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Mechanistic studies of DCC/HOBt-mediated reaction of 3-phenylpropionic acid with benzyl alcohol and studies on the reactivities of 'active ester' and the related derivatives with nucleophiles

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ABSTRACT

Despite of the extensive study for peptide synthesis, DCC-mediated esterification is left still unclear. Therefore, DCC- and DCC/HOBt-mediated reactions of 3-phenylpropionic acid (**1**) with benzyl alcohol were carried out under several mechanistic considerations. Further, in order to determine the reactivities of the so-called 'active esters' compounds changing the substituents bearing carbonyl and related derivatives group for the purpose of the development of new class of non-symmetry cross-linkers, we have studied the reaction of model compounds, *N*-(3-phenylpropionyloxy)benzotriazole (**6**), *N*-(3-phenylpropionyloxy)phthalimide (**7**), 3-phenylpropionyloxybenzothiazole (**8**), and *N*-(3-phenylpropionyl)benzotriazole (**9**) with various nucleophiles under similar conditions were carried out for the comparison. It was revealed to exhibit the order of **6**>>**8**>**9**>**7**.

1. Introduction

A variety of improvement of amide synthesis, particularly peptide synthesis using *N*,*N*′-dicyclohexylcarbodiimide (DCC) or similar derivatives have been continued to develop for long time.[1–8] Further, the activation of carboxylic acids using 1-hydroxybenzotriazole (HOBt) as an efficient coupling additive in the presence of base in peptide synthesis have been well documented.[2,4,5,9,10] For esterification under neutral conditions, DCC-mediated procedures seem to be also useful. However, the yield is not always high enough. For example, we experienced that the reaction of cholesterol with linolenic acid in the presence of DCC resulted in poor yield of the corresponding ester.[11] Therefore, to improve the yield; the use of coupling additive, such as HOBt in the DCC-mediated procedure is also conceivable similarly in the peptide syntheses. However, compared with amide (peptide) synthesis, there has been no report about the efficient coupling protocols to ester linkage between carboxylic acid and hydroxyl groups. Particularly, the mechanism in the presence of HOBt has been left uncertain. Thus, in order to apply the DCC/HOBt-mediated reaction to moderate and neutral esterification procedure in our continuing research to develop new antigens for the production of monoclonal antibodies,[11,12] we need to recheck the DCC-mediated reaction under various conditions. Further, the study has been extended on reactivities of the so-called 'active ester' and the related derivatives toward hydroxyl compounds, to develop versatile methods for esterification under mild conditions. Herein, we report the mechanistic studies of DCC/HOBt-mediated reaction of 3-phenylpropionic acid (**1**) with benzyl alcohol under several conditions, and the studies on the reactivities of 'active ester' and the related derivatives,[13,14] *N*-(3-phenylpropionyloxy)benzotriazole (**6**), *N*-(3-phenylpropionyloxy)phthalimide (**7**), 3-phenylpropionyloxybenzothiazole (**8**), and *N*-(3-phenylpropionyl)benzotriazole (**9**) toward various nucleophiles.

2. Results and discussion

2.1. Mechanistic studies of DCC/HOBt-mediated reaction of 1 with benzyl alcohol

In the condensation reaction using DCC, the initial formation of the *O*-acylisourea intermediate DCC-adduct **2** (Scheme 1) and subsequent formation of acid anhydride **5** were proposed by Khorana.[15] The existence of this intermediate **2** has been supported by the studies on intramolecular *O*-acylisourea formation.[16] To improve the yield and reaction time, Petersen and Balcom, have demonstrated the importance of the reaction media and concluded that less basic solvents, such as CH_2Cl_2 are more effective than THF by the kinetic investigation on the formation of acyl anhydride.[17]

In order to recheck the esterification mechanism in the presence of DCC under several conditions, we have carried out several

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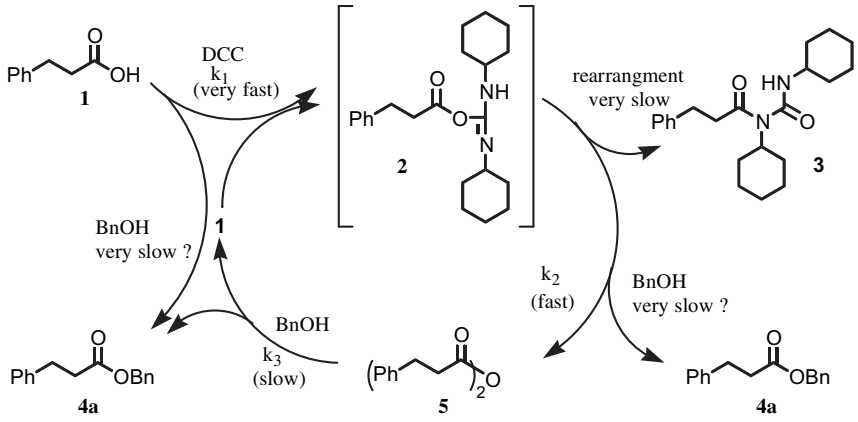
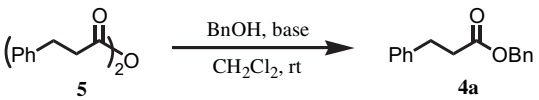


$k_1 >> k_2 > k_3$ (estimated by systematic evaluation in control experiments)

Scheme 1. Esterification of benzyl alcohol in the presence of DCC.

control-reactions in the reaction of **1** with benzyl alcohol. The reaction of **1** with 2.0 equiv benzyl alcohol in the presence of 2.0 equiv DCC found to afford benzyl 3-propionate (**4a**)[14] in a rather low yield of 53% together with the formation of acyl urea **3** in 34% yield, despite of prolonged reaction time. During the reaction, **2** was not observed and the gradual formation of 3-phenylpropionic anhydride (**5**), followed by the formation of **4a** was observed. In a short time (5 min), reaction of **1** with 0.5 equiv of DCC gave only **5** in 31% yield, indicating this reaction rate is not extremely high. The reaction of **1** with 2.0 equiv of DCC for 5 min found to afford only **5** in 62% yield and the complete absence of **2**. In this case, if the attacking rate to **2** by **1** is slow compared with that of the formation of **2**, the formation of **2** should be observed. This means that the attacking rate to **2** by **1** is faster than that of the formation of **2**. The reaction of **5** with benzyl alcohol in the absence of DCC found to be not very fast, and showed almost same reaction rate as in the presence of DCC. The same reaction in the presence of base, such as 4-dimethylaminopyridine (4-DMAP) observed to be very fast (cf. entry 3 in Table 1). The reaction of *N*, *N*′-dicyclohexyl urea with **5** found to undergo slow formation of **3**. When the same DCC-mediated reaction of **1** with benzyl alcohol in the presence of 2.0 equiv 4-DMAP revealed to be rapid formation of **4a** in 83% yield. This result is interpreted by base catalysis by 4-DMAP in acylation step of benzyl alcohol with **5**. The reaction of **1** with benzyl alcohol in the presence of 4-DMAP was also examined, however, expectedly none of **4a** was observed after 3 days. To evaluate the ability of DCC as a base, the reaction of **5** with benzyl alcohol in the presence of DCC was carried out; however, the rate acceleration was not observed. In this case **3** was also formed. These results are summarized in Table 1. All these observations clearly suggest that the real intermediate of the DCC-mediated esterification of **1** with benzyl alcohol in the absence of base is not **2** but **5**, and the rate determining step for **4a** formation is the attacking of alcohol to **5**. The reaction mechanistic was depicted in Scheme 1.

Table 1
Reaction of **5** with benzyl alcohol under several conditions

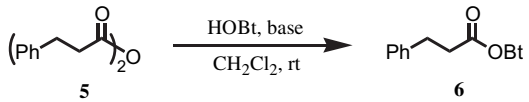


5 **4a**

Entry	Base (1.0 equiv)	Estimate rate
1	None	Very slow (>10 h)
2	DCC	Slow (10 h)
3	4-DMAP	Fast (5 min)

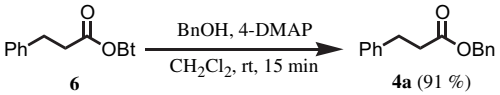
Next, we examined the effect of addition of HOBt in the DCC-mediated esterification of **1** with benzyl alcohol in the absence of base. However, only the rapid formation of **6** was observed and none of **4** was obtained after prolonged reaction time. The addition of 2.0 equiv amount of 4-DMAP as a base under the same conditions revealed the rapid formation of **4a** in excellent yield in a very short time. In this reaction the attacking step of alcohol to **6** seems to be crucial and the addition of the base influences greatly to increase nucleophilicity by base catalysis. The formation of the 'active ester' as intermediate **5** apparently by the isolation of **6** in the reaction of HOBt with **1** in the presence of DCC.[18,19] For the formation of **6** in this reaction, two routes are possible: one is via the DCC-adduct **2** and the other is via the anhydride **5**. Because of the formation of anhydride **5** in the reaction of **1** in the presence of DCC was fast. To obtain clue to distinguish the two routes, we checked the reactivity of HOBt with **5** under several conditions and the results are shown in Table 2. As shown in Table 2 the reaction was very fast in all cases, surprisingly even in the absence of base (entry 1). Therefore, the mechanism for the formation of the ester **4a** in this protocol (acid/alcohol/DCC/HOBt/4-DMAP) will be depicted as in Scheme 2. Namely, initially the 'active-ester' **6** is formed by the reaction of HOBt with **5** that was formed by the reaction of **2** with **1** and, then subsequently, **6** was attacked rapidly by benzyl alcohol to form **4a** under base catalysis of 4-DMAP.

Table 2
Reaction of **5** with 1-hydroxybenzotriazole under several conditions



5 **6**

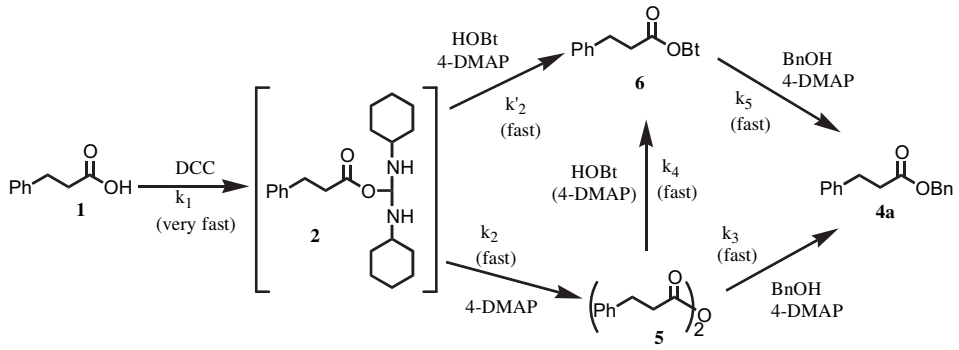
Entry	Base (1.0 equiv)	Estimate rate
1	None	Fast (5 min)
2	DCC	Fast (5 min)
3	4-DMAP	Fast (5 min)



6 **4a** (91 %)

Scheme 2. Reaction of **6** with benzyl alcohol in the presence of 4-DMAP.

Consequently, the addition of HOBt in the esterification reaction in the presence of DCC and suitable base revealed to be very effective as similarly in the amide (peptide) synthesis, and the actual intermediate found to be the so-called 'active ester' derivative, such as **6**. Therefore, the most probable mechanism for this reaction is illustrated in Scheme 3.



k_4 (k_5) > k_3 (estimated by systematic evaluation in control experiments)

Scheme 3. Esterification of **1** with benzyl alcohol in the presence of DCC, BtOH, and 4-DMAP.

Furthermore, to study the difference of the reactivities of 'active ester' derivative under nucleophilic conditions and develop versatile methods for esterification under mild conditions, we have prepared their several model compounds and related derivatives, **6**, **7**, **8**, and **9** and studied their reactivity toward various nucleophiles.

2.2. Reactivities of 6, 7, 8, and 9 toward benzyl alcohol in the presence of various bases

In the initial study, we examined the reactivities of **6**, **7**, **8**, and **9** toward benzyl alcohol in the presence of a variety of bases in CH_2Cl_2 where, the active ester **6**, **7**, **8**, and **9** were synthesized in excellent yields by the following procedure, which was reported previously.[14] Experimental results by using various bases are listed in Table 3.

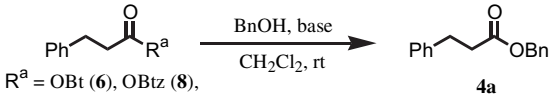
Inspection of Table 3 clearly shows the yields of the ester, **4a** are high and in cases of 4-DMAP (entry 1), DBU (entry 3), and DBN (entry 4) the reaction times were very short within 15 min except Et_3N (entry 2), and pyridine (entry 5) as a base. In the case of pyridine the reaction was very slow and only gave 42% yield when excess amount (ca. ten times) was used. As we can see substrate of Table 3, in all cases the compound **6**, reacted with benzyl alcohol in short reaction time within 15 min and corresponding **4a** is obtained in high yields. Contrarily, in the case of **7** the yields of **4a** are relatively the same compared with the case of **6**, **8**, and **9** after long reaction time. The results in Table 3 shows that the reactivities of **6** is greater than that of **8**, and the reactivities of **8** is greater than that of **9**, and the reactivities of **9** is greater than that of **7** toward benzyl alcohol. Interestingly, in this case except pyridine small amounts of by-products were found that presumed via the Lossen-type rearrangement.[14]

2.3. Reactivities of 6, 7, 8, and 9 toward various nucleophiles in the presence of 4-DMAP

We studied the reactivities of **6**, **7**, **8**, and **9** toward several alcohols in the presence of 4-DMAP in CH_2Cl_2. The results are summarized in Table 4. As shown in Table the yields of the corresponding ester are high. Nucleophiles containing both electron-donating and electron-withdrawing groups underwent the conversation smoothly. However, nucleophiles possessing electron-donating groups required longer reaction times (entries 2 and 5) though the yields were high. Lower alcohols were more reactive than higher carbon numbered alcohols to give the corresponding esters in good yields (entries 1 and 4) and the reaction rate of secondary alcohol was obviously slower than that of primary alcohol (entries 5 and 6). To our surprise when these reaction conditions were applied to trityl alcohol as a represent of tertiary alcohol (entry 7), no desired product was obtained probably due to the sterically hindered OH group at trityl alcohol. When phenol and amines were used, the corresponding esters were also obtained in good to high yields (entries 8–10).

In the case of **6**, the yields of the ester are high and the reaction time is short particularly, compared with in case of **7**, **8**, and **9**. The result in Table 4 shows again that the same reactivities of **6** is greater than that of **7**, **8**, and **9** toward alcohols, phenol, and amines compounds.

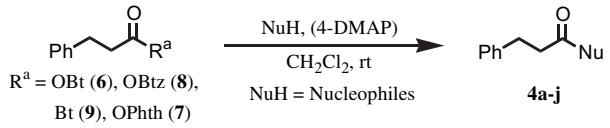
Table 3
Reaction of **6**,**7**, **8** or **9** with benzyl alcohol in the presence of various bases



Entry	Base (1.0 equiv)	**6** (R=OBt)		**8** (R=OBtz)		**9** (R=Bt)		**7** (R=OPhth)	
		Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)
1	4-DMAP	15 min	91	1 h	93	3.5 h	87	30 h	80
2	Et_3N	2.5 h	79	6 h	46	25 h	44	40 h	43
3	DBU	15 min	88	45 min	87	2 h	80	40 h	42
4	DBN	15 min	80	45 min	82	4 h	89	40 h	51
5	Pyridine	2 days	42	2 days	35	2 days	Trace	2 days	Trace

[a] OBt=1-oxybenzotriazolyl, OBtz=2-oxybenzothiazolyl, Bt=1-benzotriazolyl, and OPhth=*N*-oxyphthalimidoyl.
[b] Isolated yields (not optimized).

Table 4
Reaction of **6**, **7**, **8** or **9** with various nucleophiles in the presence of 4-DMAP



Entry	NuH (1.0 equiv)	Product	**6** (R=OBt)		**8** (R=OBtz)		**9** (R=Bt)		**7** (R=OPhth)	
			Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)
1	$PhCH_2OH$	**4a**	15 min	91	1 h	93	3.5 h	87	30 h	80
2	$4\text{-}CH_3O\text{-}C_6H_4CH_2OH$	**4b**	15 min	91	1 h	90	3.5 h	76	30 h	74
3	$4\text{-}NO_2\text{-}C_6H_4CH_2OH$	**4c**	5 min	90	10 min	94	1.5 h	81	19 h	85
4	$PhCH_2CH_2CH_2OH$	**4d**	20 min	86	2.5 h	87	14 h	86	44 h	75
5	$PhCH(CH_3)OH$	**4e**	50 min	85	9 h	89	40 h	79	35 h	39
6	Ph_2CHOH	**4f**	40 min	88	2.5 h	90	19 h	87	36 h	36
7	Ph_3COH	**4g**	2 days	0	2 days	0	2 days	0	2 days	0
8	PhOH	**4h**	8 min	90	20 min	95	2 h	80	28 h	78
9	$PhCH_2CH_2NH_2$	**4i**	5 min	92[c]	8 min	89[c]	15 min	95[c]	6 h	70[c]
10	$PhCH_2CH(NH_2)COOCH_3.HCl$	**4j**	40 min	84	1.5 h	77	4.5 h	73	8 h	72

[a] OBt=1-oxybenzotriazolyl, OBtz=2-oxybenzothiazolyl, Bt=1-benzotriazolyl, and OPhth=*N*-oxyphthalimidoyl.
[b] Isolated yields (not optimized).
[c] Reaction was proceeded without base.

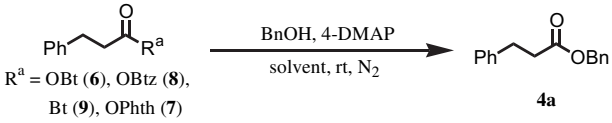
2.4. Solvent Effect in the reactivities of 6, 7, 8, and 9 toward benzyl alcohol in the presence of 4-DMAP

We investigated the effect of the solvent in the reactivities of **6**, **7**, **8**, and **9** toward benzyl alcohol in the presence of 4-DMAP, using CH_2Cl_2 and THF as a solvent. The results are summarized in Table 5. As shown and compared with the results in the table, reaction time was relatively very short in the case of **6** (15–30 min) compared with the case of **8** (1 h to 3 h), **9** (3.5 h to 24 h), and **7** (26 h to 3 days) in all solvents used. In THF, the polar solvating effect may be operating to decrease the basicity of the used bases and the rate of the reaction. Concerning the yield, in all solvents, **4a** was formed relatively rapidly in almost high yields around 70–95% in both cases.

2.5. Reactivities of 6, 7, 8 and 9 toward cholesterol in the presence of various bases

In order to apply and test in the actual biological molecule system, we studied the reaction of **6**, **7**, **8**, and **9** with cholesterol under the same conditions. The results are summarized in Table 6. In the case of **6** as 'active ester' relatively high yields of 3-phenylpropionyloxycholesterol ester (**10**) was observed in relatively short times compared with the

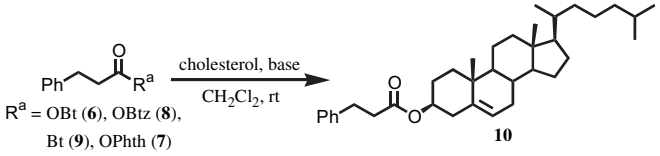
Table 5
Solvent effect of the reactions of **6**, **7**, **8** or **9** with benzyl alcohol in the presence of 4-DMAP



Entry	Solvent	**6** (R=OBt)		**8** (R=OBtz)		**9** (R=Bt)		**7** (R=OPhth)	
		Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)
1	CH_2Cl_2	15 min	91	1 h	93	3.5 h	87	30 h	80
2	THF	30 min	90	3 h	85	24 h	81	3 days	71

[a] OBt=1-oxybenzotriazolyl, OBtz=2-oxybenzothiazolyl, Bt=1-benzotriazolyl, and OPhth=*N*-oxyphthalimidoyl.
[b] Isolated yields (not optimized).

Table 6
Reaction of **6**, **7**, **8**, or **9** with cholesterol in the presence of various bases



Entry	Base (1.0 equiv)	**6** (R=OBt)		**8** (R=OBtz)		**9** (R=Bt)		**7** (R=OPhth)	
		Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)
1	4-DMAP	1 h	78	8 h	78	24 h	75	45 h	31
2	Et_3N	2 h	44	24 h	[c]	24 h	[c]	40 h	[c]
3	DBU	1 h	80	6 h	81	15 h	90	40 h	27
4	Py(excess)	2 days	19	24 h	[c]	24 h	[c]	40 h	[c]

[a] OBt=1-oxybenzotriazolyl, OBtz=2-oxybenzothiazolyl, Bt=1-benzotriazolyl, and OPhth=*N*-oxyphthalimidoyl.
[b] Isolated yields (not optimized).
[c] Reaction proceeded very slowly and yield was not determined.

case of **7**, **8**, and **9**. The results clearly indicate that the reactivity order toward cholesterol is **6**>>**8**>**9**>**7**. In all cases, the trend of the reactivity revealed as similar as toward conventional nucleophiles as shown in Table 4. As the consequence, in the case of 4-DMAP (entry 1) the compound **6** revealed to have the acceptable ability in both the yield and the reaction time as the reactive site of 'cross-linking reagent' for the formation of ester linkage.

3. Conclusion

We have reported the mechanistic study of DCC- and DCC/HOBt-mediated reaction of **1** with benzyl alcohol. On the basis of mechanistic studies two pathways leading to the formation of **4a**. One is direct esterification of benzyl alcohol with anhydride **5**, and the other is via the 'active ester' **6**, that is, formed by the reaction of HOBt with anhydride in the presence of 4-DMAP as a base-catalysis. Furthermore, we prepared several active esters **6**, **7**, **8**, and **9** and studied their reactivities toward various nucleophiles to produce corresponding esters in fair to good yields, and in order to apply and test in the actual biological molecule system we also studied the same reaction with cholesterol. It was revealed to exhibit the order **6**>>**8**>**9**>**7**. Additionally, this methodology does not require any strong acid, acid halides, unstable toxic metallic reagents, or other expensive reagents.

4. Experimental section

4.1. General

Melting points were measured using 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. Elemental analyses were performed at Micro Analytical Laboratory of the Department of Material Systems Engineering and Life Science, University of Toyama. All the reagents were of highest quality and further purified by distillation or recrystallization.

4.2. Preparation of *N*-(3-phenylpropionyloxy)benzotriazole 6

DCC (892.9 mg, 4.32 mmol) was added to a stirred solution of hydrocinnamic acid (500.0 mg, 3.32 mmol) and 1-hydroxybenzotriazole (584.8 mg, 4.32 mmol) in CH_2Cl_2 (8 mL) at 0 °C under N_2 and stirred for 3 h. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (AcOEt/hexane=1:1) gave the title compound **6** (851.8 mg, 96%) as a colorless solid; mp 92–93 °C (from AcOEt/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (t, J=7.6 Hz, 2H), 3.48 (t, J=7.6 Hz, 2H), 7.22–7.31 (m, 5H), 7.54–7.58 (m, 1H), 7.75–7.79 (m, 1H), 8.00 (d, J=8.4 Hz, 1H), 8.40 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 36.5, 115.5, 116.0, 126.5, 126.7, 128.3, 128.6, 132.5, 133.0, 139.4, 169.1; IR (KBr) 1736 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.68; H, 5.01; N, 15.80.

4.3. Preparation of *N*-(3-phenylpropionyloxy)phthalimide 7

DCC (1786.8 mg, 8.66 mmol) was added to a stirred solution of hydrocinnamic acid (1000 mg, 6.66 mmol) and *N*-hydroxyphthalimide (1412.2 mg, 8.66 mmol) in CH_2Cl_2 (15 mL) at 0 °C under N_2 and stirred for 3 h. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (AcOEt/hexane=1:1) gave the title compound **7**[14] (1808.7 mg, 92%) as a colorless solid; mp 84–85 °C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96–3.00 (m, 2H), 3.11 (t, J=7.2 Hz, 2H), 7.23–7.27 (m, 3H), 7.31–7.35 (m, 2H), 7.77–7.81 (m, 2H), 7.86–7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 32.7, 123.9, 126.7, 128.3, 128.7, 128.9, 134.7, 139.1, 161.9, 168.8; IR (KBr) 1789, 1740 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.14; H, 4.52; N, 4.69.

4.4. Preparation of 3-phenylpropionyloxybenzothiazole 8

DCC (44.3 mg, 0.21 mmol) was added to a stirred solution of hydrocinnamic acid (25.0 mg, 0.16 mmol) and 2-hydroxybenzothiazole (32.0 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) at room temperature under N_2 and stirred for 3 h. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (CH_2Cl_2) gave the title compound **8** (29.0 mg, 64%) as a colorless solid; mp 83–84 °C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (t, J=7.4 Hz, 2H), 3.45 (t, J=7.6 Hz, 2H), 7.18–7.37 (m, 7H), 8.25–8.27 (dd, J=8.2, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 40.6, 117.7, 121.8, 125.4, 126.3, 126.9, 128.5, 128.5, 134.6, 140.2, 170.9, 173.3; IR (KBr) 1732 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94. Found: C, 67.89; H, 4.75; N, 4.98.

4.5. Preparation of *N*-(3-phenylpropionyl)benzotriazole 9

Method A: A mixture of hydrocinnamic acid (53.0 mg, 0.35 mmol) and 1-(methanesulfonyl)benzotriazole (70.0 mg, 0.35 mmol) and Et_3N (50.0 μL, 0.48 mmol) were refluxed in THF (2 mL) under N_2 for overnight. The solvent was evaporated and the residue was dissolved in $CHCl_3$. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to give a crude product, which was purified by TLC on silica gel (AcOEt/hexane=1:1) gave the title compound **9** (74.7 mg, 85%) as a colorless solid; mp 58–59 °C (from AcOEt/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (t, J=7.6 Hz, 2H), 3.76 (t, J=3.0 Hz, 2H), 7.19–7.32 (m, 5H), 7.47–7.51 (m, 1H), 7.62–7.66 (m, 1H), 8.10 (dd, J=8.3, 8.3 Hz, 1H), 8.28 (dd, J=8.0, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 37.0, 114.3, 120.1, 126.1, 126.4, 128.4, 128.6, 130.3, 131.0, 139.7, 146.1, 171.5; IR (KBr) 1755 cm^{-1}.

Method B: Benzotriazole (158.4 mg, 1.33 mmol) was added to a solution of hydrocinnamic acid (200.0 mg, 1.33 mmol) and DCC (328.0 mg, 1.59 mmol) in CH_2Cl_2 (4 mL) at room temperature under N_2 and stirred for overnight. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (AcOEt/hexane=1:1) gave the title compound **9** (220.5 mg, 66%) as a colorless solid.

4.6. Preparation of hydrocinnamic anhydride 5

DCC (137.2 mg, 0.66 mmol) was added to a solution of hydrocinnamic acid (200.0 mg, 1.33 mmol) in CH_2Cl_2 (3 mL) at room temperature under N_2 and stirred for 3 h. The precipitate was filtered and washed with CH_2Cl_2 to afford **5** (196.3 mg, 99%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (t, J=3.6 Hz, 2H), 2.92 (t, J=7.8 Hz, 2H), 7.15–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 36.6, 126.4, 128.2, 128.5, 139.4, 168.4; IR (NaCl disc) 1818 cm^{-1}.

4.7. Preparation of 3-phenylpropionic acid benzyl ester 4a

Method A: *Typical procedure*: 4-DMAP (45.6 mg, 0.37 mmol) was added to a stirred solution of benzyl alcohol (38.7 μL, 0.37 mmol) and **6** (100.0 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 15 min. 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 gave a colorless oil crude product, which was purified by

TLC on silica gel (CH_2Cl_2) gave the title compound **4a**[14] (81.7 mg, 91%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (t, J=7.8 Hz, 2H), 2.96 (t, J=8.0 Hz, 2H), 5.10 (s, 2H), 7.17–7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 35.8, 66.2, 126.2, 128.1, 128.2, 128.4, 128.5, 135.8, 140.3, 172.6; IR (NaCl disc) 1734 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{16}O_2$: 240.1150; found: m/z 240.1123.

Method B: DCC (82.5 mg, 0.39 mmol) was added to a stirred solution of hydrocinnamic acid (30.0 mg, 0.19 mmol) and benzyl alcohol (44.0 μL, 0.39 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 19 h. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (AcOEt/hexane=1:5) gave the title compound **4a** (24.2 mg, 53%) as a colorless liquid.

Method C: DCC (82.5 mg, 0.39 mmol) was added to a stirred solution of hydrocinnamic acid (30.0 mg, 0.19 mmol) and benzyl alcohol (44.0 μL, 0.39 mmol) and 4-DMAP (47.6 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 1 h. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (AcOEt/hexane=1:10) gave the title compound **4a** (38.0 mg, 83%) as a colorless liquid.

Method D: DCC (82.5 mg, 0.39 mmol) was added to a stirred solution of hydroycinnamic acid (30.0 mg, 0.19 mmol) and 1-hydroxybenzotriazole (53.0 mg, 0.39 mmol) and benzyl alcohol (44.0 μL, 0.39 mmol), and 4-DMAP (47.6 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 and stirred for 1 h. The precipitate was filtered and washed with CH_2Cl_2. Purification by TLC on silica gel (AcOEt/hexane=1:10) gave the title compound **4a** (45.2 mg, 99%) as a colorless liquid.

4.8. Preparation of 3-phenylpropionic acid 4-methoxybenzyl ester 4b

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of 4-methoxybenzyl alcohol (48.6 mg, 0.35 mmol) and **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 1 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 gave a colorless oil crude product, which was purified by TLC on silica gel ($CHCl_3$) gave the title compound **4b**[20] (85.1 mg, 90%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (t, J=7.8 Hz, 2H), 2.93 (t, J=7.8 Hz, 2H), 3.75 (s, 3H), 5.02 (s, 2H), 6.83–6.86 (m, 2H), 7.17–7.25 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 35.7, 55.0, 65.9, 113.7, 126.0, 127.9, 128.1, 128.3, 129.9, 140.3, 159.4, 172.5; IR (NaCl disc) 1733 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{18}O_3$: 240.1256; found: m/z 240.1254.

4.9. Preparation of 3-phenylpropionic acid 4-nitrobenzyl ester 4c

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of 4-nitrobenzyl alcohol (53.9 mg, 0.35 mmol) and **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 10 min. 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 gave a colorless oil crude product, which was purified by TLC on silica gel ($CHCl_3$) gave the title compound **4c**[21] (93.8 mg, 94%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (t, J=7.4 Hz, 2H), 2.86 (t, J=7.6 Hz, 2H), 5.05 (s, 2H), 7.06–7.17 (m, 5H), 7.17–7.27 (m, 2H), 8.00–8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 35.4, 64.4, 123.4, 126.2, 128.0, 128.1, 128.3, 139.9, 143.0, 147.3, 172.1; IR (NaCl disc) 1738 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{15}NO_4$: 285.1001; found: m/z 285.1000.

4.10. Preparation of 3-phenylpropionic acid 3-phenyl-1-propyl ester 4d

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of 3-phenyl-1-propanol (47.8 mg, 0.35 mmol) and **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 2.5 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 gave a colorless oil crude product, which was purified by TLC on silica gel ($CHCl_3$) gave the title compound **4d**[22] (81.7 mg, 87%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86–1.93 (m, 2H), 2.58–2.62 (m, 2H), 2.93 (t, J=7.8 Hz, 2H), 4.06 (t, J=6.4 Hz, 2H), 7.11–7.19 (m, 6H), 7.23–7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 30.8, 32.0, 35.7, 63.6, 125.8, 126.1, 128.1, 128.2, 128.3, 128.4, 140.3, 141.0, 172.7; IR (NaCl disc) 1733 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{20}O_2$: 268.1463; found: m/z 268.1459.

4.11. Preparation of 3-phenylpropionic acid 1-methylbenzyl ester 4e

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of 4-methylbenzyl alcohol (41.2 μL, 0.35 mmol) and **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 9 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 gave a colorless oil crude product, which was purified by TLC on silica gel (CH_2Cl_2) gave the title compound **4e**[14] (79.2 mg, 89%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, J=6.8 Hz, 3H), 2.71 (dt, J=7.8, 8.2 Hz, 2H), 3.0 (t, J=8.2 Hz, 2H), 5.94 (q, J=13.2 Hz, 1H), 7.22–7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 30.9, 36.1, 72.3, 126.0, 126.1, 127.7, 128.2, 128.4, 140.4, 141.5, 172.0; IR (NaCl disc) 1733 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{18}O_2$: 254.1307; found: m/z 254.1303.

4.12. Preparation of 3-phenylpropionic acid diphenylmethyl ester 4f

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of benzohydrol (65.0 mg, 0.35 mmol) and **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 2.5 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 gave a solid product, which was purified by TLC on silica gel (AcOEt/hexane=1:3) gave the title compound **4f**[14] (99.6 mg, 90%) as a colorless solid; mp 50–51 °C (from AcOEt/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71–2.75 (m, 2H), 2.96 (t, J=7.8 Hz, 2H), 6.88 (s, 1H), 7.10–7.31 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 36.0, 76.8, 126.2, 126.4, 127.0, 127.8, 128.2, 128.4, 128.5, 140.0, 140.2, 171.8; IR (KBr) 1734 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{20}O_2$: 316.1463; found: m/z 316.1461.

4.13. Preparation of 3-phenylpropionic acid phenyl ester 4h

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of phenol (32.9 mg, 0.35 mmol) and **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 20 min. 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, which was

purified by TLC on silica gel (CH_2Cl_2) gave the title compound **4h**[14] (75.2 mg, 95%) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, J=7.6 Hz, 2H), 3.06 (t, J=7.6 Hz, 2H), 6.98–7.01 (m, 2H), 7.17–7.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 35.9, 121.5, 125.7, 126.4, 128.3, 128.5, 129.3, 140.0, 150.6, 171.3; IR (NaCl disc) 1759 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{20}O_2$: 226.0994; found: m/z 226.0990.

4.14. Preparation of *N*-2-phenylethyl-3-phenyl propanamide 4i

Typical procedure: 2-Phenylethylamine (44.4 μL, 0.35 mmol) was added to a stirred solution of **8** (100.0 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 8 min. 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 gave a solid product, which was purified by TLC on silica gel (AcOEt/hexane=2:1) gave the title compound **4i**[23] (78.9 mg, 89%) as a colorless solid; mp 96–97.5 °C (from AcOEt/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (t, J=7.6 Hz, 2H), 2.71 (t, J=7.0 Hz, 2H), 2.92 (t, J=7.8 Hz, 2H), 3.45 (q, J=13.4 Hz, 2H), 5.59 (s, 1H), 7.06–7.08 (m, 2H), 7.15–7.28 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 35.5, 38.3, 40.5, 126.1, 126.3, 128.2, 128.4, 128.5, 128.6, 138.7, 140.7, 171.9; IR (KBr) 3301, 1637 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{19}NO$: 253.1467; found: m/z 253.1466.

4.15. Preparation of 3-phenyl-2-(3-phenyl-propionylamino) propionic acid methyl ester 4j

Typical procedure: 4-DMAP (43.0 mg, 0.35 mmol) was added to a stirred solution of L-phenylalanine methyl ester hydrochloride (76.2 mg, 0.35 mmol) and **8** (100 mg, 0.35 mmol) in CH_2Cl_2 at room temperature under N_2 and stirred for 1.5 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 gave a solid product, which was purified by TLC on silica gel (AcOEt/hexane=1:1) gave the title compound **4j**[24] (83.9 mg, 77%) as a colorless solid; mp 70–71.5 °C (from AcOEt/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43–2.56 (m, 2H), 2.91–2.96 (m, 2H), 3.06 (d, J=5.2 Hz, 2H), 3.70 (s, 3H), 4.86–4.91 (m, 1H), 5.83 (d, J=7.2 Hz, 1H), 6.92–6.94 (m, 2H), 7.18–7.31 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 37.8, 38.1, 52.2, 52.9, 126.2, 127.0, 128.3, 128.5, 129.2, 135.6, 140.6, 171.4, 171.9; IR (KBr) 3324, 1753, 1647 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{21}NO_3$: 311.1521; found: m/z 311.1520.

4.16. Preparation of 3-phenylpropionyloxycholesterol ester 10

Typical procedure: 4-DMAP (41.2 mg, 0.37 mmol) was added to a stirred solution of cholesterol (144.6 mg, 0.37 mmol) and **6** (100.0 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 and stirred for 1 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 gave a solid product, which was purified by TLC on silica gel (CH_2Cl_2) gave the title compound **10** (149.7 mg, 78%) as a colorless solid; mp 99–100 °C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.86 (dd, J=1.6, 12.8 Hz, 6H), 0.93 (d, J=6.4 Hz, 3H), 0.94–1.08 (m, 6H), 1.10–1.21 (m, 7H), 1.24–1.40 (m, 4H), 1.42–1.60 (m, 7H), 1.78–1.90 (m, 3H), 1.91–2.02 (m, 2H), 2.27 (d, J=7.6 Hz, 2H), 2.58–2.62 (m, 2H), 2.94 (t, J=8.0 Hz, 2H), 4.56–4.65 (m, 1H), 5.36 (d, J=4.0 Hz, 1H), 7.17–7.21 (m, 3H), 7.25–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ11.8, 18.7, 19.3, 21.0, 22.5, 22.8, 23.8, 24.2, 27.7, 28.0, 28.2, 31.0, 31.8, 31.9, 35.7, 36.1, 36.2, 36.5, 36.9, 38.1, 39.5, 39.7, 42.2, 50.0, 56.1, 56.6, 74.0, 122.6, 126.1, 128.3, 128.4, 139.6, 140.5, 172.3; IR (KBr) 1734 cm^{-1}. Anal. Calcd for $C_{36}H_{54}O_2$: C, 83.34; H, 10.49. Found: C, 83.39; H, 10.42.

Supplementary data

Supplementary data associated with this article can found in online version at doi:10.1016/j.tet.2010.07.011.

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