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PAPER

Syntheses and reactivities of non-symmetrical "active ester" bi-dentate cross-linking reagents having a phthalimidoyl and acid chloride, 2-benzothiazole, or 1-benzotriazole group†

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We have newly synthesized the non-symmetrical "phthalimidoyl active ester" bi-dentate cross-linking reagents having an acid chloride, 2-benzothiazole, or 1-benzotriazole group (*i.e.*, **9**, **15**, and **16**) on the basis of the reactivity study of the "active ester" model compounds, **11–14**, toward the various nucleophiles and examined their reaction selectivity towards the same nucleophiles. Then, we applied for the modification of cholesterol at the more reactive site of the bi-dentate linkers to give 3β-cholesteryl 4-(phthalimidoyloxycarbonyl)butyrate (**39**), and the subsequent reaction of **39** with several amines, such as benzylamine, 4-chlorobenzylamine, 2-phenylethylamine, L-phenylalanine methyl ester, or diphenylalanine benzyl ester as a protein model of the cholesterol antigen.

Introduction

To date, various cross-linking reagents have been used not only in the field of bio-conjugation of proteins, but also in other macromolecules, such as glycoprotein, nucleic acids, or even synthetic polymers *etc*. Particularly, covalent linking of small molecules to proteins has been a target of numerous synthetic endeavours since this process converts non-immunogenic molecules into immunogenic materials. Among many other commercially available cross-linking reagents, active ester linkers[1] such as disuccinimidyl glutarate (DSG), and *m*-maleimidobenzoyl-*N*-hydroxysuccinimide ester (MBS) have become very useful in the area of bio-conjugation chemistry.[2] The MBS linker is particularly useful as a non-symmetrical cross-linking reagent. However, apparently its limitation is that the maleimidoyl group is useful fundamentally only for the Michael addition of SH group. Previously, using MBS linker we have succeeded in synthesizing the particular antigen bearing oxidized cholesterol moiety (**1a–c**) after tremendous efforts to introduce SH group in the cholesterol framework.[3] Seeking more convenient and shorter synthetic route, we have finally used the stepwise route. Though we could not find good conditions to obtain **7a**, resulting in the substantial undesired formation of **8a** (Scheme 1).[4] Under these backgrounds, for the purpose of modification of versatile compounds it is very interesting and challenging to develop new type of non-symmetrical cross-linking reagents having two different reactivities toward the various nucleophiles, such as alcohol, amine, thiol, phenol, and so on.

As the first example of the non-symmetrical bi-dentate cross-linking reagent, we have aimed to synthesize phthalimido 4-chloroformylbutanoate (**9**) by the chlorination of phthalimido 4-carboxybutanoate (**10**).[5] After using several chlorination methods and carefully repeated recrystallization, **9** was successfully obtained as a pure solid form. Furthermore, in order to develop the more stable non-symmetrical bi-dentate cross-liking reagents, we have studied the reactivities of model compounds of so called "active ester" derivatives, *i.e.*, *N*-(3-phenylpropionyloxy)benzotriazole (**11**), *N*-(3-phenylpropionyloxy)phthalimide (**12**), 3-phenylpropionyloxy)benzothiazole (**13**), and *N*-(3-phenylpropionyl)benzotriazole (**14**) towards various nucleophiles.[5–8] From these results, we have designed and synthesized the new class of non-symmetrical bi-dentate cross-linking reagents, *i.e.*, phthalimido 4-(2-benzothiazolyloxycarbonyl)butanoate (**15**) and phthalimido 4-(1-benzotriazolylcarbonyl)butanoate (**16**) which are stable, safe for handling, and longer storage.[5]

Herein, we report the full details synthesis of new class of non-symmetrical cross-linking reagents **9**, **15**, and **16** and their reactivities towards several nucleophiles. We also describe the preliminary examination of introducing the linkers **9**, **15**, and **16** into β-OH of cholesterol and the further reaction with several amines such as benzylamine, 4-chlorobenzylamine, 2-phenylethylamine, L-phenylalanine methyl ester, or diphenylalanine benzyl ester as a protein model for the cholesterol antigen.

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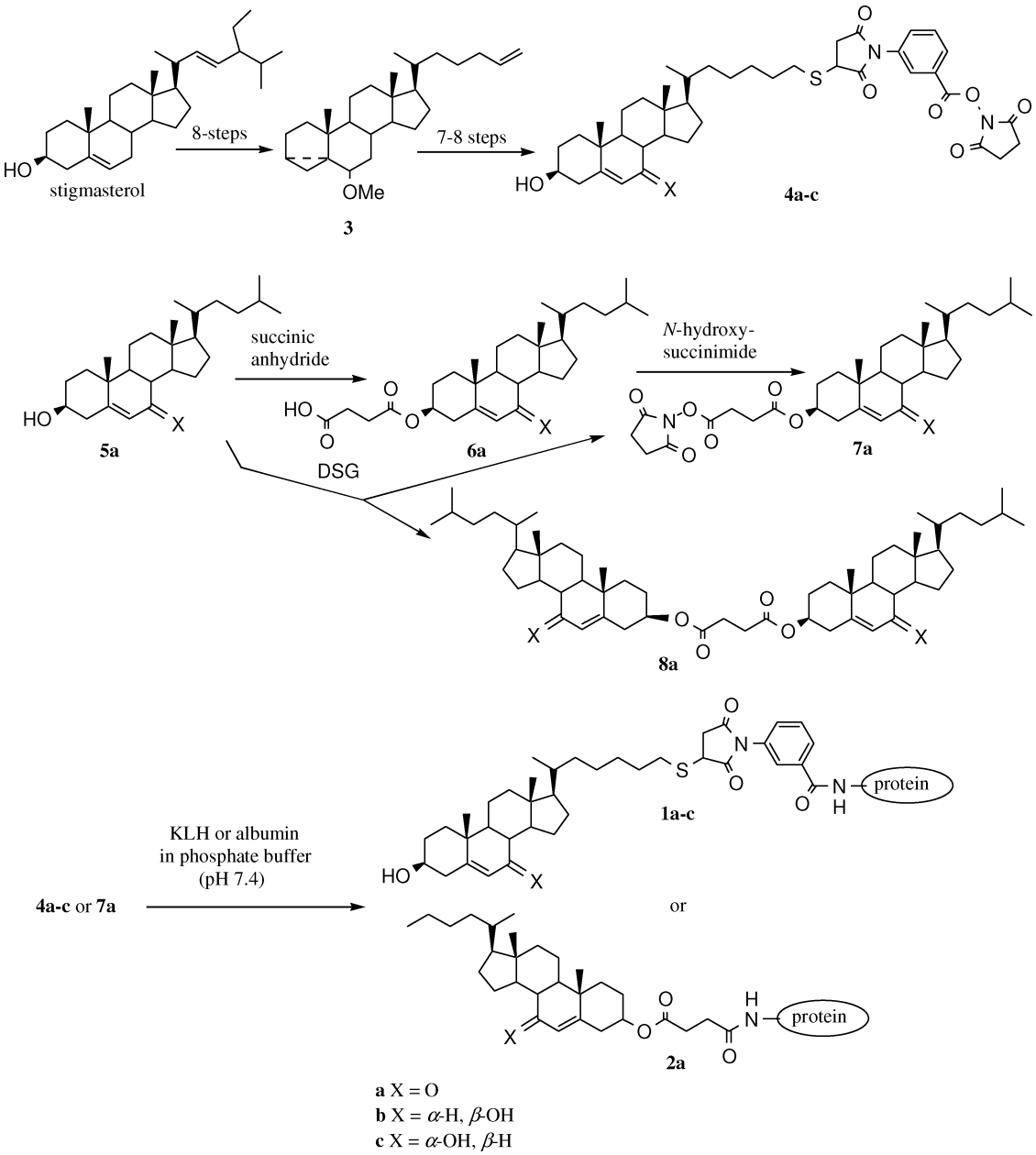


a X = O
b X = α-H, β-OH
c X = α-OH, β-H

Scheme 1 Preparation of antigens.

Results and discussion

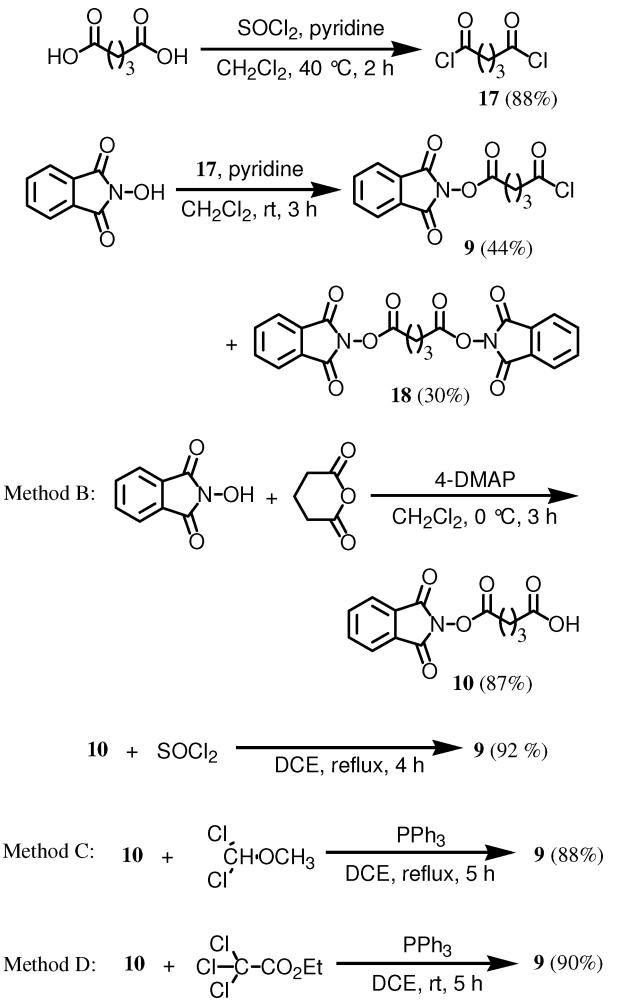
Synthesis of acid chloride linker with "active ester" moiety 9

In order to synthesize non-symmetrical cross-linking reagent, first we have prepared acid chloride linker **9** having "active ester" group. Linker **9** was prepared by the following four procedures: (A) the one step reaction of *N*-hydroxyphthalimide (we selected *N*-hydroxyphthalimide instead of *N*-hydroxysuccimide by the reason of ease to monitor the reaction by TLC) with glutaryl dichloride (**17**) in the presence of pyridine in 44% yield, where undesired bis-(1,3-diphthalimidyl glutarate) (**18**) was obtained in 30% yield, or (B) the reaction of thionyl chloride with **10** in 92% yield, where **10** was synthesized by the reaction of *N*-hydroxyphthalimide with glutaric anhydride in the presence of 4-dimethylaminopyridine (4-DMAP) in 87% yield, or (C) the reaction of **10** with dichloromethyl methyl ether in the presence of Ph_3P in 88% yield, or (D) the reaction of **10** with trichloroacetic acid ethyl ester in the presence of Ph_3P in 90% yield (Scheme 2).

The target linker **9** was obtained as a pure solid form after repeated recrystallization from AcOEt–hexane. Although, linker **9** is sensitive to moisture and decomposed gradually, however, it can be stored under N_2 for a long time.

Reactivities of the model "active ester" compounds 11–14 towards various nucleophiles

Previously, reported *N*-acyloxybenzotriazole[9] and *N*-acylbenzotriazole[10,11] are revealed to be efficient acylating reagents. However, there has been no report about the reactivity



Scheme 2 Synthesis of 4-(Phthalimidoyloxycarbonyl)butanoyl chloride (**9**).

difference between the so-called "active ester" groups. For the preparation of more stable non-symmetrical cross-linkers having two different "active ester" groups, it is necessary to determine the reactivities of the "active ester" groups towards nucleophiles.

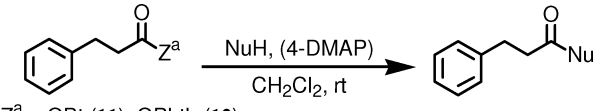
Therefore, at first we examined the reactivity difference of several so-called "activated carbonyl" groups using the model compounds toward benzyl alcohol as a nucleophile in the presence of 4-DMAP as a base.[5] For careful inspection of the reactivity further we studied the reactivity towards various nucleophiles, *i.e.*, 4-methylbenzyl alcohol, 4-chlorobenzyl alcohol, 2-phenylethanol, 2-phenylethylamine, 4-chlorobenzylamine, and benzyl mercaptan. The results are summarized in Table 1. These results indicate clearly that the reactivities of **11** towards all the above mentioned nucleophiles are highest in view of both the yields of the desired esters **19–24** in short reaction times although the yields were not optimized (entries 1, 5, 9, 13, 17, and 21).[12–16] Careful inspection of the data reveals that the reactivity order towards nucleophiles is **11** ≫ **13** > **14** > **12** (*cf.* entries 1–24).

Further, their leaving ability by reacting with nucleophilic agents was estimated by determining reaction rate constants by using ^{1}H NMR spectrum. The reaction of model compounds (**11–14**) with 10 equiv. of benzyl alcohol as a nucleophilic agent was carried out in the presence of 1.0 equiv. of 4-DMAP in $CDCl_3$ to give the benzyl 3-propionate[5] under the pseudo-first-order reaction condition. The yield was determined by ^{1}H-NMR and the Pseudo-first order rate constant was calculated graphically.

Then, a leaving ability of four compounds were determined in the order of the compounds are shown in Fig. 1.

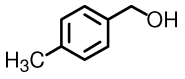
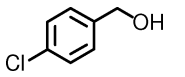
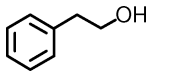
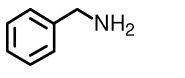
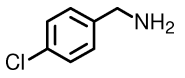
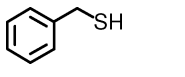
Considering the difference of the reactivity, we have selected the combinations among benzotriazolyloxycarbonyl, *N*-phthalimidoyloxycarbonyl, and 2-benzothiazolyloxycarbonyl groups as the candidate of the "active ester" groups for the synthesis of bi-dentate cross-linking reagents.

Table 1 Reactivities of the model "active ester" compound towards various nucleophiles

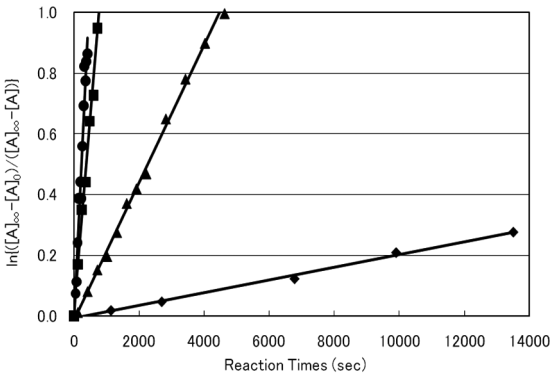


Z^a = OBt (**11**), OPhth (**12**), OBtz (**13**), Bt (**14**)

19-24

Entry	Compound	NuH (1.0 equiv)	Time	Product	Yield[b] (%)
1	**11**		20 min		90
2	**12**		20 h	**19**	82
3	**13**		2 h		89
4	**14**		5 h		90
5	**11**		15 min		86
6	**12**		38 h	**20**	83
7	**13**		25 min		94
8	**14**		3 h		81
9	**11**		15 min		91
10	**12**		40 h		82
11	**13**		2 h	**21**	86
12	**14**		14 h		92
13	**11**		5 min		90[c]
14	**12**		6 h	**22**	87[c]
15	**13**		5 min		96[c]
16	**14**		5 min		95[c]
17	**11**		5 min		89[c]
18	**12**		8 h	**23**	71[c]
19	**13**		5 min		96[c]
20	**14**		25 min		89[c]
21	**11**		5 min		94
22	**12**		12 h		77
23	**13**		5 min	**24**	95
24	**14**		1 h		82

[a] Phth = *N*-Phthalimidoyl, Bt = 1-Benzotriazolyl, Btz = 2-Benzothiazolyl. [b] Isolated yields (not optimized). [c] Reaction proceeded without base



●: compound **11** ($k = 2.28 \times 10^{-3}$),
♦: compound **12** ($k = 1.26 \times 10^{-5}$),
■: compound **13** ($k = 1.28 \times 10^{-3}$),
▲: compound **14** ($k = 2.42 \times 10^{-4}$).

Fig. 1 Plots of k_{obs} for the reaction of **11**, **12**, **13** or **14** (1 equiv) with benzyl alcohol (10 equiv) in the presence of 4-DMAP (1 equiv) in $CDCl_3$ at 20.5 °C.

Synthesis of the non-symmetrical "active ester" bi-dentate cross-linking reagents 15 and 16

In our initial experiment, we attempted to synthesize the cross-linkers having benzotriazolyloxy carbonyl as one of the "active ester" group, such as phthalimido 4-(1-benzotriazolyloxycarbonyl)butanoate (**25**) (Fig. 2). When **9** was reacted with *N*-hydroxybenzotriazole at room temperature in CH_2Cl_2 in the presence of 4-DMAP. The reaction proceeded smoothly and the crude ^1H NMR spectrum showed that the crude product of **25** contained an inseparable by-product. However, we were not able to isolate as a pure form at this stage, probably due to the very reactive nature of benzotriazolyloxycarbonyl group.

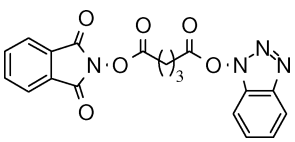
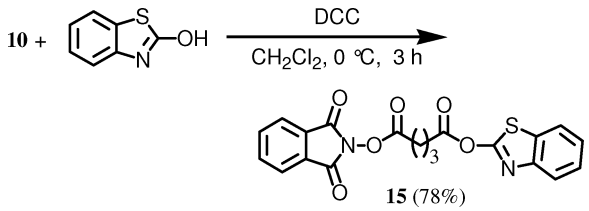


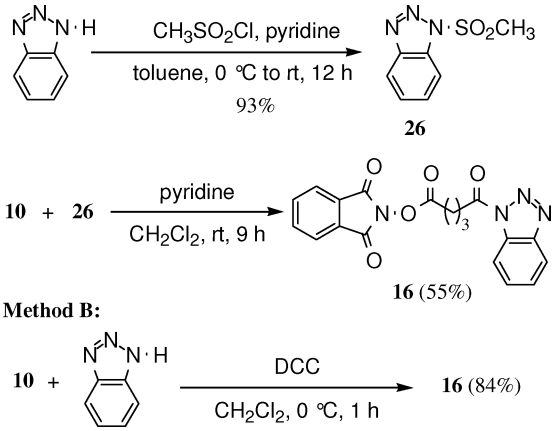
Fig. 2 The cross-linking reagent having benzotriazolyloxy group (**25**).

As a result, we planned to synthesize the linkers having the other combinations of PhthOCO-, BtzOCO-, and BtCO-groups as activated carbonyl groups. After examination of the reaction and separation conditions, we have successfully synthesized **15** by the reaction of **9** with 2-hydroxybenzothiazole in the presence of 1,4-diazabicyclo[*2*,*2*,*2*]octane (DABCO) to generate **15** in 46% yield which was reported previously.[5] We now report the linker **15** is produced in 78% yield by direct treatment of 2-hydroxybenzothiazole with **10** in the presence of DCC (Scheme 3).

Next, the target reagent **16** was synthesized by the following two procedure: (A) the one step reaction of **10** with 1-(methanesulfonyl)benzotriazole (**26**) in the presence of pyridine, where **26** was prepared by the reaction of benzotriazole with methanesulfonyl chloride in the presence of pyridine, or (B) the reaction of **10** with benzotriazole in the presence of DCC (Scheme 4). Expectedly, linkers **15** and **16** thus obtained were found to be stable, safe for handling, and longer storage.



Scheme 3 Synthesis of 4-(2-benzothiazolyloxycarbonyl)butyric-*N*-hydroxyphthalimide ester (**15**).



Scheme 4 Synthesis of 4-(1-benzotriazoleoxa)butyric-*N*-hydroxyphthalimide ester (**16**).

X-Ray crystallographic analysis of phthalimido 4-(1-benzotriazolylcarbonyl)butanoate 16

A detailed structural analysis of **16** was performed by an X-ray crystallographic analysis. Selected bond distances and bond angles of **16** are collected in Table 2. An ORTEP drawing of **16** is depicted in Fig. 3.

Reactions of linker 9, 15, or 16 with various nucleophiles in the presence of 4-DMAP

We examined the reactivities of the linkers **9**, **15**, or **16** toward the various common nucleophiles, such as alcohols, amines, phenol, and thiol in the presence of 4-DMAP as a base in CH_2Cl_2. The reaction times and yields are summarized in Table 3. From these results it is evident and important that the desired

Table 2 Selected structural data for phthalimido 4-(1-benzotriazolylcarbonyl) butanoate (**16**)[a]

Bond angle(Å)		Bond distance(Å)	
N(3)–N(2)	1.384(2)	N(2)–N(3)–C(7)	120.8(1)
N(3)–C(5)	1.381(2)	N(2)–N(3)–C(5)	109.3(1)
N(3)–C(7)	1.406(2)	C(5)–N(3)–C(7)	129.8(2)
C(7)–O(1)	1.196(2)	N(3)–C(7)–O(1)	118.5(2)
C(7)–C(8)	1.501(3)	N(3)–C(7)–C(8)	115.8(2)
C(8)–C(9)	1.511(3)	O(1)–C(7)–C(8)	125.7(2)
C(9)–C(10)	1.514(3)	C(10)–C(11)–O(3)	109.1(2)
C(10)–C(11)	1.491(	C(10)–C(11)–O(2)	130.2(2)
C(11)–O(2)	1.163)	O(2)–C(11)–O(3)	120.8(2)
O(11)–O(3)	1.376(2)		
O(3)–N(4)	1.388(2)		

[a] Number in parentheses are estimated standard deviation in the least significant digits.

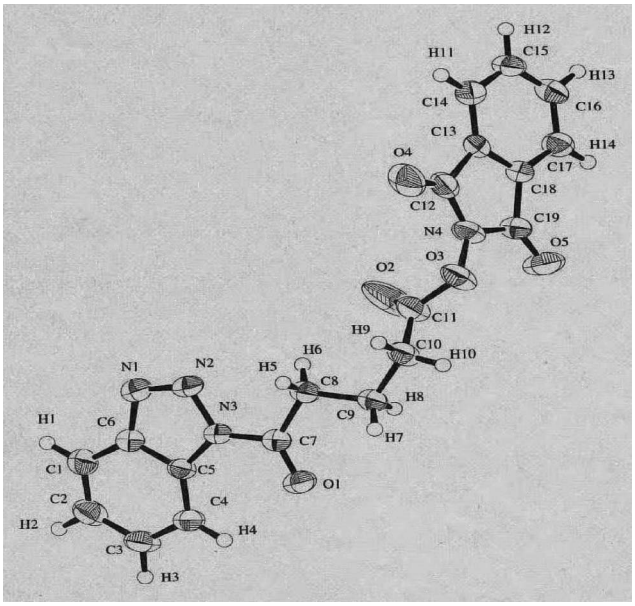


Fig. 3 ORTEP drawing of **16**.

mono-substituted esters **27–38**, which was formed by the preferential attacking of nucleophiles to more reactive site of the compound, was obtained exclusively in high yield.

Concerning the reactivity, it is apparent the acid chloride linker **9** exhibited the highest reactivity towards all nucleophiles used in view of the relatively higher yields in the shortest reaction time (entries 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, and 34). As compared with the results in Table 3 the reactivity order of the cross-linking reagents thus prepared was revealed to be **9** ≫ **15** > **16**.

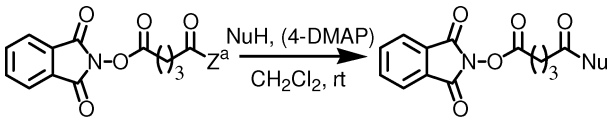
Reactions of linker 9, 15, or 16 with cholesterol and the successive reaction of 39 with various amines in the presence of 4-DMAP

In order to test and apply in the actual biological molecule system, we studied the reaction of the linker **9**, **15**, or **16** with cholesterol in the presence of 4-DMAP or DABCO as a base. However, we selected DABCO, because of the easy removal after the reactions. The corresponding yield of the product 3β-cholesteryl 4-(phthalimidoyloxycarbonyl)butyrate (**39**)[5] are summarized in Table 4.

As the result, relatively higher yield of **39** was obtained in the cases of **9** and **15** (entries 1, 2, 4 and 5). The low yield in the case of **16** (entries 3 and 6) will be explained by the relatively low leaving ability of benzotriazole group (*cf.* Table 1). In comparison with the results of Table 3 (for example, in the case of benzyl alcohol as a nucleophile; entries 1–3). It is noticeable that in all cases (Table 4, entries 1–6) both the yields and reactivities became lower substantially, probably due to the nucleophilic attacking by sterically hindered secondary hydroxyl group at 3-β position of cholesterol.

Successively, we studied the reaction of **39** with benzylamine (a model compound of protein) in the presence of DABCO as a model reaction for the synthesis of an antigen, the corresponding product was **40** in high yield.[5] Furthermore, we studied the reaction of **39** with several amines, such as benzylamine, 4-chlorobenzylamine, 2-phenylethylamine in the absence of base and the corresponding products **40–42** was relatively same compared with the presence

Table 3 Reactions of linker **9**, **15**, or **16** with various nucleophiles in the presence of 4-DMAP



Z^a = Cl (**9**), OBtz (**15**), Bt (**16**) **27-38**

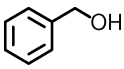
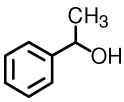
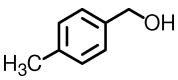
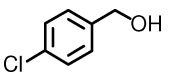
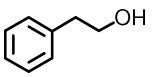
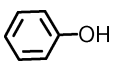
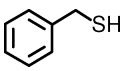
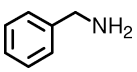
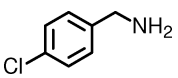
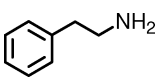
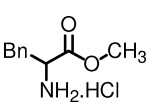
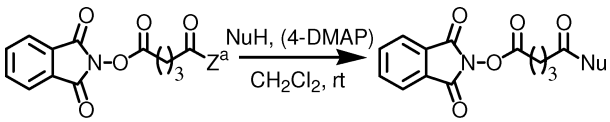
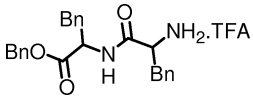
Entry	Linker	NuH (1.0 equiv)	Time	Product	Yield[a] (%)
1	**9**		30 min		73
2	**15**		1 h	**27**	79
3	**16**		4 h		73
4	**9**		1 h		65
5	**15**		10 h	**28**	71
6	**16**		38 h		62
7	**9**		40 min		73
8	**15**		2 h	**29**	77
9	**16**		5 h		74
10	**9**		20 min		79
11	**15**		30 min	**30**	80
12	**16**		3 h		65
13	**9**		30 min		71
14	**15**		2 h	**31**	68
15	**16**		14 h		71
16	**9**		10 min		82
17	**15**		10 min	**32**	79
18	**16**		4.5 h		70
19	**9**		10 min		74
20	**15**		10 min	**33**	74
21	**16**		70 min		67
22	**9**		10 min		83[c]
23	**15**		10 min	**34**	78[c]
24	**16**		15 min		75[c]
25	**9**		10 min		79[c]
26	**15**		10 min	**35**	76[c]
27	**16**		40 min		73[c]
28	**9**		10 min		84[c]
29	**15**		10 min	**36**	77[c]
30	**16**		15 min		75[c]
31	**9**		50 min		67[b]

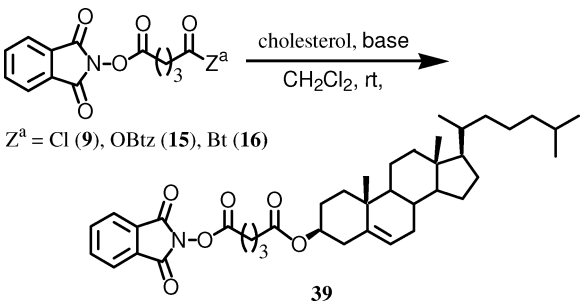
Table 3 *(Contd.)*



Entry	Linker	NuH (1.0 equiv)	Time	Product	Yield[a] (%)
32	**15**		1.5 h	**37**	61
33	**16**		5 h		61
34	**9**		1 h		64
35	**15**		2.5 h	**38**	59
36	**16**		6 h		56

[a] OBtz = 2-Benzothiazolyl, Bt = 1-Benzotriazolyl. [b] Isolated yields (not optimized). [c] Reaction proceeded without base.

Table 4 Reactions of linker **9**, **15** and **16** with cholesterol in the presence of DABCO or 4-DMAP



Entry	Linker	Base	Equiv (base)	Time	Yield[b] (%)
1	**9**			7 h	62
2	**15**	4-DMAP	1.0	19 h	79
3	**16**			24 h	56
4	**9**			7 h	68
5	**15**	DABCO	1.3	20 h	80
6	**16**			25 h	58

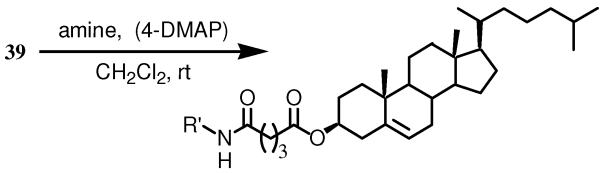
[a] OBtz = 2-Benzothiazolyl, Bt = 1-Benzotriazolyl. [b] Isolated yields (not optimized).

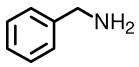
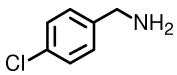
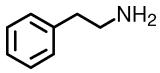
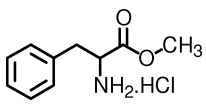
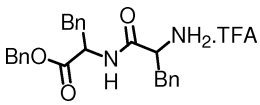
of base after long reaction time (Table 5, entries 1–3). Base revealed to be rapid formation of product. Then, we examined the reaction of **39** with L-phenylalanine methyl ester hydrochloride, or diphenylalanine benzyl ester trifluoroacetic acid in the presence of 1.0 equiv of 4-DMAP as a base the corresponding products **43–44** in high yields (Table 5, entries 4–5).

Reaction of 37 with various nucleophiles in the presence of 4-DMAP

In order to apply for the modification of various compounds, it is interesting to extend the preparative utility and generality of these multicomponent reactions. We carried out the reaction of **37** with various nucleophiles, *i.e.*, benzyl alcohol, 4-methylbenzyl alcohol, phenol, benzylamine, and benzyl mercaptan under the same reaction conditions, and obtained the corresponding products, **45–49** in high yields and the results are shown in Table 6. All the products were purified by flash column chromatography on silica gel.

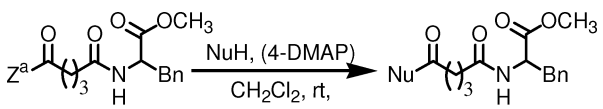
Table 5 Reactions of **39** with various amines in the presence of 4-DMAP

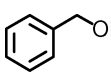
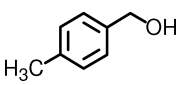
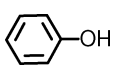
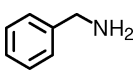
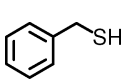


Entry	Amine (1.0 equiv)	Time (h)	Product	Yield[a] (%)
1		10.5 h	**40**	82[b]
2		12.5 h	**41**	64[b]
3		11 h	**42**	65[b]
4		10 h	**43**	68
5		Overnight	**44**	59

[a] Isolated yields (not optimized). [b] Reaction proceeded without base.

Table 6 Reaction of **37** with various nucleophiles in the presence of 4-DMAP



Entry	NuH (1.0 equiv)	Time	Product	Yield[b] (%)
1		32 h	**45**	75
2		25 h	**46**	78
3		28 h	**47**	78
4		10.5 h	**48**	85[c]
5		Overnight	**49**	72

[a] Phth = *N*-Phthalimidoyl. [b] Isolated yields (not optimized). [c] Reaction proceeded without base.

Previously, we reported[3] several antigens **7** having oxidized cholesterol as haptens as shown in Scheme 1. We have demonstrated that the target monoclonal antibodies were successfully obtained by the *in situ* immunization with the antigens **7a–c** obtained by the reaction of **2a–c** with a suitable protein. Therefore, it is expected that many kinds of monoclonal antibodies can be easily obtained by using the non-symmetrical cross-linkers **9**, **15**, and **16** which were newly synthesized by the authors.

Conclusions

To conclude, we have synthesized the new class of bi-dentate cross-linking reagents **9**, **15** and **16**, and studied their selective reactivities towards various nucleophiles. Also, we introduced the linkers into cholesterol through selective reaction with 3β-OH, and successively with amines as protein model of the cholesterol antigen. A simple route to conjugateable model derivatives **39** which is able to link to suitable protein covalently under mild reaction conditions by using these cross-linking reagents described here. In addition, it is interesting to modify sugar derivatives, such as cellulose (include modified celluloses), starch (modified starches), cyclodextrin *etc.*, using these linkers. We are now applying to introduce these linkers into filter papers and modified starches to develop the useful functionalized papers and starches.

Experimental section

General

All the melting points were uncorrected using a micro melting point apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using TMS as an internal standard. All the reactions were monitored with TLC and the products were separated by column chromatography using Silica Gel 60 and by preparative layer chromatography using Silica Gel 60 PF_{254} with UV or PMA and DNP detection. Mass spectra were obtained on a JEOL-JMS-D300 mass spectrometer. The elemental analyses were performed in the Micro Analytical Laboratory of the Department of Material Systems Engineering and Life Science, University of Toyama. All the reagents were the highest quality and were further purified by distillation, or recrystallization.

Preparation of phthalimido 4-chloroformylbutanoate (9)

Method (A): Glutaryl dichloride **17** (1457.4 mg, 8.62 mmol) was added to a stirred solution of *N*-hydroxyphthalimide (469.8 mg, 2.87 mmol) and pyridine (749.0 µL, 2.87 mmol) in CH_2Cl_2 (7 mL) at rt under N_2, and the reaction mixture was stirred for 3 h. Then, hexane was added to the reaction mixture and the precipitate was removed by glass funnel. The solution was concentrated by evaporation and purification by kugelrohr distillation and finally repeated re-crystallization from AcOEt–hexane to yield acid chloride **9** (373.8 mg, 44%) as a colorless solid; Method (B): Thionyl chloride (316.1 µL, 4.33 mmol) was added to a stirred solution of **10** (1.00 g, 3.60 mmol) in $ClCH_2CH_2Cl$ (13 mL) under N_2 and the reaction mixture was refluxed with stirring for 3 h. Then, the solvent was removed under vacuum. The residue was purified by repeated re-crystallization from AcOEt–hexane to yield acid chloride **9** (979.0 mg, 92%) as a colorless solid; Method (C): Compound **10** (50.0 mg, 0.18 mmol) was added to a stirred solution of dichloromethyl methyl ether (47.8 µL, 0.54 mmol) in CH_2Cl_2 (1 mL) and C_6H_6 (1 mL) at reflux under N_2, and stirred for 5 h. Then, the solvent was removed under vacuum. The residue was purified by repeated re-crystallization from AcOEt–hexane to yield acid chloride **9** (46.8 mg, 88%) as a colorless solid; Method (D): Compound **10** (115.0 mg, 0.42 mmol) was added to a stirred solution of trichloroacetic acid ethyl ester (114.3 µL, 0.83 mmol) in the presence of Ph_3P (217.7 mg, 0.83 mmol) in $ClCH_2CH_2Cl$ (3 mL) at rt under N_2, and the reaction mixture was stirred for 5 h. Then, the solvent was removed under vacuum. The residue was purified by repeated re-crystallization from AcOEt–hexane to yield acid chloride **9** (111.7 mg, 90%) as a colorless solid; mp 88–90 °C; IR (KBr)) 1805, 1791, 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13–2.21 (m, 2H), 2.80 (t, J = 7.9 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H), 7.79–7.83 (m, 2H), 7.88–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9, 29.2, 45.2, 123.9, 124.0, 128.7, 134.7, 134.8, 161.7, 168.5, 173.1. Anal. Calcd for $C_{13}H_{10}ClNO_5$: C, 52.81; H, 3.41; N, 4.74. Found: C, 53.02; H, 3.56; N, 4.78.

Phthalimido 4-carboxybutanoate (10)

Colorless solid; mp 119–119.8 °C (from CH_2Cl_2–hexane); IR (KBr) 3131, 1787, 1741, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09–2.16 (m, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 7.77–7.82 (m, 2H), 7.87–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 29.9, 32.3, 124.0, 124.0, 128.8, 134.7, 161.8, 168.9, 177.8; Anal. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 55.89; H, 4.02; N, 5.18.

Modified procedure for the preparation of phthalimido 4-(2-benzothiazolyloxycarbonyl) butanoate (15)

DCC (96.5 mg, 0.46 mmol) was added to a stirred solution of **10** (100.0 mg, 0.36 mmol) and 2-hydroxybenzothiazole (54.4 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) and the reaction mixture was stirred for 3 h under N_2 at 0 °C. Then, the reaction mixture was neutralized by dil. AcOH solution and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified after repeated recrystalization from AcoEt-hexane to afford **15** (115.1 mg, 78%) as a colorless solid; mp 150–151 °C (from CH_2Cl_2–hexane); IR (KBr) 1787, 1739, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23–2.30 (m, 2H), 2.86 (t, J = 7.4 Hz, 2H), 3.32 (t, J = 7.0 Hz, 2H), 7.25–7.28 (m, 1H), 7.32–7.39 (m, 2H), 7.78–7.81 (m, 2H), 7.87–7.90 (m, 2H), 8.33 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 29.9, 37.5, 117.8, 121.8, 121.9, 123.9,125.5, 127.0, 128.8, 134.7, 161.8, 169.0, 172.9; Anal. Calcd for $C_{20}H_{14}N_2O_6S$: C, 58.53; H, 3.44; N, 6.83. Found: C, 57.94; H, 3.52; N, 6.81.

Preparation of phthalimido 4-(1-benzotriazolylcarbonyl)butanoate (16)

Method (A): To a stirred solution of **26** (156.2 mg, 0.79 mmol) in CH_2Cl_2 (4 mL) was added to a solution of **10** (200.0 mg, 0.72 mmol) in CH_2Cl_2 (4 mL) in the presence of pyridine (75.5 µL, 0.93 mmol) at rt under N_2, and stirred for 9 h. Then, the solvent was removed under vacuum. The residue was purified by repeated re-crystallization from CH_2Cl_2–hexane to yield **16** (145.6 mg, 55%) as a colorless solid; Method (B): Compound **10** (1.00 g, 3.82 mmol) was dissolved in CH_2Cl_2 (8 mL) and this solution was added

to a solution of benzotriazole (456.4 mg, 3.82 mmol) and DCC (948.1 mg, 4.59 mmol) in CH_2Cl_2 (17 mL) and stirred for 1 h under N_2 at 0 °C. The precipitate was filtered and washed with CH_2Cl_2. Then, the removal of solvent afforded crude product, which were purified by flash chromatography (AcOEt–hexane; 1 : 1) to yield **16** (1.215 g, 84%) as a colorless solid; mp 155.5–157 °C (from CH_2Cl_2–hexane); IR (KBr) 1812, 1785, 1752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37–2.44 (m, 2H), 2.95 (t, J = 7.2 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 7.50–7.54 (m, 1H), 7.65–7.69 (m, 1H), 7.78–7.82 (m, 2H), 7.87–7.90 (m, 2H), 8.12–8.15 (m, 1H), 8.29–8.31(m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 30.0, 34.1, 114.3, 120.2, 124.0, 126.2, 128.8, 130.5, 134.7, 146.1, 161.8, 168.8, 171.3; Anal. Calcd for $C_{19}H_{14}N_4O_5$: C, 60.32; H, 3.73; N, 14.81. Found: C, 60.46; H, 3.73; N, 14.85. HRMS (EI) calcd for $C_{19}H_{14}N_4O_5$: 378.0964; found: m/z 378.0949.

X-Ray crystal data; Empirical formula: $C_{19}H_{14}N_4O_4$; Formula weight 362.34; Crystal system = triclinic; Space group $P\bar{1}$ (#2); Lattice parameters: a = 8.781(2) Å; b = 14.847(2) Å, c = 7.735(2) Å; α = 90.96(2)°, β = 114.70(2)°, γ = 74.50(1)°; V = 877.7(3) Å^3; T = 23.0 °C; Z = 2; m (M_oKa) = 0.99 cm^{-1}; 5427 reflections measured, 2839 unique (R_{int} = 0.048); final R value 0.066. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 751600

Bis(1,3-diphthalimidyl glutarate) (18)

Colorless solid; mp 216.5-217.5 °C (from CH_2Cl_2–hexane); IR (KBr) 1816, 1787, 1741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.24–2.31 (m, 2H), 2.89 (t, J = 7.4 Hz, 2H), 7.78-7.82 (m, 2H), 7.87-7.92 (m, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 19.7, 29.7, 124.0, 128.9, 134.8, 161.8, 168.7; Anal. Calcd for $C_{21}H_{14}N_2O_8$: C, 59.72; H, 3.34; N, 6.63. Found: C, 59.77; H, 3.58; N, 6.66.

Reaction of model "active ester" compound 11–14 with several nucleophiles (product 19 as an example)

Typical procedure: To a solution of 4-DMAP (86.1 mg, 0.70 mmol) was added to a stirred solution of 4-methylbenzyl alcohol (86.1 mg, 0.70 mmol) and **13** (200.0 mg, 0.70 mmol) in CH_2Cl_2 (4 mL) under N_2 at rt and stirred for 2 h. Then, the reaction mixture was neutralized by dil. AcOH solution and extracted with CH_2Cl_2. The organic layer was separated, successively washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of solvent in vacuum, to give oil crude product, which was purified by flash chromatography yielded 3-phenylpropionic acid 4-methylbenzyl ester **19** (159.7 mg, 89%) as a colorless liquid; IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 2.61–2.65 (m, 2H), 2.93 (t, J = 7.8 Hz, 2H), 5.04 (s, 2H), 7.11–7.26 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 30.8, 35.7, 66.0, 126.1, 128.1, 128.2, 128.3, 129.0, 132.8, 137.8, 140.3, 172.5; HRMS (EI) calcd for $C_{17}H_{18}O_2$: 254.1307; found: m/z 254.1304.

3-Phenylpropionic acid 4-chlorobenzyl ester (20)

Colorless liquid; IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.66 (t, J = 7.6 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 5.03 (s, 2H), 7.15–7.29 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8, 35.6, 65.2, 126.2, 128.1, 128.4, 128.5, 129.4, 133.9, 134.3, 140.1, 172.4; HRMS (EI) calcd for $C_{16}H_{15}ClO_2$: 274.0761; found: m/z 274.0741.

3-Phenyl propionic acid 2 phenylethyl ester (21)

Colorless liquid; IR (neat) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.49–2.54 (m, 2H), 2.79–2.84 (m, 4H), 4.17–4.21 (m, 2H), 7.06–7.21 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8, 35.0, 35.8, 64.8, 126.1, 126.4, 128.2, 128.4, 128.8, 137.7, 140.4, 172.7; HRMS (EI) calcd for $C_{17}H_{18}O_2$: 254.1307; found: m/z 254.1282.

N-Benzyl-3-phenylpropionamide (22)

Colorless solid; mp 76.5–77.0 °C (from CH_2Cl_2–hexane); IR (KBr) 3292, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.51 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H), 4.39 (d, J = 6.0 Hz, 2H), 5.62 (s, 1H), 7.13–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.6, 38.5, 43.6, 126.2, 127.4, 127.7, 128.3, 128.5, 128.6, 138.1, 140.7, 171.8; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.34; H, 7.16; N, 5.90.

N-4-Chlorobenzyl-3-phenylpropionamide (23)

Colorless solid; mp 114.5–115.5 °C (from CH_2Cl_2–hexane); IR (KBr) 3282, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.48 (t, J = 7.8 Hz, 2H), 2.93 (t, J = 7.8 Hz, 2H), 4.28 (s, 2H), 6.11 (s, 1H), 6.96–6.99 (m, 2H); 7.00–7.27 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.5, 38.1, 42.5, 126.1, 128.2, 128.4, 128.5, 128.7, 132.9, 136.6, 140.5, 172.0; HRMS (EI) calcd for $C_{17}H_{16}ClNO$: 273.0920; found: m/z 273.0917.

3-Phenylthiopropionic *S*-benzyl ester (24)

Colorless liquid; IR (neat) 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.85-2.89 (m, 2H), 2.99 (t, J = 7.6 Hz, 2H), 4.12 (s, 2H), 7.15–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3, 33.1, 45.2, 126.3, 127.2, 128.2, 128.5, 128.6, 128.7, 137.5, 139.9, 197.8; HRMS (EI) calcd for $C_{16}H_{16}OS$: 256.0922; found: m/z 256.0920.

Reaction of linker 9, 15, or 16 with various nucleophiles in the present of 4-DMAP (product 27 as an example)

Typical procedure: To a stirred solution of 4-DMAP (29.3 mg, 0.24 mmol) and benzyl alcohol (25.3 μL, 0.24 mmol) in CH_2Cl_2 (1 mL) dropwise added to a stirred solution of **15** (100.0 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) at rt under N_2, and stirred for 1 h. Then, the reaction mixture was neutralized by $NaHCO_3$ solution and extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$, and concentrated under vacuum, to give crude product which was purified by flash chromatography yielded, phthalimido 4-benzyloxycarbonylbutanoate **27** (69.6 mg, 79%) as a colourless solid; mp 33.5–35 °C (from CH_2Cl_2–hexane); IR (KBr) 1814, 1787, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.09–2.16 (m, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 5.15 (s, 2H), 7.30–7.38 (m, 5H), 7.76–7.80 (m, 2H), 7.85–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 29.9, 32.6, 66.3, 123.9, 128.1, 128.2, 128.5, 128.8, 134.7, 135.7, 161.8, 168.9, 172.3; Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.71; H, 4.75; N, 3.72.

Phthalimido 4-(4-methylbenzyloxycarbonyl)butanoate (28)

Colorless liquid; IR (neat) 1814, 1788, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54–1.61 (m, 3H), 2.08–2.13 (m, 2H), 2.50–2.54 (m, 2H), 2.69–2.75 (m, 2H), 5.88–5.91 (m, 1H),

7.25–7.37 (m, 5H), 7.77–7.80 (m, 2H), 7.87–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 22.2, 29.9, 32.9, 72.6, 123.9, 126.0, 126.1, 127.9, 128.5, 128.6, 128.8, 134.7, 141.5, 161.8, 169.0, 171.7; HRMS (EI) calcd for $C_{21}H_{19}NO_6$: 381.1212; found: *m/z* 381.1198.

Phthalimido 4-(1-methylbenzyloxycarbonyl)butanoate (29)

Colorless solid; mp 48.5–50.5 °C (from CH_2Cl_2–hexane); IR (KBr) 1817, 1787, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98–2.05 (m, 2H), 2.25 (s, 3H), 2.44 (t, J = 7.2 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 7.05–7.08 (m, 2H), 7.12–7.17 (m, 2H), 7.67–7.70 (m, 2H), 7.75–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 21.0, 29.9, 32.6, 66.2, 123.8, 128.3, 128.7, 129.0, 129.1, 132.7, 134.6, 138.0, 161.7, 168.9, 172.2; HRMS (EI) calcd for $C_{21}H_{19}NO_6$: 381.1212; found: *m/z* 381.1220.

Phthalimido 4-(4-chlorobenzyloxycarbonyl)butanoate (30)

Colorless liquid; IR (neat) 1813, 1788, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99–2.06 (m, 2H), 2.46 (t, J = 7.4 Hz, 2H), 2.67 (t, J = 8.0 Hz, 2H), 5.01 (s, 2H), 7.18–7.24 (m, 5H), 7.67–7.71 (m, 2H), 7.75–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 29.8, 32.4, 65.4, 123.8, 128.4, 128.6, 129.5, 134.0, 134.2, 134.7, 161.7, 168.8, 172.1; HRMS (EI) calcd for $C_{20}H_{16}ClNO_6$: 401.0666; found: *m/z* 401.0668.

Phthalimido 4-phenylethyloxycarbonylbutanoate (31)

Colorless liquid; IR (neat) 1814, 1788, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03–2.12 (m, 2H), 2.45–2.49 (m, 2H), 2.68–2.72 (m, 2H), 2.95 (t, J = 7.2 Hz, 2H), 4.30–4.34 (m, 2H), 7.21–7.31 (m, 5H), 7.77–7.80 (m, 2H), 7.87–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 29.9, 32.6, 35.0, 123.9, 126.5, 128.4, 128.7, 128.8, 134.7, 137.6, 161.8, 168.9, 172.3; HRMS (EI) calcd for $C_{21}H_{19}NO_6$: 381.1212; found: *m/z* 381.1194.

Phthalimido 4-phenyloxycarbonylbutanoate (32)

Colorless solid; mp 105–106 °C (from CH_2Cl_2–hexane); IR (KBr) 1808, 1781, 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19–2.26 (m, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 7.08–7.12 (m, 2H), 7.21–7.26 (m, 2H), 7.21–7.26 (m, 1H), 7.36–7.41 (m, 2H), 7.77–7.82 (m, 1H), 7.87–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 29.9, 32.6, 121.5, 124.0, 125.8, 128.8, 129.4, 134.8, 150.5, 161.8, 168.9, 171.0; Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.34; H, 4.33; N, 4.04. HRMS (EI) calcd for $C_{19}H_{15}NO_6$: 353.0899; found: *m/z* 353.0868.

Phthalimido 4-(*S*-benzyloxycarbonyl)butanoate (33)

Colorless solid; mp 49–50 °C (from CH_2Cl_2–hexane); IR (KBr) 1810, 1745, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11–2.19 (m, 2H), 2.73–2.78 (m, 4H), 4.14 (s, 2H), 7.21–7.31 (m, 5H), 7.77–7.81 (m, 2H), 7.86–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.9, 33.2, 41.9, 123.9, 127.3, 128.6, 128.7, 128.8, 134.7, 137.3, 161.8, 168.8, 197.5; Anal. Calcd for $C_{20}H_{17}NO_5S$: C, 62.65; H, 4.47; N, 3.65. Found: C, 63.04; H, 4.54; N, 3.59.

Phthalimido 4-(*N*-benzyloxycarbonyl)butanoate (34)

Colorless solid; mp 149.0–149.5 °C (from CH_2Cl_2–hexane); IR (KBr) 3316, 1808, 1787, 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14–2.21 (m, 2H), 2.40 (t, J = 7.2 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H), 4.46 (d, J = 5.6 Hz, 2H), 6.27 (s, 1H), 7.21–7.32 (m, 5H), 7.78–7.82 (m, 2H), 7.85–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 29.9, 34.4, 43.6, 124.0, 127.4, 127.8, 128.6, 128.7, 134.8, 138.1, 162.0, 169.3, 171.5; Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.13; H, 4.88; N, 7.52.

Phthalimido 4-(*N*-4-cholorobenzyloxycarbonyl)butanoate (35)

Colorless solid; mp 144.5–147 °C (from CH_2Cl_2–hexane); IR (KBr) 3293, 1807, 1783, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12–2.22 (m, 2H), 2.40 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 6.6 Hz, 2H), 4.43 (d, J = 5.6 Hz, 2H), 6.33 (s, 1H), 7.21–7.27 (m, 4H), 7.80–7.83 (m, 2H), 7.86–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 29.8, 34.3, 42.9, 123.5, 124.0, 128.7, 129.2, 134.3, 134.9, 171.6, 147.9; HRMS (EI) calcd for $C_{20}H_{17}ClN_2O_5$: 400.0826; found: *m/z* 400.0868.

Phthalimido 4-(*N*-phenylethyloxycarbonyl)butanoate (36)

Colorless solid; mp 100.5–102 °C (from CH_2Cl_2–hexane); IR (KBr) 3312, 1816, 1791, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99–2.06 (m, 2H), 2.22 (t, J = 7.0 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 3.48 (q, J = 12.8 Hz, 2H), 6.00 (s, 1H), 7.03–7.19 (m, 5H), 7.70–7.77 (m, 2H), 7.78–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 29.8, 34.4, 35.4, 40.4, 123.9, 126.3, 128.4, 128.6, 128.7, 133.9, 134.7, 134.8, 138.6, 161.9, 169.2, 171.6; HRMS (EI) calcd for $C_{21}H_{20}N_2O_5$: 380.1372; found: *m/z* 380.1414.

Phthalimido 4-(*N*-phenylalaninocarbonyl methyl ester)butanoate (37)

Colorless solid; mp 94.5–95.5 °C (from CH_2Cl_2–hexane); IR (KBr) 3293, 1785, 1745, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04–2.12 (m, 2H), 2.33–2.37 (m, 2H), 2.59–2.75 (m, 2H), 3.06 (dd, J = 6.8 Hz, 14.0 Hz, 1H), 3.19 (dd, J = 5.6 Hz, 14.0 Hz, 1H), 3.73 (s, 3H), 4.93 (q, J = 13.6 Hz, 1H), 6.21 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.2 Hz, 2H), 7.18–7.29 (m, 3H), 7.80–7.82 (m, 2H), 7.87–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 29.8, 34.2, 37.8, 52.3, 53.0, 124.0, 127.0, 128.5, 128.8, 129.1, 134.8, 135.8, 161.9, 169.2, 171.2, 172.0; Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 63.02; H, 5.10; N, 6.40.

Phthalimido 4-(*N*-diphenylalaninocarbonyl benzyl ester)butanoate (38)

Colorless solid; mp 134–136 °C (from CH_2Cl_2–hexane); IR (KBr) 3289, 1813, 1788, 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99–2.05 (m, 2H), 2.29 (t, J = 8.0 Hz, 2H), 2.57–2.64 (m, 2H), 2.97–3.10 (m, 4H), 4.64–4.70 (m, 1H), 4.78–4.85 (m, 1H), 5.10 (s, 2H), 6.34 (d, J = 8.0 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 6.93–6.96 (m, 2H), 7.16–7.37 (m, 13H), 7.80–7.83 (m, 2H), 7.83–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 29.6, 29.8, 34.2, 37.8, 53.3, 54.2, 67.2, 124.0, 127.0, 127.0, 128.5, 128.5, 128.6, 128.6, 128.8, 129.2, 129.2, 134.8, 135.0, 135.5, 136.4, 161.9, 169.2, 170.4, 170.7, 171.6; HRMS (EI) calcd for $C_{38}H_{35}N_3O_8$: 661.2424; found: *m/z* 661.2433.

Preparation of 3β-cholesteryl 4-(phthalimidoyloxycarbonyl)butyrate (39)

Typical procedure: To a stirred solution of 4-DMAP (59.8 mg, 0.48 mmol) and cholesterol (188.3 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **15** (200.0 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) at rt under N_2 and stirred for 19 h. Then, the reaction mixture was neutralized by $NaHCO_3$ solution and extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$, and concentrated under vacuum, to give crude product which was purified by flash chromatography yielded **39** (248.4 mg, 79%) as a colorless solid; mp 83–85 °C (from CH_2Cl_2–hexane); IR (KBr) 1814, 1789, 1741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3H), 0.86 (dd, J = 1.6 Hz, 6.4 Hz, 6H), 0.91 (d, J = 6.4 Hz, 3H), 0.94–1.04 (m, 5H), 1.05–1.17 (m, 6H), 1.23–1.37 (m, 6H), 1.42–1.58 (m, 7H), 1.78–1.88 (m, 3H), 1.93–2.03 (m, 2H), 2.06–2.13 (m, 2H), 2.33 (d, J = 7.6 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 4.60–4.68 (m, 1H), 5.38 (d, J = 4 Hz, 1H), 7.77–7.81 (m, 2H), 7.86–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 18.7, 19.3, 19.9, 21.0, 22.5, 22.8, 23.8, 24.3, 27.8, 27.9, 28.2, 30.1, 31.8, 31.9, 33.1, 35.8, 36.2, 36.6, 36.9, 38.1, 39.5, 39.7, 42.3, 49.9, 56.1, 56.7, 74.2, 122.7, 123.9, 128.8, 134.8, 139.6, 161.8, 169.1, 171.9; Anal. Calcd for $C_{40}H_{55}NO_6$: C, 74.38; H, 8.58; N, 2.17. Found: C, 74.79; H, 8.71; N, 2.12.

Reaction of 39 with several amines (product 40 as an example)

Typical procedure: To a stirred solution of benzylamine (16.5 μL, 0.15 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of **39** (100.0 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) at rt under N_2 and stirred for 10.5 h. Then, the reaction mixture was neutralized by dil. AcOH solution and extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$, and concentrated under vacuum, to give solid crude product which was purified by flash chromatography yielded, 3β-cholesteryl 4-(benzylaminocarbonyl)butyrate **40** (74.4 mg, 82%) as a colorless solid; mp 115–117 °C (from CH_2Cl_2–hexane); IR (KBr) 3276, 1729, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3H), 0.86 (dd, J = 1.6 Hz, 7.2 Hz, 6H), 0.91 (d, J = 6.4 Hz, 3H), 0.94–1.04 (m, 5H), 1.08–1.21 (m, 6H), 1.24–1.39 (m, 6H), 1.42–1.61 (m, 7H), 1.78–1.87 (m, 3H), 1.94–2.02 (m, 4H), 2.25–2.29 (m, 4H), 2.35 (t, J = 7.0 Hz, 2H), 4.43 (d, J = 5.6 Hz, 1H), 4.55–4.63 (m, 1H), 5.36 (d, J = 4.4 Hz, 2H), 5.86 (s, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 18.6, 19.2, 20.9, 22.5, 22.8, 23.7, 24.2, 27.7, 27.9, 28.2, 31.8, 31.9, 33.6, 35.4, 35.7, 36.1, 36.5, 36.9, 38.1, 39.4, 39.6, 42.2, 43.6, 49.9, 56.0, 56.6, 74.0, 122.6, 127.5, 127.8, 128.7, 138.2, 139.5, 171.9, 172.5; Anal. Calcd for $C_{39}H_{59}NO_3$: C, 79.41; H, 10.08; N, 2.37. Found: C, 78.93; H, 9.87; N, 2.35.

3β-Cholesteryl 4-(4-cholorobenzylaminocarbonyl)butyrate (41)

Colorless solid; mp 122–124 °C (from CH_2Cl_2–hexane); IR (KBr) 3262, 1724, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3H), 0.86 (dd, J = 2.0 Hz, 6.4 Hz, 6H), 0.91 (d, J = 6.4 Hz, 3H), 0.94–1.0 (m, 6H), 1.05–1.16 (m, 7H), 1.20–1.35 (m, 5H), 1.41–1.58 (m, 7H), 1.80–1.90 (m, 3H), 1.95–2.02 (m, 4H), 2.27–2.37 (m, 6H), 4.41 (d, J = 5.6 Hz, 1H), 4.40–4.61 (m, 1H), 5.36 (d, J = 4.8 Hz, 1H), 6.38 (s, 1H), 7.20–7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 18.7, 19.2, 20.9, 21.0, 22.5, 22.8, 23.8, 24.2, 27.7, 27.9, 28.2, 31.8, 31.9, 33.4, 35.1, 35.7, 36.1, 36.5, 36.9, 38.0, 39.5, 39.7, 42.2, 43.1, 49.9, 56.1, 56.6, 74.3, 122.7, 128.8, 129.2, 133.4, 136.3, 139.4, 172.8; HRMS (EI) calcd for $C_{39}H_{58}ClNO_3$: 623.4105; found: m/z 623.4081.

3β-Cholesteryl 4-(2-phenylethylaminocarbonyl)butyrate (42)

Colorless solid; mp 128–129.5 °C; (from CH_2Cl_2–hexane); IR (KBr) 3292, 1729, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3H), 0.86 (dd, J = 1.6 Hz, 6.6 Hz, 6H), 0.91 (d, J = 6.4 Hz, 4H), 0.92–1.03 (m, 6H), 1.04–1.20 (m, 7H), 1.20–1.34 (m, 4H), 1.40–1.58 (m, 7H), 1.78–1.99 (m, 7H), 2.19 (t, J = 7.4 Hz, 2H), 2.30 (t, J = 7.4 Hz, 4H), 2.81 (t, J = 6.8 Hz, 2H), 4.55–4.65 (m, 1H), 5.36 (d, J = 3.6 Hz, 2H), 5.65 (s, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 18.6, 19.2, 20.9, 21.0, 22.5, 22.7, 23.7, 24.2, 27.7, 28.1, 31.7, 31.8, 33.5, 35.4, 35.6, 36.1, 36.5, 36.9, 38.0, 39.4, 39.6, 40.5, 42.2, 49.9, 56.0, 56.6, 73.9, 122.6, 126.4, 128.5, 128.6, 138.7, 139.5, 172.1, 172.5; HRMS (EI) calcd for $C_{40}H_{61}NO_3$: 603.4651; found: m/z 603.4631.

3β-Cholesteryl 4-(L-phenylalaninocarbonyl methyl ester)butyrate (43)

Colorless solid; mp 80–82 °C (from CH_2Cl_2–hexane); IR (KBr) 3431, 1789, 1733, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.60 (s, 3H), 0.78 (dd, J = 1.6 Hz, 6.8 Hz, 6H), 0.84 (d, J = 6.4 Hz, 3H), 0.87–0.97 (m, 5H), 0.98–1.09 (m, 6H), 1.10–1.27 (m, 6H), 1.36–1.51 (m, 7H), 1.73–1.95 (m, 7H), 2.16 (t, J = 7.0 Hz, 2H), 2.19–2.24 (m, 4H), 2.98 (dd, J = 6.0 Hz, 14.2 Hz, 1H), 3.10 (dd, J = 6.0 Hz, 13.8 Hz, 1H), 3.65 (s, 3H), 4.49–4.57 (m, 1H), 4.79–4.84 (m, 1H), 5.30 (d, J = 4.4 Hz, 1H), 5.90 (d, J = 8.0 Hz, 2H), 7.01–7.03 (m, 2H), 7.15–7.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 18.6, 19.2, 20.7, 20.9, 22.5, 22.8, 24.2, 27.7, 27.9, 28.2, 31.8, 31.9, 33.5, 35.2, 36.1, 36.9, 37.8, 38.0, 39.4, 39.6, 42.2, 49.9, 52.3, 52.9, 56.0, 56.6, 73.9, 122.6, 123.4, 127.1, 128.5, 128.6, 128.8, 129.1, 134.0, 135.8, 139.5, 171.7, 172.0, 172.4; HRMS (EI) Calcd for $C_{42}H_{63}NO_5$: 661.4706; found: m/z 661.4717.

3β-Cholesteryl 4-(diphenylalaninocarbonyl benzyl ester)butyrate (44)

Colorless solid; mp 145.5–147 °C (from CH_2Cl_2–hexane); IR (KBr) 3295, 1728, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3H), 0.86 (dd, J = 2.0 Hz, 6.8 Hz, 6H), 0.91 (d, J = 6.4 Hz, 3H), 0.93–1.04 (m, 6H), 1.05–1.21 (m, 7H), 1.20–1.34 (m, 5H), 1.41–1.58 (m, 7H), 1.80–1.87 (m, 5H), 1.90–2.02 (m, 2H), 2.16–2.22 (m, 4H), 2.30 (d, J = 8.0 Hz, 2H), 2.99 (d, J = 6.8 Hz, 3H), 3.08 (dd, J = 14.0 Hz, 6.0 Hz, 1H), 4.55–4.65 (m, 2H), 4.77 (q, J = 6.4 Hz, 1H), 5.09 (s, 2H), 5.36 (d, J = 4.4 Hz, 1H), 6.31 (s, 1H), 6.42 (s, 1H), 6.94 (t, J = 3.4 Hz, 2H), 7.13–7.27 (m, 10H), 7.34–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 18.6, 19.2, 20.7, 21.0, 22.5, 23.8, 24.2, 27.7, 27.9, 28.2, 31.8, 31.9, 33.4, 35.0, 35.7, 36.1, 36.9, 37.7, 38.0, 38.1, 39.4, 39.6, 42.2, 49.9, 53.5, 54.4, 56.1, 56.6, 67.2, 74.0, 122.7, 127.0, 127.1, 128.5, 128.5, 128.6, 129.2, 129.3, 135.0, 135.4, 136.2, 139.5, 170.5, 170.6, 172.4; HRMS (FAB) Calcd for $C_{42}H_{63}NO_5$ (M+1): 885.5703; found (M+1): 885.6105.

Reaction of 37 with various nucleophiles (product 45 as an example)

Typical procedure: 4-DMAP (55.7 mg, 0.45 mmol) was added to a stirred solution of **37** (200.0 mg, 0.45 mmol) and benzyl alcohol

(47.1 μL, 0.45 mmol) in CH_2Cl_2 (2 mL) at rt under N_2 and stirred for 32 h. Then, the reaction mixture was neutralized by dil. AcOH solution and extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$, and concentrated under vacuum, to give oil crude product which was purified by flash column chromatography yielded, *O*-benzyl 4-(L-phenylalaninocarbonyl methyl ester)butyrate (**45**) (130.8 mg, 75%) as a colorless oil; IR (neat) 3301, 1814, 1787, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.89–1.97 (m, 2H), 2.21 (t, J = 7.2 Hz, 2H), 2.34–2.40 (m, 2H), 3.05 (dd, J = 6.0 Hz, 14.0 Hz, 1H), 3.14 (dd, J = 5.6 Hz, 14.0 Hz, 1H), 3.72 (s, 3H), 4.85–4.90 (m, 1H), 5.10 (s, 2H), 5.92 (d, J = 7.6 Hz, 1H), 7.07–7.09 (m, 2H), 7.20–7.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 33.1, 35.0, 37.8, 52.3, 52.9, 66.2, 127.1, 128.2, 128.2, 128.5, 128.6, 129.1, 135.7, 135.8, 171.5, 172.0, 172.8; HRMS (EI) Calcd for $C_{22}H_{25}NO_5$: 383.1733; found: m/z 383.1734.

O-4-Methlbenzyl 4-(L-phenylalaninocarbonyl methyl ester)butyrate (46)

Colorless solid; mp 53.5–55 °C (from CH_2Cl_2–hexane); IR (KBr) 3299, 1733, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.88–1.96 (m, 2H), 2.21 (t, J = 7.0 Hz, 2H), 2.30–2.39 (m, 2H), 2.33 (s, 3H), 3.05 (dd, J = 6.0 Hz, 13.8 Hz, 1H), 3.14 (dd, J = 6.0 Hz, 13.8 Hz, 1H), 3.72 (s, 3H), 4.85–4.90 (m, 1H), 5.06 (s, 2H), 5.91 (d, J = 7.2 Hz, 1H), 7.06–7.08 (m, 2H), 7.16 (d, J = 7.2 Hz, 2H), 7.23–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.6, 21.1, 33.1, 35.1, 37.8, 52.3, 52.9, 66.1, 127.1, 128.3, 128.5, 129.1, 129.2, 132.8, 135.7, 138.1, 171.6, 172.0, 172.9; HRMS (EI) Calcd for $C_{23}H_{27}NO_5$: 397.1889; found: m/z 397.1886.

O-Phenyl 4-(L-phenylalaninocarbonyl methyl ester)butyrate (47)

Colorless solid; mp 43–45 °C (from CH_2Cl_2–hexane); IR (KBr) 3315, 1749, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.00–2.07 (m, 2H), 2.30–2.33 (m, 2H), 2.55–2.59 (m, 2H), 3.07 (dd, J = 6.0 Hz, 13.8 Hz, 1H), 3.17 (dd, J = 5.6 Hz, 14.0 Hz, 1H), 3.73 (s, 3H), 4.88–4.93 (m, 1H), 5.97 (d, J = 7.6 Hz, 1H), 7.04–7.11 (m, 4H), 7.20–7.30 (m, 4H), 7.35–7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 33.1, 34.9, 37.8, 52.3, 52.9, 121.4, 125.7, 127.1, 128.5, 129.1, 129.3, 135.7, 150.5, 171.5, 171.6, 172.0; HRMS (EI) Calcd for $C_{21}H_{23}NO_5$: 369.1576; found: m/z 369.1579.

N-Benzyl 4-(L-phenylalaninocarbonyl methyl ester)butanamide (48)

Colorless solid; mp 100–101 °C (from CH_2Cl_2–hexane); IR (KBr) 3289, 1747, 1643, 1546 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.90–1.98 (m, 2H), 2.14–2.25 (m, 4H), 2.92 (dd, J = 7.2 Hz, 14.0 Hz, 1H), 3.09 (dd, J = 5.6 Hz, 14.0 Hz, 1H), 3.72 (s, 3H), 4.33–4.45 (m, 2H), 4.83 (q, J = 6.9 Hz 1H), 5.92 (d, J = 7.6 Hz, 1H), 6.28 (s, 1H), 7.07 (d, J = 6.8 Hz, 2H), 7.20–7.35 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 34.8, 34.9, 37.6, 43.4, 52.4, 52.9, 127.1, 127.5, 127.8, 128.6, 128.7, 129.0, 135.8, 138.5, 172.2, 172.3, 172.4; Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32; found: C, 68.81; H, 6.64; N, 7.23.

S-Benzyl 4-(L-phenylalaninocarbonyl methyl ester)butyrate (49)

Colorless syrup; IR (KBr) 3291, 1743, 1683, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92–1.99 (m, 2H), 2.18–2.22 (m, 2H), 2.50–2.62 (m, 2H), 3.05 (dd, J = 6.0 Hz, 13.8 Hz, 1H), 3.15 (dd, J = 5.6 Hz, 14.0 Hz, 1H), 3.72 (s, 3H), 4.11 (s, 2H), 4.85–4.90 (m, 1H), 5.96 (d, J = 8 Hz, 1H), 7.07–7.20 (m, 2H), 7.20–7.31 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 33.1, 34.8, 37.8, 42.3, 52.3, 52.9, 127.1, 127.2, 128.5, 128.6, 128.7, 129.1, 135.7, 137.4, 171.3, 172.0, 198.2; Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.35; H, 6.10; N, 3.61. HRMS (EI) Calcd for $C_{22}H_{25}NO_4S$: 399.1504; found: m/z 399.1519.

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