4, 10.0, 1H); *minor diastereomer* (as a 0.32:1 mixture with major diastereomer): δ 1.31 (t, *J* = 7.1, 3H), 1.81 (d, *J* = 6.8, 3H), 4.17-4.23 (m, 2H), 4.38 (dq, *J* = 6.8, 3.8, 1H), 4.88 (dd, *J* = 9.2, 3.8, 1H), 6.08 (d, *J* = 15.3, 1H), 7.01 (dd, *J* = 15.3, 9.2, 1H). ^{13}C NMR ($CDCl_3$): *major diastereomer*: δ 14.3 (CH_3), 24.8 (CH_3), 49.6 ($\underline{C}HBrCH_3$), 55.1 (CHBr), 60.9 (OCH_2), 124.2 (=CH), 143.9 (CH=), 165.4 (C=O); *minor diastereomer* (as a 0.32:1 mixture with major diastereomer): δ 14.3 (CH_3), 21.2 (CH_3), 49.3 ($\underline{C}HBrCH_3$), 55.6 (CHBr), 61.0 (OCH_2), 125.9 (=CH), 140.9 (CH=), 165.3 (C=O). IR (KBr, ν, cm^{-1}): 1654 (C=C), 1720 (C=O). MS (EI) *m/z* (relative intensity): 220 (M^+ - HBr + 1, 11), 218 (15), 175 (26), 173 (17), 139 (34), 111 (100), 83 (19). Calcd. for $C_8H_{12}Br_2O_2$: C 32.03, H 4.03; found C 31.93, H 4.02.

Ethyl (*E*)-4,5-Dibromohex-2-enoate (7b). Yield: 84 mg (11%) (from 2.5 mmol of **5b**); oil; **TLC**: R_f = 0.53 (10:1 hexane : diethyl ether). ^{1}H NMR ($CDCl_3$): δ 1.33 (t, *J* = 7.1, 3H), 1.78 (d, *J* = 6.6, 3H), 4.28 (q, *J* = 7.1, 2H), 4.39 (d, *J* = 11.2, 1H), 4.88 (dd, *J* = 10.7, 10.7, 1H), 5.55 (ddd, *J* = 15.0, 10.2, 1.6, 1H), 5.89 (qd, *J* = 15.0, 6.6, 1H). ^{13}C NMR ($CDCl_3$): δ 14.0 ($\underline{C}H_3CH_2$), 17.8 (CH_3), 47.4 ($\underline{C}HBrC=O$), 51.7 (CHBr), 62.6 (OCH_2), 128.6 (=CH), 133.4 (CH=), 167.8 (C=O). IR (KBr, ν, cm^{-1}): 1630 (C=C), 1711 (C=O). MS (EI) *m/z* (relative intensity): 255 (M^+ - OEt, 13), 227 (13), 221 (62), 219 (65), 193 (22), 191 (22), 139 (46), 111 (42), 97 (27), 95 (40), 67 (100), 66 (41), 65 (75).

Ethyl (*E*)-2,3-dibromo-5-phenylpent-4-enoate (7c) as a (1:2) mixture of diastereomers. Yield: 215 mg (99%) (from 0.6 mmol of **5c**); beidge solid; without chromatographical purification. ^{1}H NMR ($CDCl_3$): *major diastereomer*: δ 1.36 (t, *J* = 7.2, 3H), 4.33 (q, *J* = 7.2, 2H), 4.55 (d, *J* = 11.1, 1H), 5.12 (dd, *J* = 11.1, 10.3, 1H), 6.22 (dd, *J* = 10.3, 15.5, 1H), 6.74 (, *J* = 15.5, 1H), 7.29-7.44 (m, 5H); *minor diastereomer*: δ 1.31 (t, *J* = 7.1, 3H), 4.27 (q, *J* = 7.1, 2H), 4.63 (d, *J* = 6.6, 1H), 5.01 (ddd, *J* = 8.0, 6.6, 1.2, 1H), 6.65 (2, 2H), 7.29-7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): *major diastereomer*: δ 14.0 (CH_3), 47.1 ($\underline{C}HBrC=O$), 51.8 ($\underline{C}HBr$), 62.7 (OCH_2), 125.8 (=CH), 127.1 (C^o), 128.8 (C^m), 128.9 (C^p), 135.3 (C^i), 136.0 (CH=), 167.7 (C=O); *minor diastereomer*: δ 14.1 (CH_3), 48.6 ($\underline{C}HBrC=O$), 53.0 ($\underline{C}HBr$), 62.7 (OCH_2), 125.0 (=CH), 127.2 (C^o), 128.8 (C^m), 128.9 (C^p), 129.0 (C^i), 135.6 (CH=), 167.0 (C=O). IR (KBr, ν, cm^{-1}): 1643 (C=C), 1742 (C=O). MS (EI) *m/z* (relative intensity): 282 (13), 280 (12), 155 (28), 129 (100), 128 (73), 115 (12). We had troubles obtaining suitable elemental analysis for compounds **7b,c** due to their low stability and propencity to loss HBr.

General procedure for synthesis of tetrabromoesters 9a-c.
Bromine (2.2 ÷ 2.5 equiv.) in $CHCl_3$ (5 mL for 1 mmol) was added dropwise into a stirred solution of the dienoates **5a-c** (1 equiv.) in $CHCl_3$ (2 mL for 1 mmol). During the addition the temperature was kept at 0 ÷ 10°C. The mixture was then stirred under appropriates conditions (rt (for **9a,c**) or 50°C (for **9b**)) until disappearance of the deep bromine coloration. After solvent evaporation tetrabromoderivatives **9a-c** were isolated by column chromatography.

Ethyl 2,3,4,5-Tetrabromopentanoate (9a). Yield: 212 mg (48%) (from 1.0 mmol of **1a**); colorless oil; TLC: R_f = 0.8 (7:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1746 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, *J* = 7.2, 3H), 3.83 (dd, *J* = 10.7, 10.4, 1H), 3.90 (dd, *J* = 10.4, 5.0, 1H), 4.31 (q, *J* = 7.2, 2H), 4.59 (d, *J* = 11.1, 1H), 4.74 (ddd, *J* = 10.7, 5.0, 1.8, 1H), 4.91 (dd, *J* = 11.1, 1.8, 1H). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 33.5 (CH_2Br), 47.2 ($\underline{C}HBrCH_2$), 51.6 (CHBr), 52.8 ($\underline{C}HBrCO$), 62.9 (OCH_2), 167.2 (C=O). MS (EI) ***m/z*** (relative intensity): 447 (M^+ +1, <1), 367, 365 (80), 339, 337 (100), 285 (39), 257 (46), 213 (69), 133, 131 (54).

Ethyl 2,3,4,5-Tetrabromohexanoate (9b). Yield: 734 mg (66%) (from 2.5 mmol of **5b**); yellow oil; TLC: R_f = 0.4 (20:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1747 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, *J* = 7.1, 3H), 2.00 (d, *J* = 6.5, 3H), 4.31 (q, *J* = 7.2, 2H), 4.37 (dq, *J* = 6.5, 10.5, 1H), 4.57 (dd, *J* = 10.5, 1.8, 1H), 4.63 (d, *J* = 11, 1H), 5.13 (dd, *J* = 11, 1.8, 1H). ^{13}C NMR ($CDCl_3$): δ 14.0 ($CH_2\underline{C}H_3$), 25.9 (CH_3), 47.7 (CHBr), 49.9 ($\underline{C}HBrC=O$), 55.3 (CHBr), 59.8 (OCH_2), 62.9 ($\underline{C}HBrCH_3$), 167.3 (C=O). MS (EI) ***m/z*** (relative intensity): 383 (15), 381 (46), 379 (46), 377 (15), 352 (19), 351 (19), 301 (21), 299 (42), 297 (22), 191 (27), 189 (25), 147 (25), 145 (27), 66 (100). Calcd. for $C_8H_{12}Br_4O_2$: C 20.90, H 2.63; found C 21.16, H 2.60.

Ethyl 2,3,4,5-Tetrabromo-5-phenylpentanoate (9c). Yield: 154 mg (30%) (from 1 mmol of **5c**); white powder (m.p. = 107-109°C); **TLC**: R_f = 0.3 (20:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1744 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.37 (t, *J* = 7.1, 3H), 4.34 (q, *J* = 7.0, 2H), 4.70 (d, *J* = 11.0, 1H), 5.07 (dd, *J* = 11.0, 1.8, 1H), 5.24 (d, *J* = 11.0, 1H), 5.32 (dd, *J* = 11.0, 1.7, 1H), 7.35-7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.6 (CH_3), 47.8 ($\underline{C}HBrCHBrC=O$), 55.0 ($\underline{C}HBrC=O$), 55.2 ($\underline{C}HBrCHBrC_6H_5$), 57.3 ($\underline{C}HBrC_6H_5$), 63.0 ($CH_2$), 128.3 ($C^o$), 129.0($C^m$), 129.4 ($C^p$), 139.3 ($C^i$), 167.3 (C=O). Calcd. for $C_{13}H_{14}Br_4O_2$: C 29.92, H 2.70; found C 30.23, H 2.62.

General procedure for dehydrobromination of dibromoester 6a,b or 7b,c.
The solution of triethylamine (1.1 equiv.) in THF (1 mL for 1 mmol) was added dropwise into a stirred solution of the dibromoesters (**6a,b** or **7b,c**) (1 equiv.) in THF (2 mL for 1 mmol). The reaction mixture was stirred for *ca* 2 h, white precipitate was filtered, and residue was purified by column chromatography to give the target monobromoenoates **2a,b** or **3b,c**. The following bromoderivatives were obtained by this procedure.

Ethyl (*E*)-4-bromopenta-2,4-dienoate (2a). Yield: 64 mg (63%) (for 0.5 mmol of **6a**); colorless oil; TLC: R_f = 0.55 (7:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1655 (C=C), 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.1, 3H), 4.21 (q, *J* = 7.1, 2H), 5.94 (s, 1H), 6.15 (s, 1H), 6.22 (d, *J* = 14.8, 1H), 7.22 (d, *J* =14.8, 1H). ^{13}C NMR ($CDCl_3$): δ 14.3 ($\underline{C}H_3$), 60.9 (OCH_2), 125.5 ($=\underline{C}HC=O$), 127.0 ($=CH_2$), 127.5 (CBr), 142.0 (CH=), 166.2 (C=O). Calcd. for $C_7H_9BrO_2$: C 29.40, H 3.52; found C 29.55, H 3.61.

Ethyl 4-bromohexa-2,4-dienoate (2b). Mixture of two geometric isomers. Yield: 69 mg (81%) (from 0.39 mmol of **6b**); colorless oil; TLC: R_f = 0.6 (10:1 hexane : diethyl ether). ***Major (2E,4E)-isomer*** **(2b)**. IR (KBr, ν, cm^{-1}): 1631 (C=C), 1718 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.1, 3H), 1.92 (d, *J* = 7.6, 3H), 4.21 (q, *J* = 7.1, 2H), 6.24 (d, *J* = 14.7, 1H), 6.41 (q, *J* = 7.6, 1H), 7.54 (d, *J* =14.7, 1H). ^{13}C NMR ($CDCl_3$): δ 14.4 ($\underline{C}H_3CH_2$), 16.0 ($\underline{C}H_3CH=$), 60.8 (OCH_2), 119.7 (=CBr), 124.5 ($=\underline{C}HCO$), 136.6 ($CH_3\underline{C}H=$), 138.5 ($\underline{C}H=CBr$), 166.7 (C=O). MS (EI) ***m/z*** (relative intensity): 220 (M^++1, 14), 218 (M^+-1, 14), 175 (20), 173 (20), 139 (34), 111 (100). Calcd. for $C_8H_{11}BrO_2$: C 43.86, H 5.06; found C 43.66, H 5.11. ***Minor (2E,4Z)-isomer*** **(2b)** as a mixture with (*2E,4E*)-isomer (**2b)**. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 7.1, 3H), 1.96 (d, *J* = 7.1, 3H), 4.22 (q, *J* = 7.1, 2H), 6.19 (d, *J* = 14.9, 1H), 6.43 (q, *J* = 7.1, 1H), 7.28 (d, *J* =14.9, 1H). ^{13}C NMR ($CDCl_3$): δ 14.4 ($\underline{C}H_3CH_2$), 18.1 ($\underline{C}H_3CH=$), 60.7 (OCH_2), 121.9 (=CBr), 124.6 ($=\underline{C}HCO$), 138.0 ($CH_3\underline{C}H=$), 143.4 ($\underline{C}H=CBr$), 166.8 (C=O). MS (EI) ***m/z*** (relative intensity): 220 (M^+ +1, 14), 218 (M^+ -1, 14), 175 (20), 173 (19), 139 (34), 111 (100).

Ethyl (*Z,E*)-2-Bromohexa-2,4-dienoate (3b). Yield: 141 mg (91%) (from 0.7 mmol of **7b**); light yellow oil; TLC: R_f = 0.4 (10:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1575, 1630 (C=C), 1711 (C=O). ^{1}H NMR (CD_3CN): δ 1.31 (t, *J* = 7.1, 3H), 1.83 (dd, *J* = 6.9, 1.7, 3H), 4.26 (q, *J* = 7.1, 2H), 6.19 (dqd, *J* = 15.1, 6.9, 0.8, 1H), 7.00 (ddq, *J* = 15.1, 11.2, 1.7, 1H), 7.18 (d, *J* = 11.2, 1H). ^{13}C NMR (CD_3CN): δ 14.4 ($\underline{C}H_3CH_2$), 18.9 ($\underline{C}H_3CH$=), 63.0 (OCH_2), 109.6 (=CBr), 129.0 (=CH), 142.3 ($\underline{C}H$=CBr), 146.2 ($CH_3\underline{C}H$=), 163.6 (C=O). HRMS (ES+) $[M+H]^+$ calcd. for $C_8H_{11}BrO_2$ 219.0021, found 219.0019.

Ethyl (*2E,4E*)-2-bromo-5-phenylpenta-2,4-dienoate (3c).
(*2E,4E*)-isomer. Yield: 33 mg (39%) (from 0.3 mmol of **7c**); yellow oil; **TLC**: R_f = 0.4 (20:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1578, 1610 (C=C), 1713 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 7.1, 3H), 4.33 (q, *J* = 7.1, 2H), 6.81 (d, *J* = 15.8, 1H), 7.29 (d, *J* = 11.6, 1H), 7.32-7.52 (m, 5H), 7.81 (dd, *J* = 15.7, 11.3, 1H). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 62.4 (CH_2), 111.2 (=CBr), 125.0 (=CH-), 127.6 (C^o), 129.0 (C^m), 129.4 (C^p), 136.2 (C^i), 141.5 (Ph-CH=), 146.2 ($\underline{C}H$=CBr), 163.0 (C=O). HRMS (ES+) $[M+H]^+$ calcd. for $C_{13}H_{13}BrO_2$ 281.0177, found 281.0177.
(*2Z,4E*)-isomer. Yield: 50 mg (59%) (from 0.3 mmol of **7c**); yellow oil; TLC: R_f = 0.2 (20:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1584, 1614 (C=C), 1715 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.37 (t, *J* = 7.1, 3H), 4.32 (q, *J* = 7.1, 2H), 7.07 (d, *J* = 15.6, 1H), 7.17 (dd, *J* = 15.5, 10.3, 1H), 7.32-7.56 (m, 5H), 7.83 (d, *J* = 10.3, 1H). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 62.6 (CH_2), 114.5 (=CBr), 125.0 (=CH-), 127.0 (C^o), 129.0 (C^m), 129.7 (C^p), 136.2 (C^i), 140.1 (Ph-CH=), 142.4 ($\underline{C}H$=CBr), 163.1 (C=O). HRMS (ES+) $[M+H]^+$ calcd. for $C_{13}H_{13}BrO_2$ 281.0177, found 281.0177.

Ethyl (*Z*)-2,4-dibromopenta-2,4-dienoate (4a). Yield: 44 mg (62%) (from 0.25 mmol of **9a**); yellow oil; the reaction mixture was filtered through a small pad of silica gel and concentrated in vacuo. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.1, 3H), 1.67 (dd, *J* = 7.4, 1.5, 3H), 6.06 (d, *J* = 2.3, 1H), 6.43 (dd, *J* =2.3, 1.3, 1H), 7.64 (d, *J* = 1.3, 1H). ^{13}C NMR ($CDCl_3$): δ 14.3 ($\underline{C}H_3CH_2$), 63.3 (OCH_2), 117.1 (=$\underline{C}$BrCO), 122.2 (=$\underline{C}$Br), 125.3 ($\underline{C}H$=), 139.6 ($H_2\underline{C}$=), 162.3 (C=O).

Ethyl 2,4-dibromohexa-2,4-dienoate (4b). Yield: 68 mg (69%) (from 0.33 mmol of **9b**); yellow oil; the reaction mixture was filtered through a small pad of silica gel and concentrated in vacuo. *Major (2Z,4E)-isome* **(4b)**: ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.1, 3H), 1.67 (dd, *J* = 7.4, 1.5, 3H), 4.31 (q, *J* = 7.1, 2H), 6.20 (dq, *J* =7.4, 1.3, 1H), 7.67 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2 ($\underline{C}H_3CH_2$), 17.3 ($\underline{C}H_3CH$=), 63.2 (OCH_2), 113.3 (=CBr), 119.3 (=$\underline{C}$BrCO), 133.0 ($CH_3\underline{C}H$=), 138.5 ($\underline{C}H$=CBr), 162.2 (C=O). IR (KBr, ν, cm^{-1}): 1600, 1647 (C=C), 1726 (C=O). *Minor (2E,4Z)-isomer* **(4b)** as a mixture with (*2E,4E*)-isomer **(4b)**: ^{1}H NMR ($CDCl_3$): δ 1.34 (t, *J* = 7.1, 3H), 1.91 (dd, *J* = 6.7, 1.3, 3H), 4.30 (q, *J* = 7.1, 2H), 6.69 (d, *J* = 6.7, 1.2, 1H), 7.67 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.3 ($\underline{C}H_3CH_2$), 18.0 ($\underline{C}H_3CH$=), 63.1 (OCH_2), 115.0 (=CBr), 118.5 (=$\underline{C}$BrCO), 134.6 ($CH_3\underline{C}H$=), 140.4 ($\underline{C}H$=CBr), 162.7 (C=O). MS (EI) *m/z* (relative intensity): 298 (M^+, 15), 253 (6), 219 (28), 217 (27), 191 (100), 189 (98), 139 (34), 109 (8).

Ethyl (*Z*)-2,4,5-tribromohex-2-enoate (10b)
Yield 134 mg (22%) (from 1.6 mmol of **9b**); yellow oil; TLC: R_f = 0.6 (10:1 hexane : diethyl ether). IR (KBr, ν, cm^{-1}): 1625 (C=C), 1729 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.1, 3H), 1.92 (d, *J* = 6.6, 3H), 4.32 (m, 3H), 5.00 (dd, *J* = 10.1, 1H), 7.37 (d, *J* = 10.2, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2 ($CH_2\underline{C}H_3$), 24.7 (CH_3), 49.3 (CHBr), 53.4 ($CH_3\underline{C}HBr$), 63.2 (OCH_2), 119.4 (CBr=), 141.5 (CH=), 161.7 (C=O).

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