Supporting Information

One-Pot Sequential Reactions for the Synthesis of Versatile ^{11}C-Labeled Olefin Frameworks

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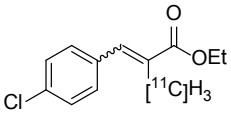
1. Structures of products

1-1. ^{11}C-labeled compounds



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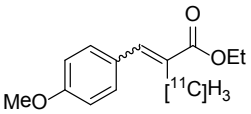

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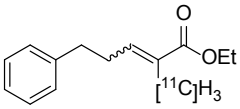

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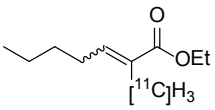

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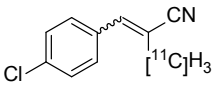

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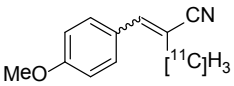

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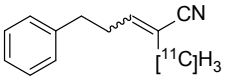

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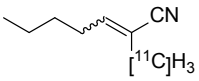

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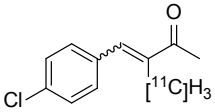

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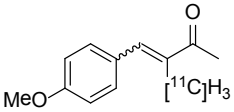

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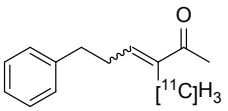

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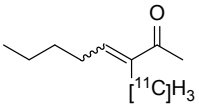

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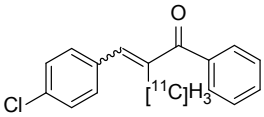

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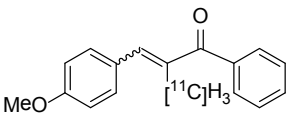

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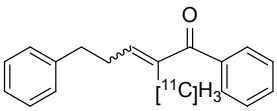

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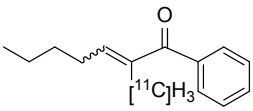
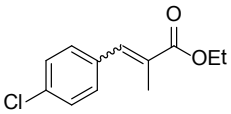


5dd

1-2. Reference compounds



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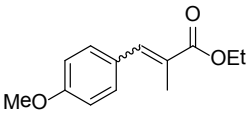

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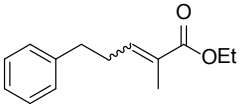

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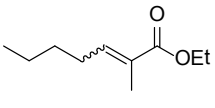

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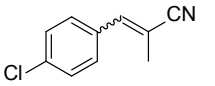

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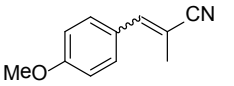

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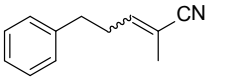

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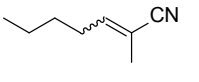

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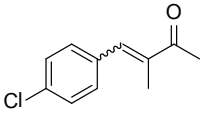

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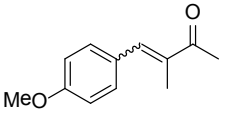

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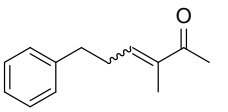

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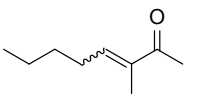

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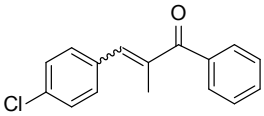

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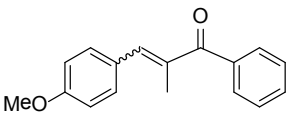

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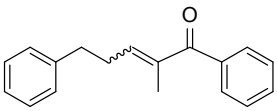

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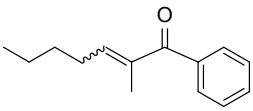


6dd

Compounds, **6aa**-**6dd** were already known.[1-12] They were prepared from the corresponding diethyl phosphonate and aldehyde by HWE reaction using NaOH or KO^{t}Bu or TBAF as base. *E*/*Z* ratio of products which were prepared by

TBAF-mediated HWE reaction was shown below. They were determined by ^{1}H NMR.

Product	*E*:*Z*	Product	*E*:*Z*	Product	*E*:*Z*	Product	*E*:*Z*
6aa	>99:<1	**6ba**	72:28	**6ca**	>99:<1	**6da**	97:3
6ab	>99:<1	**6bb**	69:31	**6cb**	>99:<1	**6db**	>99:<1
6ac	72:28	**6bc**	70:30	**6cc**	>99:<1	**6dc**	85:15
6ad	73:27	**6bd**	68:32	**6cd**	51:48	**6dd**	75:25

2. Experimental section

All chemicals and solvents were purchased from Sigma-Aldrich Japan (Tokyo, Japan), Wako Pure Chemical Industries (Osaka, Japan), Tokyo Kasei Kogyo (Tokyo, Japan), Nacalai Tesque (Kyoto, Japan), or ABX (Radeberg, Germany) and were used without further purification. NMR spectra were recorded on a JEOL JNM-GSX270WB spectrometer (Tokyo, Japan). ESI-mass spectra were measured with an LCMS-2020 system (Shimadzu, Kyoto, Japan). Microwave irradiation was carried out in a Biotage Initiator (Tokyo, Japan) in a sealed vessel. Radioactivity was quantified with an ATOMLAB 500 dose calibrator (BIODEX, New York). Analytical HPLC was performed on a Shimadzu system equipped with pumps and a UV detector, and effluent radioactivity was measured with a flow count radio HPLC analyzer FC1000 (BIOSCAN, Washington, DC). COSMOSIL C_{18} AR-II and cholester (Nacalai Tesque, Kyoto, Japan) columns were used for analytical HPLC. [^{11}C]Carbon dioxide was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction: a nitrogen target containing 0.5% oxygen was bombarded with a CYPRIS HM-12S Cyclotron (Sumitomo Heavy Industries, Tokyo, Japan). [^{11}C]Methyl iodide (**1**) was prepared via the reaction of [^{11}C]H_4 (derived from [^{11}C]O_2) and I_2 on a C-GPS100 (Sumitomo Heavy Industries) or Tracerlab FX MeI (GE, Milwaukee, WI) chemistry synthesizer.

2-1. ^{11}C-Methylation of diethyl phosphonates 1a–e

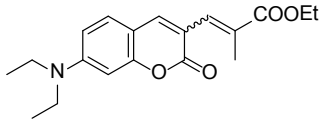
A solution of base in THF (25 μL, 25 μmol) was added to a 25 mM solution of phosphonate **2** in THF (200 μL, 5 μmol). To the solution was introduced [^{11}C]H_3I (**1**) (50–200 MBq in 100 μL of THF) at rt. After 90 s, the reaction was quenched by 100 μL of 100 mM ammonium acetate in 0.5% aqueous acetic acid, and the resulting mixture was analyzed by HPLC (column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm, 5 μm; eluent: 100

mM ammonium acetate in a 50:50 mixture of 0.5% aqueous acetic acid and CH_3CN; flow rate: 1 mL/min).

2-2. Synthesis of 3a in one-pot by sequential ^{11}C-methylation of phosphonate 1a and subsequent Horner–Wadsworth–Emmons reaction with 2a

A 1 M solution of TBAF in THF (25 μL, 25 μmol) was added to a 25 mM solution of phosphonate **2a** in THF (200 μL, 5 μmol). To the solution was introduced $[^{11}C]H_3I$ (50–100 MBq in 200 μL of THF) at rt. After 90 s, 50 mM solution of aldehyde **4a** in THF (200 μL, 10 μmol) was added, and the solution was heated for 5 min at 60 °C. The reaction mixture was quenched with 0.1% acetic acid in acetonitrile and analyzed by HPLC (column: COSMOSIL C_{18} AR-II 4.6 i.d. ×150 mm, 5 μm; eluent: H_2O:CH_3CN = 30:70; flow rate: 1 mL/min).

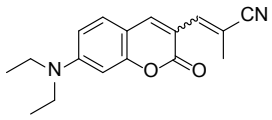
2-3. Synthesis of 3-[7-(diethylamino)-2-oxo-2*H*-1-benzopyran-3-yl]acrylic acid ethyl ester (6ae)



6ae

To a stirred mixture of 7-diethylamino-2-oxo-2H-chromene-3-carboxyaldehyde (49 mg) and diethyl (1-carboethoxy)ethylphosphonate (95 mg) in THF (2.0 mL) was added a 1.0 M solution of KO^{t}Bu in THF (0.4 mL). The reaction mixture was stirred at rt for 5 h and then partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography (Biotage ZIP cartridge, 10 g) eluting with 4:1 hexane:ethyl acetate to afford an *E*/*Z* mixture of the title compound as a yellow solid. *E*-isomer: ^1H NMR (270 MHz, $CDCl_3$): δ 7.70 (m, 1H), 7.69 (s, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.60 (dd, J = 2.7, 8.9 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 3.46 (q, J = 7.0 Hz, 4H), 2.13 (d, J = 1.6 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 6H); LC-MS (ESI) *m*/*z*: 330 $[M + H]^+$. *Z*-isomer; ^1H NMR (270 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.23 (d, J = 8.9 Hz, 1H), 6.67 (m, 1H), 6.54 (d, J = 2.7 Hz, 1H), 6.48 (d, J = 2.9 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.46 (q, J = 7.0 Hz, 4H), 2.10 (d, J = 1.6 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 6H); LC-MS (ESI) *m*/*z*: 330 $[M + H]^+$.

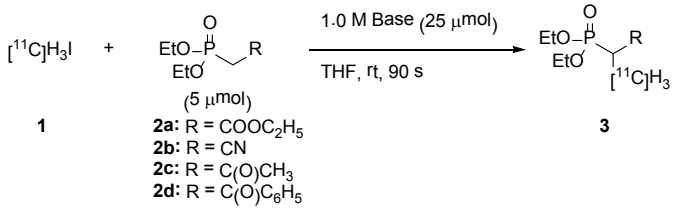
2-4. Synthesis of 2-methyl-3-[7-(diethylamino)-2-oxo-2*H*-1-benzopyran-3-yl]acrylonitrile (6be)

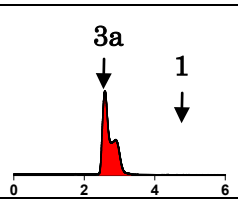
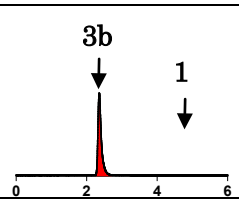
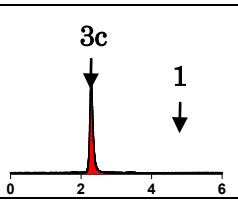
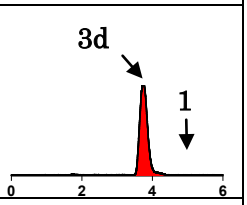
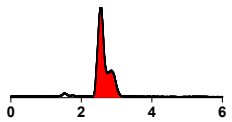
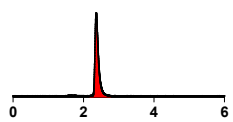
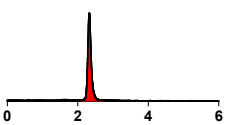
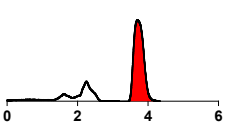
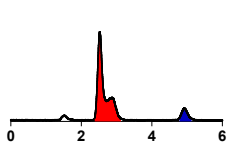
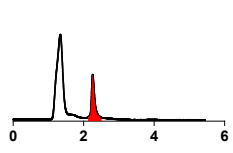
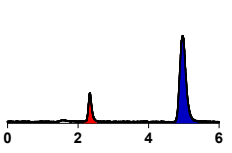
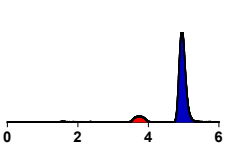
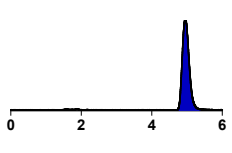
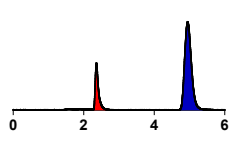
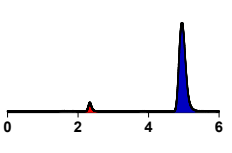
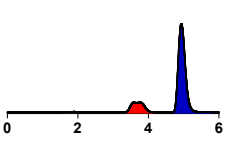


6be

The title compound was prepared from 7-diethylamino-2-oxo-2H-chromene-3-carboxyaldehyde and diethyl (1-cyanoethyl)phosphonate by means of the procedure described for the synthesis of **6ae**. *E*-isomer: ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.18 (m, 1H), 6.61 (dd, J = 2.4, 8.9 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 3.44 (q, J = 7.0 Hz, 4H), 2.15 (d, J = 2.2 Hz, 3H), 1.23 (t, J = 7.0 Hz, 6H); LC-MS (ESI) m/z: 283 $[M + H]^+$. *Z*-isomer: ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.28 (d, J = 8.9 Hz, 1H), 7.25 (s, 1H), 6.61 (dd, J = 2.4, 8.9 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 3.44 (q, J = 7.0 Hz, 4H), 2.15 (d, J = 2.2 Hz, 3H), 1.23 (t, J = 7.0 Hz, 6H); LC-MS (ESI) m/z: 283 $[M + H]^+$.

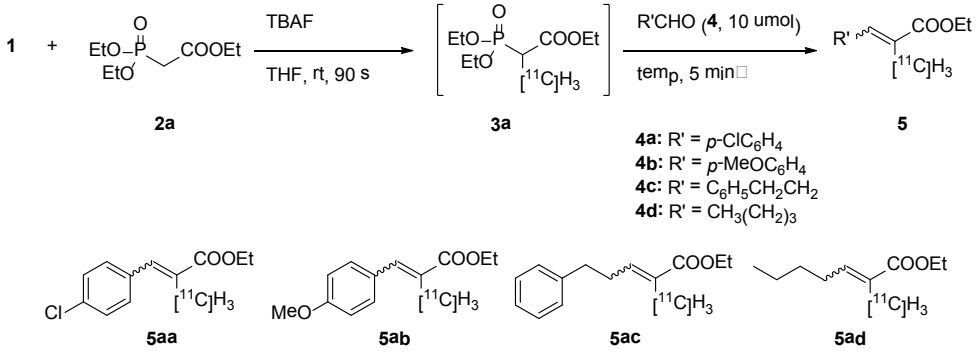
3. Radiochromatograms for Table 1

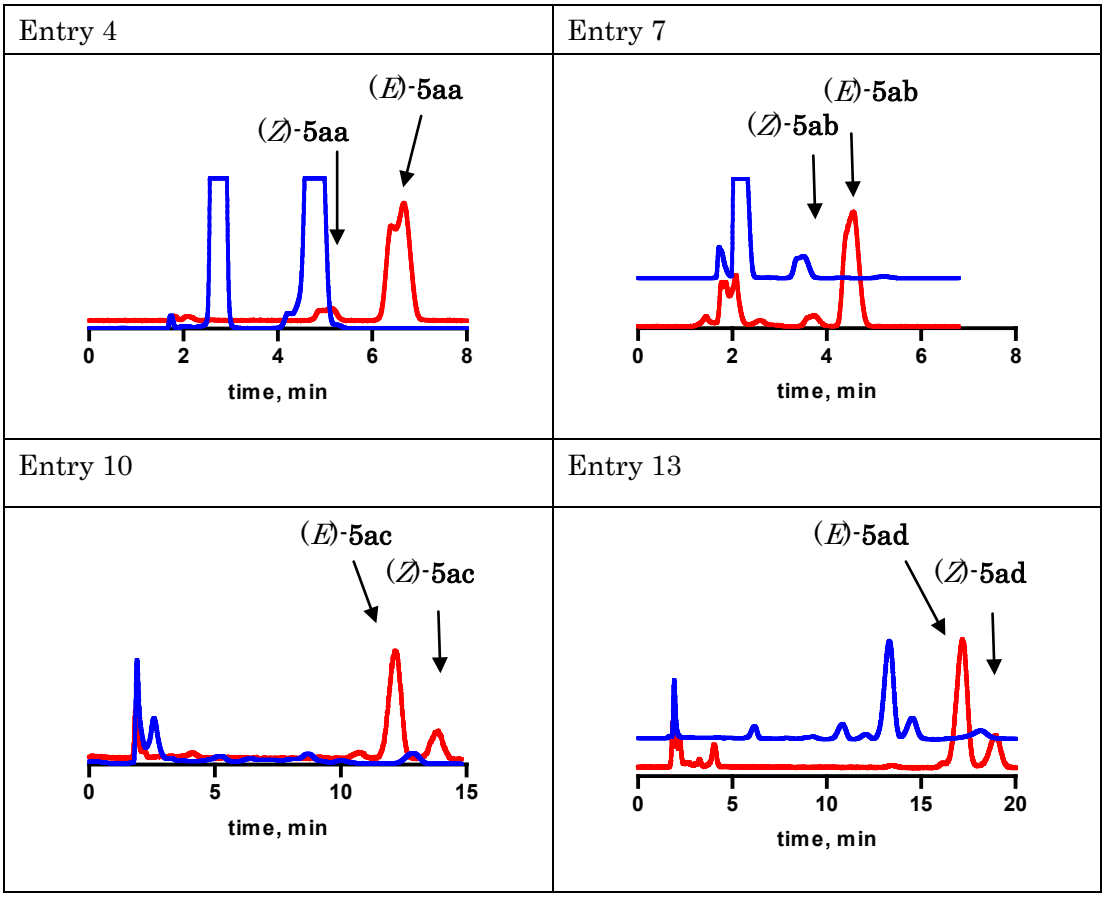


	2a	2b	2c	2d
TBAF				
Verkade's base				
NaOH				
KO^{t}Bu				

Analytical HPLC conditions for **3a–d:** column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm, 5 μm; eluent: CH_3CN:H_2O = 50:50; flow rate: 1 mL/min

4. Chromatograms for Table 2, entries 4, 7, 10, 13.





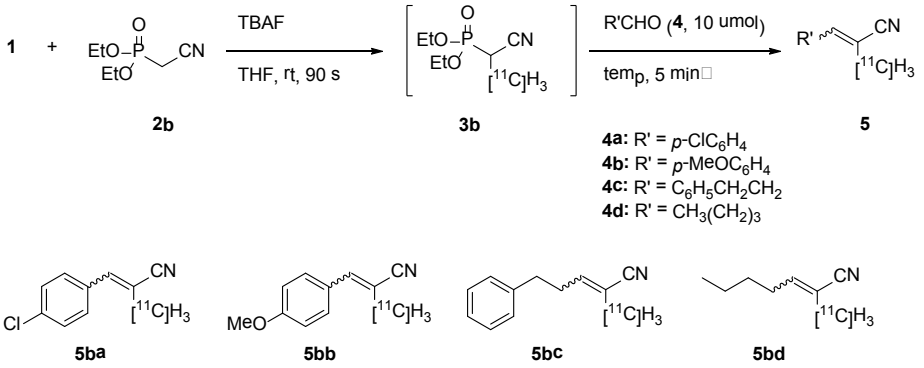
— UV, — RI

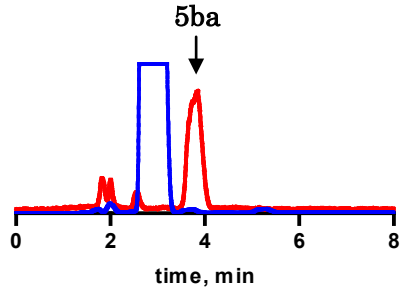
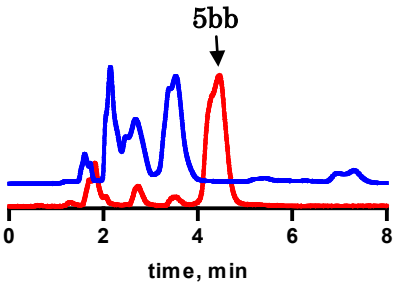
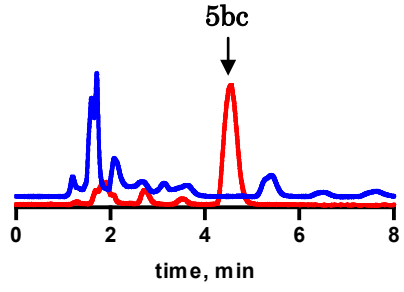
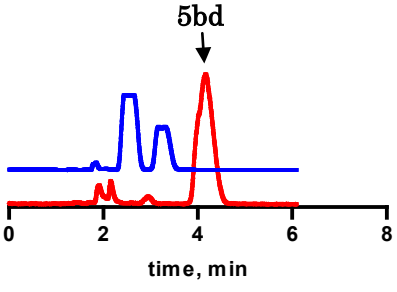
Analytical HPLC conditions for **5aa** and **5ab:** column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm, 5 μm; eluent: CH_3CN:H_2O = 70:30; flow rate: 1 mL/min; UV 254 nm

Analytical HPLC conditions for **5ac**: column: COSMOSIL Cholester 4.6 i.d. × 150 mm, 5 μm; eluent: CH_3OH:H_2O = 70:30; flow rate: 1 mL/min; UV 254 nm

Analytical HPLC conditions for **5ad**: column: Cholester 4.6 i.d. × 150 mm, 5 μm; eluent: CH_3OH:100 mM $AcONH_4$ = 70:30; flow rate: 1 mL/min; UV 254 nm

5. Chromatograms for Table 3, entries 1–4.

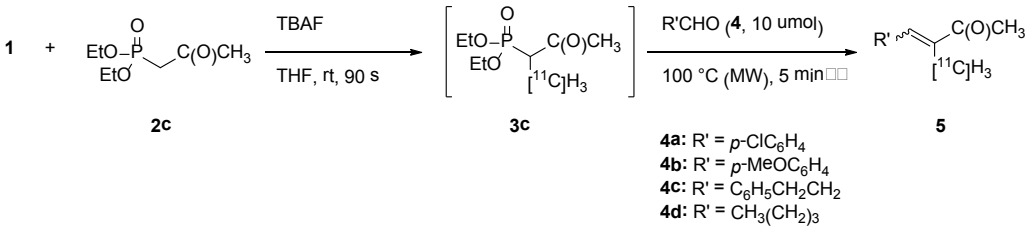


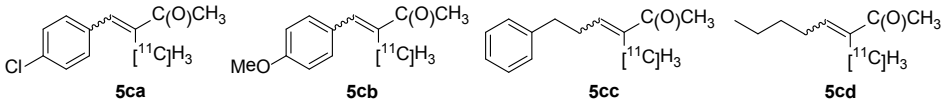
Entry 1	Entry 2
	
Entry 3	**Entry 4**
	

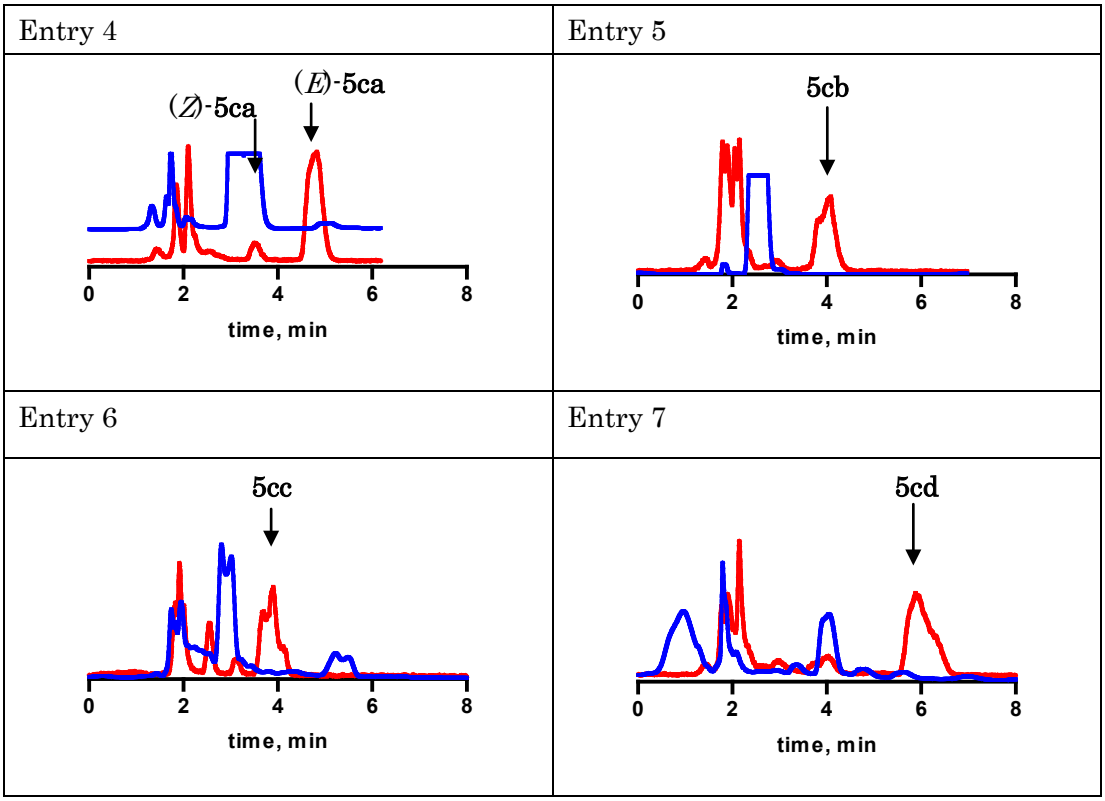
— UV, — RI

Analytical HPLC conditions for **5ba–5bd**: column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm 5 μm; eluent: CH_3CN:H_2O = 65:35; flow rate: 1 mL/min; UV 210 nm

6. Chromatograms for Table 4, entries 4–7.



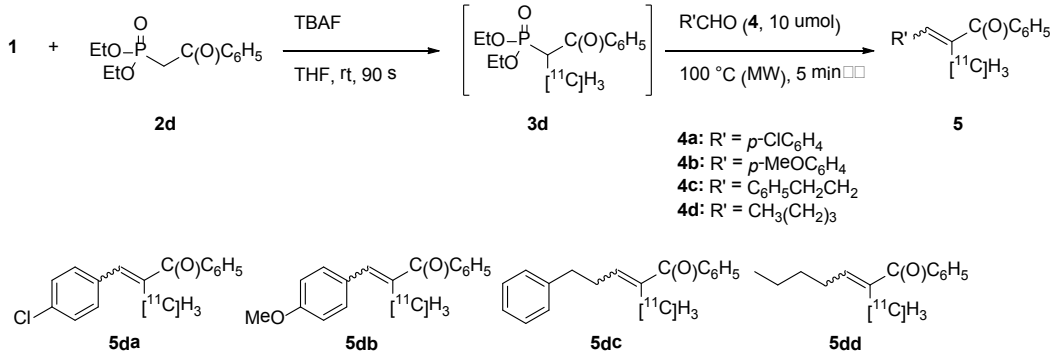


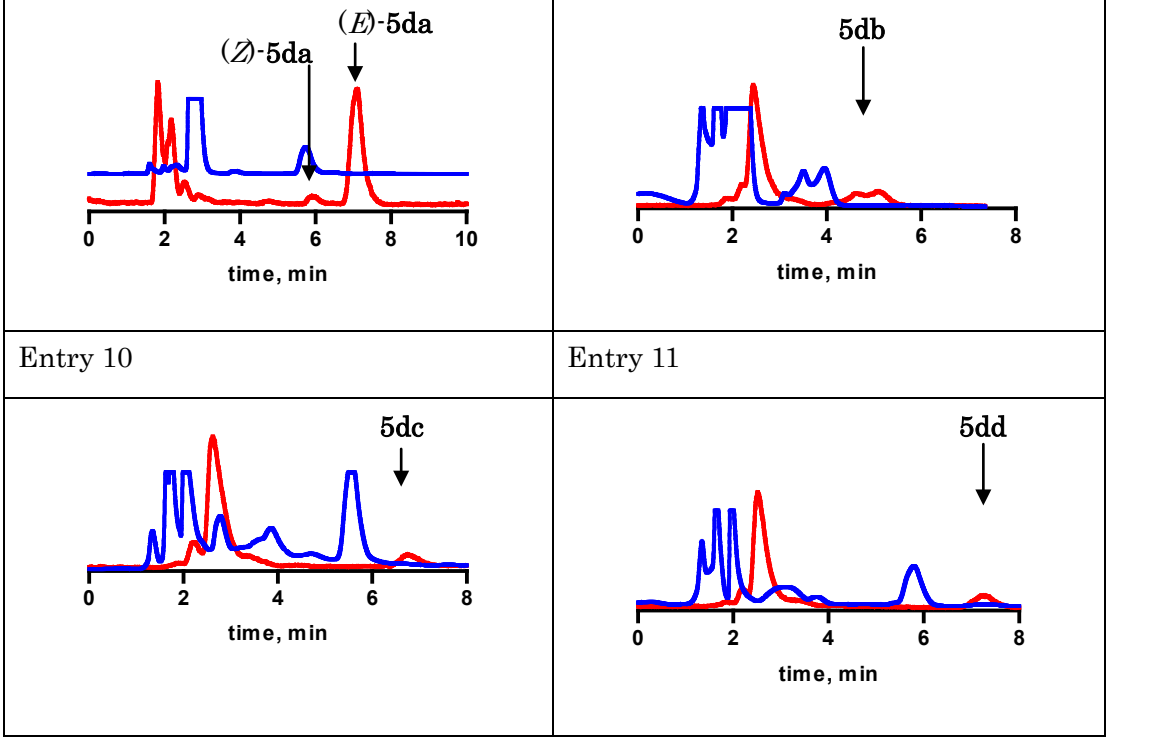


— UV, — RI

Analytical HPLC conditions for **5ca–5cd**: column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm 5 μm; eluent: CH_3CN:H_2O = 65:35; flow rate: 1 mL/min; UV 210 nm

7. Chromatograms for Table 4, entries 8–11.

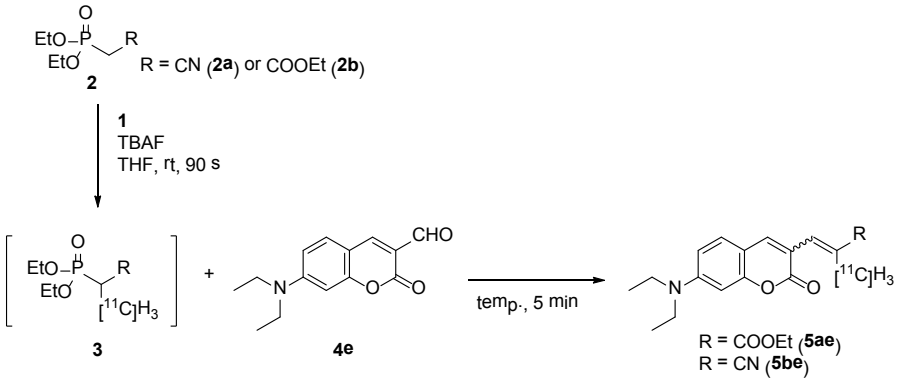




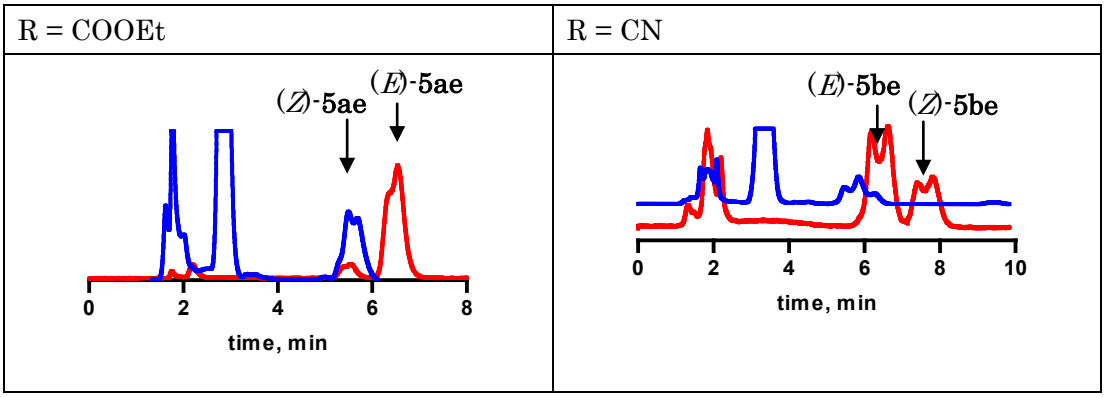
— UV, — RI

Analytical HPLC conditions for **5da–5dd**: column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm, 5 μm. Eluent: CH_3CN:H_2O = 75:25; flow rate: 1 mL/min; UV 254 nm (entry 22). Eluent: CH_3CN:H_2O = 70:30; flow rate: 1 mL/min; UV 210 nm (entries 23, 25, 27)

8. Chromatograms for Figure 2



Products	2:4e:TBAF	temp.	RCC, % (*E*:*Z*)
5ae	2:10:25	60 °C	96 ± 1 (*E*:*Z* = 1:11)
5be	5:10:25	rt	96 ± 0.4 (*E*:*Z* = 1:2)



— UV, — RI

Analytical HPLC conditions for **5ae**: column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm, 5 μm; eluent: CH_3CN:H_2O = 70:30; flow rate: 1 mL/min; UV 254 nm

Analytical HPLC conditions for **5be**: column: COSMOSIL C_{18} AR-II 4.6 i.d. × 150 mm, 5 μm; eluent: CH_3CN:H_2O = 60:40; flow rate: 1 mL/min; UV 254 nm

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