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Synthesis of Fluorescent Amino Acids via Palladium-Catalyzed Allylic Alkylations

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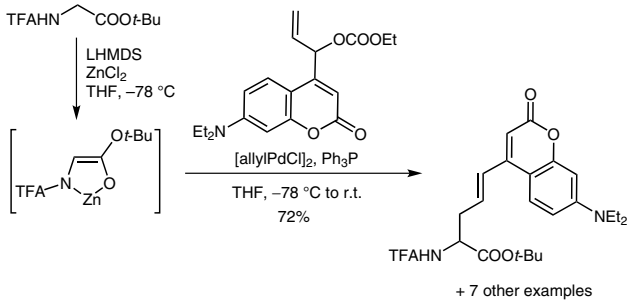
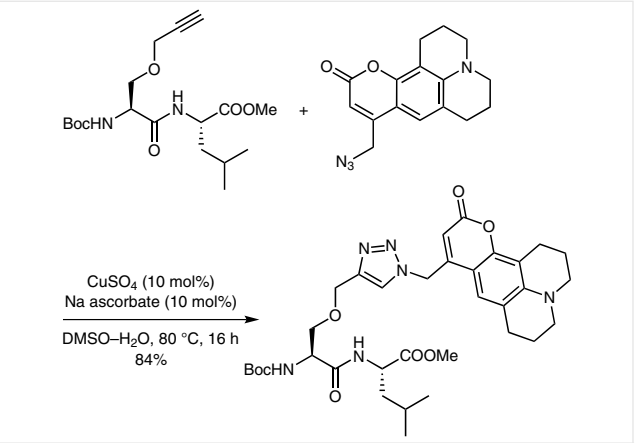


Received: 11.02.2016
Accepted after revision: 06.04.2016
Published online: 19.05.2016
DOI: 10.1055/s-0035-1561628; Art ID: ss-2016-t0104-op

Abstract Coumarin-derived allylic carbonates are found to be suitable electrophiles for the synthesis of fluorescent amino acids via palladium-catalyzed allylic alkylation of chelated glycine enolates. The formation of regioisomers can be suppressed by proper choice of the allyl carbonate.

Key words allylation, amino acids, chelates, coumarins, fluorescence labeling, palladium

Fluorescence microscopy is an important and powerful tool in the life sciences since it allows a three-dimensional imaging in living cells.[1] A wide range of fluorescence dyes can be used for the labeling, for example, of proteins.[2] Coumarins play an important role, especially those having electron-donating groups in 7-position, because of their excellent fluorescence quantum yield.[3] They were found to be ideal candidates for the development of fluorescence labels.[4] In general, those labels are coupled to functionalized amino acids such as lysines,[5] cysteines,[6] or tyrosines.[7] Alternatively, those amino acids can also be modified by incorporation of either an alkyne or an azide moiety, allowing the introduction of the fluorescence label via click chemistry.[8] Since our group is involved in the synthesis of peptidic natural products,[9] we also developed a protocol for peptide labeling using the Huisgen–Meldal–Sharpless [3+2] cycloaddition,[10] and 'clickable' aminocoumarins (Scheme 1).[8b] Another focus of our group is the development of new synthetic protocols for the synthesis of unusual amino acids via reaction of chelated amino acid ester enolates.[11] These highly reactive enolates can be used as nucleophiles, for example, in Michael additions[12] or in transition-metal-catalyzed reactions.[13] Besides the commonly used Pd-catalyzed version, also Ru[14] and Rh catalysts[15] can be applied, showing different regio- and stereoselectivities. Overall, excellent yields are obtained and the allylic alkylation can also be used for the highly stereoselective alkylation of peptides.[16]

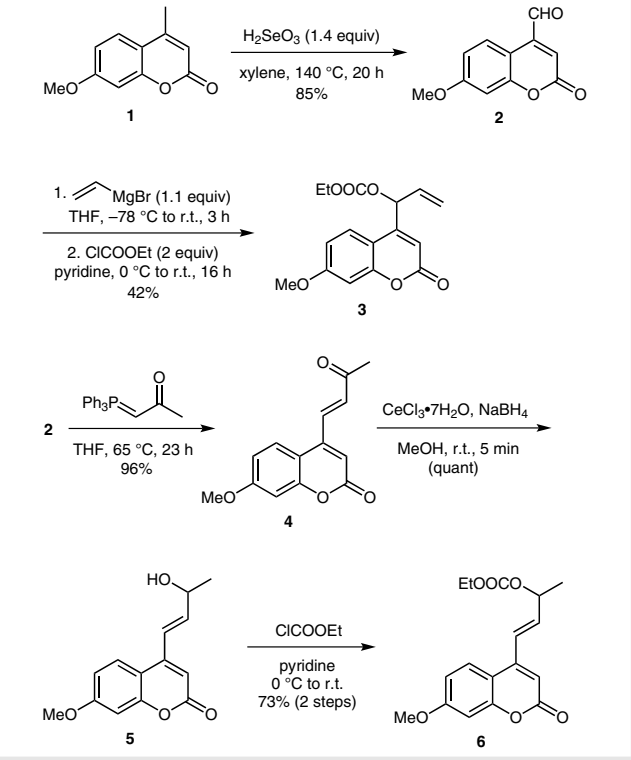


Scheme 1 Fluorescence labeling of peptides via click reaction

Therefore, we were interested to see, if, for example, the Pd-catalyzed allylic alkylation might also be suitable for the incorporation of fluorescence dyes into amino acids. Herein, we describe the synthesis of a wide range of different fluorescence labelled allylic substrates and their reaction with chelated glycine ester enolates.

We started our investigations with 7-methoxy-substituted coumarins, since these are easily available. The 4-methyl derivative **1** can be obtained from resorcin via Pechmann condensation and subsequent *O*-methylation.[17] Oxidation with selenious acid provided 4-formylcoumarin **2** in good yield (Scheme 2). Compound **2** was used for the synthesis of two different allylic substrates. On the one hand, vinyl-Grignard addition furnished an allyl alcohol, which

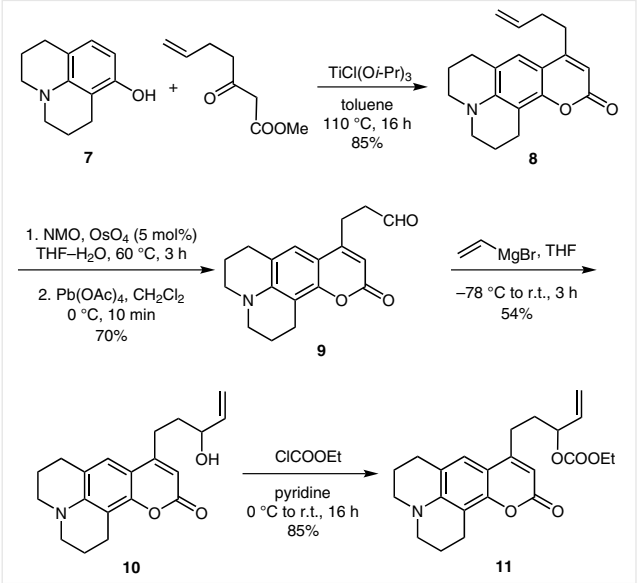
was directly acylated to allyl carbonate **3**. On the other hand, **2** was also subjected to a Wittig olefination giving access to vinyl ketone **4**, which was reduced according to the Luche protocol. The secondary alcohol **5** was also converted into the corresponding carbonate **6**.



Scheme 2 Synthesis of 7-methoxycoumarin-derived allyl carbonates

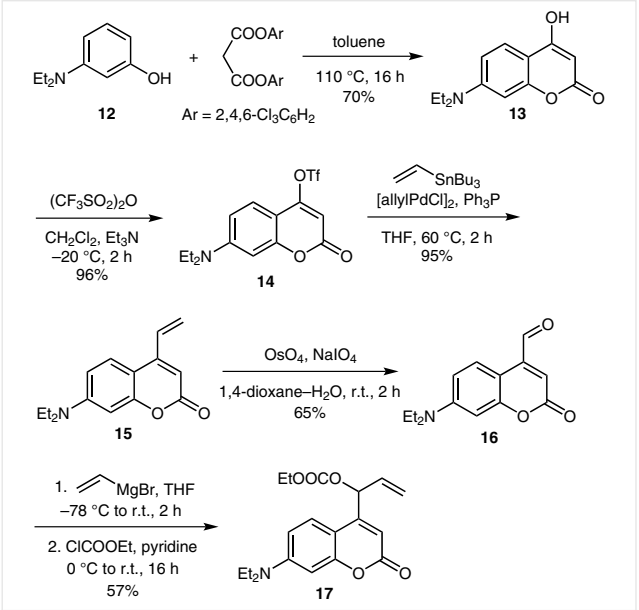
During our synthesis of clickable fluorescence labels[8b] we developed a mild version of the Pechmann condensation, which was also suitable for the sensitive 8-hydroxyjulodine (**7**) (Scheme 3). We used this approach also for the synthesis of allylic carbonate **11** containing this amino functionalized coumarin dye. Compound **7** was refluxed in toluene with methyl-3-oxo-6-heptenoate in the presence of $ClTi(Oi\text{-}Pr)_3$ affording the coumarin derivative **8** in high yield. The terminal double bond was subjected to dihydroxylation followed by an oxidative cleavage. The aldehyde **10** obtained was also subjected to a vinyl-Grignard addition and acylation as described before.

Although 8-hydroxyjulodine (**7**) is commercially available, it is rather an expensive compound. Therefore, we tried to replace it by 3-diethylaminophenol (**12**). Surprisingly, the modified Pechmann condensation, which worked perfect in the case of **7** failed almost completely with the diethylamino phenol **12**. Therefore, we had to develop an independent synthetic route (Scheme 4). According to literature,[18] **12** was reacted with bis-2,4,6-trichlorophenol



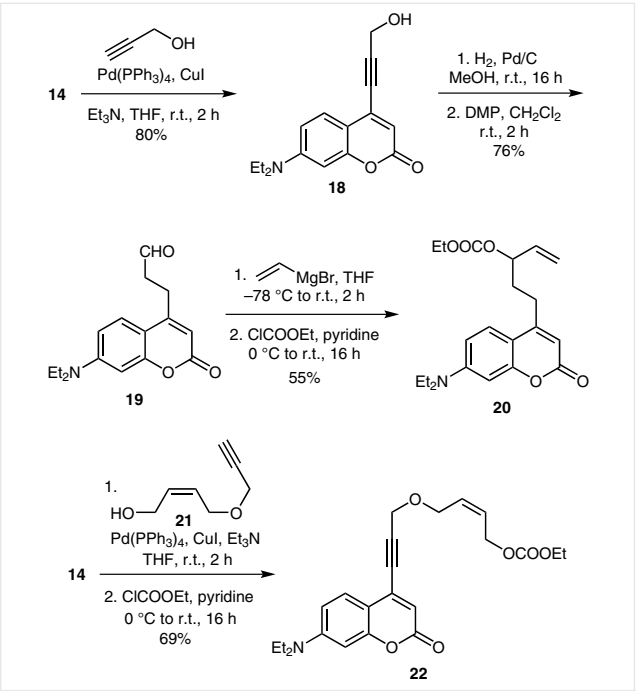
Scheme 3 Synthesis of 8-hydroxyjulodine-derived allyl carbonate **11**

malonate to the 4-hydroxycoumarin **13**, which was converted into triflate **14** in high yield. To get an allylic substrate with the dye directly substituted at the allyl moiety, **14** was subjected to a Stille coupling with vinylstannane to give 4-vinylcoumarin **15** in almost quantitative yield. Oxidative cleavage of the double bond provided aldehyde **16**, which was converted into the carbonate **17** as described before. It should be mentioned that we failed to get aldehyde **16** directly from the triflate via Pd-catalyzed carbonylation.



Scheme 4 Synthesis of 7-diethylamino-derived allyl carbonate **17**

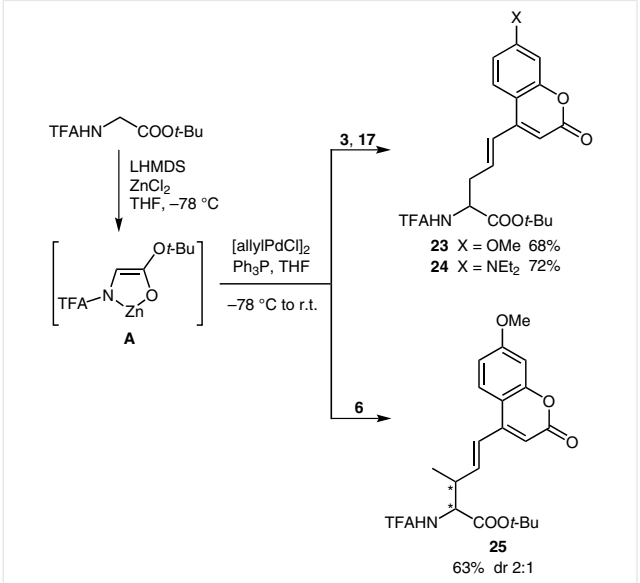
To incorporate a spacer between the dye and the allyl fragment, and to get substrates analogous to **11**, **14** was subjected to a Sonogashira coupling with propargyl alcohol, which provided alcohol **18** in almost quantitative yield (Scheme 5). Hydrogenation of the triple bond and Dess–Martin oxidation afforded the aldehyde **19**, which was converted into carbonate **20** as described. To introduce an even larger spacer, triflate **14** was also subjected to a Sonogashira coupling with butenediol-derived alkyne **21**. Subsequent acylation provided carbonate **22** in overall good yield.



Scheme 5 Synthesis of 7-diethylamino-derived allyl carbonates via Sonogashira coupling

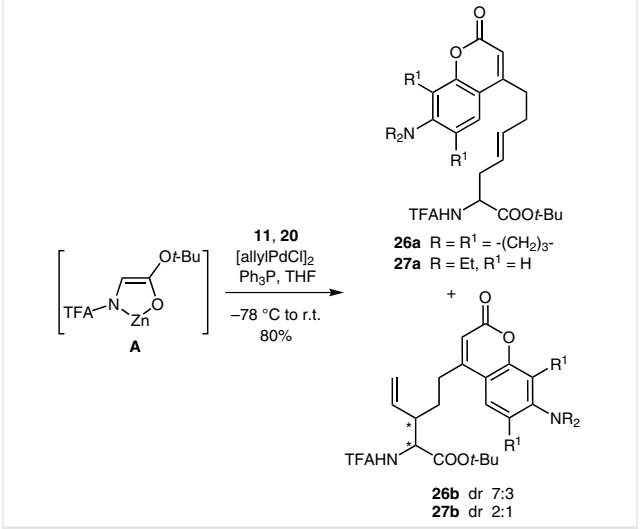
With those allylic substrates in hand, we next investigated allylic alkylations of chelated glycine ester enolate **A** to get access to fluorescence labeled amino acids (Scheme 6). With the allylic substrates **3** and **17** bearing the dye directly at the allyl moiety only one regioisomer **23** and **24** was obtained, respectively, resulting from an attack of the enolate at the sterically least hindered position. The double bond was in conjugation to the coumarin and was formed as the *E*-isomer exclusively. The same regioselectivity was also observed in the allylation using secondary carbonate **6**. In this case also, the product **25** with the *trans* double bond was obtained as a 2:1 diastereomeric mixture.

An interesting observation was made in reactions using the substrates with the 'short spacer' between the dye and the allyl moiety (Scheme 7). In the case of the terminal allyl carbonates **11** and **20**, we expected to get also the linear allylation products with high preference, which is typical for



Scheme 6 Allylic alkylations using carbonates **3**, **6**, and **17**

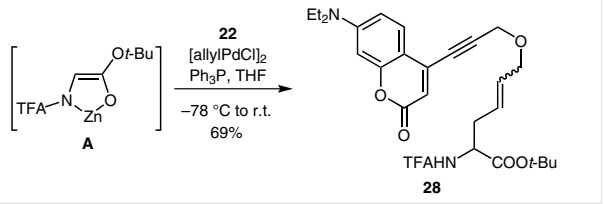
such terminal allyl complexes. Instead, a 6:4 mixture of linear and branched products **26a** and **26b** was obtained in the case of **11** (80% yield). The regioselectivity in the case of **20** was 6:1 (**27a**:**27b**), while the yield was the same. Also, the diastereoselectivities of the branched products **b** were in the same range as the results obtained with the secondary carbonate **6**.



Scheme 7 Allylic alkylations using carbonates **11** and **20**

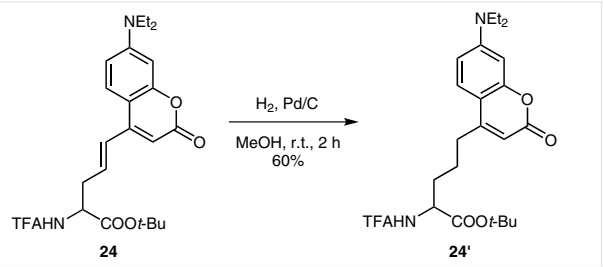
The moderate regioselectivity was the reason why we also investigated allylations of substrates with the larger spacer bearing an oxygen between the dye and the allyl moiety **22**. In general, such oxygen-substituted allylic substrates react under Pd-catalyzed conditions preferentially at

the allylic position distal to the *O*-functionality.[19] Indeed, with this substrate only the linear product **28** was obtained as a 7:3 *E*/*Z*-mixture (Scheme 8).



Scheme 8 Allylic alkylation using carbonate **22**

The formation of *E*/*Z*-mixture is a little surprising, since in most cases the *E*-isomers are formed with high preference, but it is not a serious issue, because the double bond can easily be removed by catalytic hydrogenation, as illustrated with the hydrogenation of **24** (Scheme 9). Closely related coumarin-substituted amino acids have been reported by Schultz et al. as genetically encoded fluorescent amino acids.[20]



Scheme 9 Catalytic hydrogenation of **24**

In conclusion, we could show that the Pd-catalyzed allylic alkylation is a powerful tool for the introduction of coumarin fluorescence labels into amino acids. Although terminal allylic carbonates give mixtures of linear and branched allylation products, this problem can be solved by either removing the spacer between the dye and the allyl moiety, or by introducing an oxygen into the spacer. In this case, the linear allylation products are formed preferentially. So far, the fluorescent amino acids are formed as racemic mixtures. For a stereoselective protocol one might use either chiral glycine esters, or chiral peptides as nucleophiles. In this case, the stereochemical outcome of the allylic alkylation can nicely be controlled by the stereogenic centers of the peptide chain.[16] Applications to the fluorescence labeling of peptides and natural products are currently under investigation.

All air- and moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of N_2 or argon. Anhyd solvents were distilled before use: THF was distilled from $LiAlH_4$, CH_2Cl_2 was dried with CaH_2 before distillation. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.063–0.2 mm) and with a flash chromatography system [Reveleris (Grace), RediSep-columns 4 g, 12 g, 24 g, and 40 g from Axel Semrau]. Mixtures of EtOAc, PE, or CH_2Cl_2 and MeOH were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey-Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV light, aq $KMnO_4$, or ninhydrin solution. Melting points were determined with a Dr. Tottoli (Büchi) melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS; $CHCl_3$ was used as the internal standard. Diastereomeric ratios were determined by NMR spectroscopy. Mass spectra were recorded with a Finnigan MAT 95 spectrometer using the CI technique. A Jasco V-650 spectrophotometer was used to measure the absorptions spectra, while a Jasco FP-6500 was used for the fluorescence spectra. Elemental analyses were performed at Saarland University.

7-Methoxy-2-oxo-2*H*-chromene-4-carbaldehyde (2)[17]

Selenious acid (1.47 g, 11.4 mmol) was added to a solution of 7-methoxy-4-methylcoumarin (**1**; 1.61 g, 8.46 mmol) in xylene (22 mL). The reaction mixture was refluxed for 20 h and filtered hot. On cooling, yellow crystals precipitated, which were separated and dried; yield: 1.47 g (7.19 mmol, 85%); yellow crystals; mp 193–195 °C; R_f = 0.55 (PE–EtOAc, 1:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 6.71 (s, 1 H), 6.89 (d, *J* = 2.6 Hz, 2 H), 6.92 (dd, *J* = 9.0, 2.6 Hz, 1 H), 8.49 (d, *J* = 9.0 Hz, 1 H), 10.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 101.1, 112.2, 113.3, 127.4, 143.8, 156.5, 160.8, 163.4, 166.4, 191.8.

Ethyl [1-(7-Methoxy-2-oxo-2*H*-chromen-4-yl)allylcarbonate (3)

Aldehyde **2** (613 mg, 3.00 mmol) was dissolved in THF (55 mL) and was cooled to –20 °C before vinylmagnesium bromide (1 M, 3.6 mL, 3.6 mmol) in THF was added. The cooling bath was removed and the mixture was allowed to warm to r.t.. After stirring for 3 h, the solution was diluted with CH_2Cl_2 (50 mL) and hydrolyzed with aq 1 M NH_4Cl (20 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (2 ×), the organic layers were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The crude allyl alcohol was dissolved in anhyd pyridine (3 mL) and ethyl chloroformate (0.6 mL, 1.95 g, 6.00 mmol) was added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight, before it was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with aq 1 N $CuSO_4$ to remove the excess pyridine and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by flash chromatography (PE–EtOAc, 9:1 to EtOAc); yield: 3.83 g (1.26 mmol, 42%); yellow oil; R_f = 0.24 (PE–EtOAc, 7:3).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 3.87 (s, 3 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 5.42 (dd, *J* = 10.2, 0.7 Hz, 1 H), 5.36 (dd, *J* = 17.2, 0.7 Hz, 1 H), 5.89 (m, 1 H), 6.28 (m, 1 H), 6.41 (s, 1 H), 6.81–6.88 (m, 2 H), 7.55 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 55.8, 64.8, 74.9, 101.2, 110.3, 112.6, 112.7, 120.8, 125.6, 132.7, 151.6, 154.0, 155.9, 160.9, 162.8.

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{16}H_{16}O_6$: 304.0941; found: 304.0970.

(*E*)-7-Methoxy-4-(3-oxobut-1-en-1-yl)-2*H*-chromen-2-one (4)

Aldehyde **2** (163 mg, 0.8 mmol) was added to a suspension of 1-triphenylphosphanylidene-2-propenone (261 mg, 0.82 mmol) in THF (50 mL) and the reaction mixture was refluxed for 23 h. After cooling to

r.t. and removal of the solvent, the crude product was purified by flash chromatography (PE–EtOAc, 9:1 to EtOAc); yield: 187 mg (0.77 mmol, 96%); yellow solid; mp 135–138 °C; R_f = 0.14 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.89 (s, 3 H), 6.40 (s, 1 H), 6.81 (d, *J* = 15.9 Hz, 1 H), 6.86–6.89 (m, 2 H), 7.58 (d, *J* = 8.9 Hz, 1 H), 7.72 (d, *J* = 15.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.8, 55.8, 101.4, 110.1, 112.7, 112.8, 125.4, 133.7, 134.9, 152.9, 155.7, 160.8, 163.2, 196.7.

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{14}H_{12}O_4$: 244.0730; found: 244.0766.

Anal. Calcd for $C_{14}H_{12}O_4$ (244.07): C, 68.85; H, 4.95; found: C, 68.95; H, 5.01.

(*E*)-4-(3-Hydroxybut-1-en-1-yl)-7-methoxy-2*H*-chromen-2-one (5)

Unsaturated ketone **4** (184 mg, 0.75 mmol) was dissolved in MeOH (2 mL) and $CeCl_3{\cdot}7H_2O$ (279 mg, 0.75 mmol) was added. During a period of 5 min, $NaBH_4$ (28 mg, 0.75 mmol) was added and after stirring for an additional 5 min at r.t., aq 1 N $KHSO_4$ (3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with H_2O and brine, and dried (Na_2SO_4); yield: 185 mg (0.75 mmol, 100%); R_f = 0.16 (PE–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.5 Hz, 3 H), 1.88 (br s, 1 H, OH), 3.87 (s, 3 H), 4.52 (qd, *J* = 6.5, 6.5 Hz, 1 H), 6.21 (s, 1 H), 6.43 (dd, *J* = 15.6, 6.5 Hz, 1 H), 6.70–6.83 (m, 3 H), 7.56 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 55.8, 68.0, 101.1, 107.9, 112.3, 112.4, 121.5, 128.5, 132.0, 150.5, 155.6, 161.6, 162.8.

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{14}H_{14}O_4$: 246.0886; found: 246.0861.

The crude allyl alcohol **5** was directly used in the next step to form the carbonate **6**.

Ethyl (*E*)-[4-(7-Methoxy-2-oxo-2*H*-chromen-4-yl)but-3-en-2-yl]carbonate (6)

According to the preparation of **3**, the crude alcohol **5** (185 mg, 0.75 mmol) was reacted with ethyl chloroformate (0.14 mL, 163 mg, 1.5 mmol) in pyridine (0.75 mL) to give **6**; yield: 175 mg (0.55 mmol, 73%); yellow solid; mp 76–77 °C; R_f = 0.26 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3 H), 1.50 (d, *J* = 6.7 Hz, 3 H), 3.88 (s, 3 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 5.42 (qd, *J* = 6.5, 6.5 Hz, 1 H), 6.28 (s, 1 H), 6.39 (dd, *J* = 15.7, 6.5 Hz, 1 H), 6.83–6.90 (m, 3 H), 7.56 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 20.2, 55.8, 64.2, 73.7, 101.1, 108.9, 112.2, 112.3, 124.5, 125.6, 137.4, 143.0, 149.9, 155.6, 161.3, 162.8.

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{17}H_{18}O_6$: 318.1103; found: 318.1132.

9-(But-3-en-1-yl)-2,3,6,7-tetrahydro-1*H*,5*H*,11*H*-pyrano[2,3-*f*]pyrido[3,2,1-*ij*]quinolin-11-one (8)

To a suspension of 8-hydroxyjulodine (**7**; 1.95 g, 10.3 mmol) and methyl-3-oxo-6-heptenate (1.63 g, 10.3 mmol) in toluene (30 mL) was added $ClTi(O\textit{i}\text{-}Pr)_3$ (1 M in hexane, 20 mL, 20 mmol). The mixture was refluxed overnight. After cooling to r.t., the mixture was diluted with CH_2Cl_2 and sat. aq Na/K-tartrate solution was added. Stirring was continued until the layers separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried (Na_2SO_4) and after removal of the solvent in vacuo, the crude product was purified by flash chromatography (hexanes–EtOAc, 7:3); yield: 2.60 g (8.80 mmol, 85%); ochre solid; mp 99–101 °C; R_f = 0.52 (hexanes–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.00 (m, 4 H), 2.41 (m, 2 H), 2.71–2.79 (m, 4 H), 2.88 (t, *J* = 6.5 Hz, 2 H), 3.22–3.27 (m, 4 H), 5.07 (m, 2 H), 5.82–5.92 (m, 2 H), 6.99 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 20.7, 21.6, 27.8, 31.0, 32.5, 49.5, 49.9, 107.0, 107.2, 108.0, 115.8, 117.9, 121.3, 136.9, 145.7, 151.3, 156.0, 162.6.

UV (DMSO): λ_{max} (abs) = 393 nm; λ_{max} (em) = 455 nm.

Anal. Calcd for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.02; H, 7.29; N, 4.57.

3-(11-Oxo-2,3,6,7-tetrahydro-1*H*,5*H*,11*H*-pyrano[2,3-*f*]pyrido[3,2,1-*ij*]quinolin-9-yl)propanal (9)

Alkene **8** (331 mg, 1.12 mmol) was dissolved in a 2:1 mixture of THF and H_2O (45 mL) and NMO (211 mg, 1.80 mmol) and OsO_4 (15 mg, 60 µmol) were added. The solution was stirred at 60 °C for 3 h. After cooling to r.t., $NaHSO_3$ (500 mg) and sat. aq $NaHCO_3$ (10 mL) were added. The mixture was extracted with Et_2O (2 ×) and the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The crude diol (396 mg, 1.12 mmol) was directly subjected to the subsequent oxidative cleavage as follows. The diol was dissolved in CH_2Cl_2 (90 mL) and the solution was cooled to 0 °C before $Pb(OAc)_4$ (497 mg, 1.12 mmol) was added. After 15 min, H_2O (30 mL) was added, and the organic layer was washed with aq 10% K_2CO_3 and dried ($MgSO_4$). After evaporation in vacuo the crude product was purified by flash chromatography (CH_2Cl_2–EtOAc, 98:2); yield: 234 mg (0.78 mmol, 70%); yellow solid; mp 146–149 °C; R_f = 0.08 (CH_2Cl_2–EtOAc, 98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96–2.00 (m, 4 H), 2.77 (t, *J* = 6.3 Hz, 2 H), 2.83–2.90 (m, 4 H), 2.98 (t, *J* = 6.5 Hz, 2 H), 3.23–3.28 (m, 4 H), 5.88 (s, 1 H), 6.97 (s, 1 H), 9.87 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 20.6, 21.5, 23.6, 27.8, 42.3, 49.5, 49.9, 107.0, 107.1, 107.6, 118.1, 121.0, 145.9, 151.3, 154.7, 162.3, 199.9 (d).

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{18}H_{19}NO_3$: 297.1365; found: 297.1398.

UV (DMSO): λ_{max} (abs) = 393 nm; λ_{max} (em) = 456 nm.

Anal. Calcd for $C_{18}H_{19}NO_3$ (297.35): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.84; H, 6.68; N, 4.58.

9-(3-Hydroxypent-4-en-1-yl)-2,3,6,7-tetrahydro-1*H*,5*H*,11*H*-pyrano[2,3-*f*]pyrido[3,2,1-*ij*]quinolin-11-one (10)

Aldehyde **9** (500 mg, 1.68 mmol) was reacted according to the preparation of **3** with 1 M vinylmagnesium bromide (2.0 mL, 2.0 mmol) in THF (20 mL). Flash chromatography (CH_2Cl_2–EtOAc, 98:2) provided **10**; yield: 302 mg (0.89 mmol, 54%); yellow solid; mp 104–106 °C; R_f = 0.23 (PE–EtOAc, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (m, 2 H), 1.94–2.00 (m, 5 H), 2.70–2.84 (m, 4 H), 2.89 (t, *J* = 6.5 Hz, 2 H), 3.22–3.27 (m, 4 H), 4.22 (m, 1 H), 5.18 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1 H), 5.29 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1 H), 5.88–5.96 (m, 2 H), 7.04 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 20.7, 21.6, 27.4, 27.8, 35.6, 49.5, 49.9, 72.3, 107.0, 107.1, 108.0, 115.5, 118.0, 121.5, 140.5, 145.7, 151.3, 156.6, 162.7.

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{20}H_{23}NO_3$: 325.1672; found: 325.1680.

UV (DMSO): λ_{max} (abs) = 392 nm; λ_{max} (em) = 454 nm.

Ethyl [5-(11-Oxo-2,3,6,7-tetrahydro-1*H*,5*H*,11*H*-pyrano[2,3-*f*]pyrido[3,2,1-*ij*]quinolin-9-yl)pent-1-en-3-yl]carbonate (11)

According to the preparation of **3**, allyl alcohol **10** (3.05 g, 9.0 mmol) was reacted with ethyl chloroformate (1.7 mL, 1.95 g, 18.0 mmol) in pyridine (9 mL). Flash chromatography (hexanes–EtOAc, 7:3) afforded **11**; yield: 3.04 g (7.65 mmol, 85%); yellow solid, mp 89–93 °C; R_f = 0.16 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 1.91–2.06 (m, 6 H), 2.68–2.78 (m, 4 H), 2.85 (t, *J* = 6.5 Hz, 2 H), 3.21–3.26 (m, 4 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 5.15 (ddd, *J* = 12.7, 12.7, 6.5 Hz, 1 H), 5.28 (ddd, *J* = 10.5, 1.1, 1.1 Hz, 1 H), 5.36 (ddd, *J* = 17.3, 1.1, 1.1 Hz, 1 H), 5.80–5.88 (m, 2 H), 6.96 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 20.4, 20.6, 21.5, 27.0, 27.7, 33.0, 49.4, 49.8, 64.0, 77.8, 106.9, 107.0, 107.7, 118.0, 118.2, 121.2, 135.2, 145.7, 151.3, 154.4, 155.6, 162.4.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{23}H_{27}NO_5$: 397.1883; found: 397.1905.

UV (DMSO): λ_{max} (abs) = 396 nm; λ_{max} (em) = 456 nm.

Anal. Calcd for $C_{23}H_{27}NO_5$(397.46): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.60; H, 6.84; N, 3.40.

7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl Trifluoromethanesulfonate (14)[21]

Under a N_2 atmosphere, 4-hydroxycoumarin **13**[22] (3.2 g, 13.8 mmol) was dissolved in anhyd CH_2Cl_2 (70 mL) and Et_3N (3.8 mL, 27.6 mmol) was added. The solution was cooled to –20 °C, and treated dropwise with triflic anhydride (5.0 mL, 5.0 g, 18 mmol). The resulting mixture was stirred for additional 2 h, and then passed through a pad of silica gel, which was washed with EtOAc–hexane (1:30). The filtrate was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2); yield: 4.8 g (13.2 mmol, 96%); yellow solid; mp 77–79 °C; R_f = 0.15 (CH_2Cl_2–EtOAc, 98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 6 H), 3.43 (q, *J* = 7.1 Hz, 4 H), 6.05 (s, 1 H), 6.51 (d, *J* = 2.4 Hz, 1 H), 6.64 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.42 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (2 q), 45.0 (2 t), 97.4, 98.5 (s) 102.0, 109.4, 116.9 (s) 123.5, 152.1, 156.3, 158.1, 161.3.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{14}H_{14}F_3NO_5S$: 365.0538; found: 365.0531.

UV (DMSO): λ_{max} (abs) = 351 nm; λ_{max} (em) = 384 nm.

Anal. Calcd for $C_{14}H_{14}F_3NO_5S$ (365.3249): C, 46.03; H, 3.86; N, 3.83. Found: C, 46.30; H, 3.69, N, 3.88.

7-(Diethylamino)-4-vinyl-2*H*-chromen-2-one (15)

$[AllylPdCl]_2$ (5.4 mg 15 µmol, 0.5 mol%) and PPh_3 (7.9 mg 30 µmol, 1 mol%) were dissolved in anhyd THF (10 mL) and the solution was stirred for 15 min at r.t., before it was added to a solution of tributylvinylstannane (0.9 mL, 813 mg, 2.5 mmol) and triflate **14** (1 g, 3 mmol) in THF (20 mL) at 60 °C. The reaction mixture was refluxed for 2 h, cooled to r.t. and diluted with EtOAc. After addition of sat. aq KF, the mixture was stirred overnight at r.t.. The aqueous layer was extracted with CH_2Cl_2, the organic layer was washed with H_2O, and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, CH_2Cl_2–Et_2O, 95:5) to furnish **15**. The compound is sensitive to light; yield: 579 mg (2.38 mmol, 95%); yellow solid; mp 50–53 °C; R_f = 0.33 (CH_2Cl_2–Et_2O, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 6 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 5.63 (dd, *J* = 11.0, 1.0 Hz, 1 H), 5.94 (dd, *J* = 17.3, 1.0 Hz, 1 H), 6.12 (s, 1 H), 6.52 (d, *J* = 2.6 Hz, 1 H), 6.58 (dd, *J* = 9.0, 2.6 Hz, 1 H), 6.93 (dd, *J* = 17.4, 11.0 Hz, 1 H), 7.45 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5 (2 q), 44.8 (2 t), 97.2, 104.7, 108.5, 110.0, 115.8, 130.8, 150.6, 151.1, 153.2, 156.5, 162.5.

UV (DMSO): λ_{max} (abs) = 372 nm; λ_{max} (em) = 422 nm.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{15}H_{17}NO_2$: 243.1254; found: 243.1263.

7-(Diethylamino)-2-oxo-2*H*-chromene-4-carbaldehyde (16)[23]

To a solution of alkene **15** (300 mg, 1.2 mmol) in a mixture of H_2O (1.5 mL) and 1,4-dioxane (1.6 mL) was added OsO_4 (6 µL 2.5 wt% solution in *n*-hexane, 1.68 mg, 6.6 µmol, 0.55 mol%). The reaction mixture was stirred for 5 min. During this period the mixture became dark orange (due to osmate ester formation). While maintaining the temperature of the stirred mixture at 24–26 °C, finely powdered $NaIO_4$ (513 mg, 2.4 mmol) was added in portions over a period of 30 min. The slurry was stirred for an additional 1.5 h. The mixture (now pale yellow) was extracted thoroughly with Et_2O and the combined organic layers were filtered through Celite, dried (Na_2SO_4), and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 7:3); yield: 190 mg (0.78 mmol, 65%); red solid; mp 78–80 °C; R_f = 0.20 (PE–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 6 H), 3.43 (q, *J* = 7.1 Hz, 4 H), 6.45 (s, 1 H), 6.52 (d, *J* = 2.6 Hz, 1 H), 6.63 (dd, *J* = 9.2, 2.6 Hz, 1 H), 8.30 (d, *J* = 9.2 Hz, 1 H), 10.03 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 44.8 (2 t), 97.6, 109.5, 117.3, 127.0, 127.1, 143.9, 151.0, 157.4, 161.9, 192.5.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{14}H_{15}NO_3$: 245.1045; found: 245.1050.

UV (DMSO): λ_{max} (abs) = 441 nm; λ_{max} (em) = 432 nm.

1-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]allyl Ethyl Carbonate (17)

According to the preparation of **3**, aldehyde **16** (1.0 g, 4.3 mmol) was dissolved in THF (45 mL) and 1 M vinylmagnesium bromide solution in THF (5.72 mL, 5.72 mmol) was slowly added at –20 °C and the reaction mixture was stirred for 3 h. After work up, the crude product was dissolved in CH_2Cl_2 (10 mL) and pyridine (5 mL) and treated with ethyl chloroformate (1 mL, 8.6 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. Workup and column chromatography (silica gel, PE–EtOAc, 7:3) provided **17**; yield; 848 mg (2.5 mmol, 57%); yellow oil; R_f = 0.38 (PE–EtOAc, 7:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.1 Hz, 6 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 3.34 (q, *J* = 7.1 Hz, 4 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 5.32 (d, *J* = 10.4 Hz, 1 H), 5.42 (d, *J* = 17.2 Hz, 1 H), 5.95 (ddd, *J* = 16.7, 10.4, 6.1 Hz, 1 H), 6.12 (s, 1 H), 6.18 (d, *J* = 6.1 Hz, 1 H), 6.44 (d, *J* = 2.5 Hz, 1 H), 6.50 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.36 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 14.2, 44.7 (2 t), 64.7, 75.1, 97.9, 105.8, 106.4, 108.6, 120.2, 125.5, 133.2, 150.6, 154.1, 156.6, 161.9, 162.0.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{19}H_{23}NO_5$: 345.1570; found: 345.1575.

UV (DMSO): λ_{max} (abs) = 377 nm; λ_{max} (em) = 436 nm.

7-(Diethylamino)-4-(3-hydroxyprop-1-yn-1-yl)-2*H*-chromen-2-one (18)

To a solution of $Pd(PPh_3)_4$ (23 mg, 20 µmol, 2 mol%), CuI (4.5 mg, 23 µmol, 4 mol%), and triflate **14** (365 mg, 1 mmol) in THF (5 mL) were added Et_3N (0.15 mL, 1 mmol) and propargylic alcohol (0.1 mL, 2

mmol) under N_2 at r.t.. The reaction mixture was stirred for 2 h. Workup as usual and column chromatography (silica gel, CH_2Cl_2–EtOAc, 95:5) afforded **18**; yield: 218 mg (0.8 mmol, 80%); yellow solid; mp 144–145 °C; R_f = 0.24 (CH_2Cl_2–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H), 2.15 (m, 1 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 4.60 (s, 2 H), 6.17 (s, 1 H), 6.45 (d, *J* = 2.5 Hz, 1 H), 6.57 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.57 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 44.8 (2 t), 51.5, 80.0, 97.4, 98.6, 107.8, 108.8, 111.7 (d) 127.5, 136.8, 151.1, 156.1, 161.7.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{16}H_{17}NO_3$: 271.1202; found: 271.1209.

UV (DMSO): λ_{max} (abs) = 399 nm; λ_{max} (em) = 479 nm.

Anal. Calcd for $C_{16}H_{17}NO_3$ (271.32): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.95; H, 6.41; N, 4.87.

3-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]propionaldehyde (19)

Alcohol **18** (3.8 g, 14 mmol, 1 equiv) was dissolved in MeOH (40 mL) and Pd/C (380 mg, 10 wt%) was added. The flask was evacuated and flushed with H_2. The mixture was stirred under H_2atmosphere overnight and filtered through Celite. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2) providing the saturated alcohol (3.7 g, 13.5 mmol, 96%) as a yellow oil. This alcohol (1.3 g, 4.7 mmol) was dissolved in CH_2Cl_2 (90 mL) and Dess–Martin periodinane (2.4 g, 5.64 mmol, 1.2 equiv) was added at r.t.. The reaction mixture was stirred for 2 h. Workup and column purification (silica gel, CH_2Cl_2–EtOAc, 95:5) provided **19**; yield: 1.079 g (3.72 mmol, 79%); yellow oil; R_f = 0.29 (CH_2Cl_2–EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.0 Hz, 6 H), 2.86 (t, *J* = 7.6 Hz, 2 H), 3.01 (t, *J* = 7.4 Hz, 2 H), 3.40 (q, *J* = 7.1 Hz, 4 H), 5.92 (s, 1 H), 6.49 (d, *J* = 2.5 Hz, 1 H), 6.58 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.37 (d, *J* = 9.0 Hz, 1 H), 9.87 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 23.5, 42.0, 44.7 (2 t), 97.8, 107.5, 107.7, 108.6, 124.9, 150.6, 154.7, 156.2, 162.0, 199.8 (d).

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{16}H_{19}NO_3$: 273.1358; found: 273.1353.

UV (DMSO): λ_{max} (abs) = 364 nm; λ_{max} (em) = 419 nm.

5-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]pent-1-en-3-yl Ethyl Carbonate (20)

According to the preparation of **3**, aldehyde **19** (2.5 g, 9.4 mmol) was dissolved in THF (100 mL) and vinylmagnesium bromide (12.2 mL, 12.2 mmol, 1 M in THF) was added slowly at –20 °C. The reaction mixture was stirred for 2 h. Workup as usual and column chromatography provided the desired allyl acohol (2.03 g, 6.7 mmol, 71%) as a yellow oil. The allyl alcohol (253 mg, 0.8 mmol) was dissolved in CH_2Cl_2 (2 mL) and pyridine (0.8 mL) and ethyl chloroformate (0.2 mL, 174 mg, 1.6 mmol) was added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. Workup and column chromatography (silica gel, PE–EtOAc, 7:3) provided **20**; yield: 238 mg (0.62 mmol, 78%); yellow oil; R_f = 0.36 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 6 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.96–2.10 (m, 2 H), 2.71–2.77 (m, 2 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 5.17 (dd *J* = 12.7, 6.5 Hz, 1 H), 5.29 (ddd, *J* = 10.5, 1.0, 1.0 Hz, 1 H), 5.38 (ddd, *J* = 17.2, 1.1, 1.1 Hz, 1 H) 5.85 (ddd, *J* = 17.2, 10.5, 6.6 Hz, 1 H), 5.93 (s, 1 H), 6.50 (d, *J* = 2.6 Hz, 1 H), 6.58 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.37 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 14.2 (q) 27.1, 33.0, 44.7 (2 t), 60.4, 64.1, 97.8, 107.7, 107.9, 108.4, 118.3, 125.1, 135.2, 150.5, 154.5, 155.5, 156.2, 162.2.

HRMS (CI): *m*/*z* (M)$^+$calcd for $C_{21}H_{27}NO_5$: 373.1883; found: 373.1850.

UV (DMSO): λ_{max} (abs) = 371 nm; λ_{max} (em) = 420 nm.

(*Z*)-4-({3-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]prop-2-yn-1-yl}oxy)but-2-en-1-yl Ethyl Carbonate (22)

According to the preparation of **18**, Et_3N (1.7 mL, 1.3 g, 12.4 mmol) and propargyl ether **21**[24] (3.0 g 24.8 mmol) were added to a suspension of $Pd(PPh_3)_4$ (311 mg, 248 µmol, 2 mol%), CuI (94.5 mg, 496 µmol, 4 mol%), and triflate **14** (4.5 g, 12.4 mmol) in THF (60 mL) at r.t. The reaction mixture was stirred at this temperature for 2 h. Workup and column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5) furnished the desired allyl alcohol (3.3 g, 9.8 mmol, 79%) as a yellow oil. The allyl alcohol (3.3 g, 9.8 mmol) was dissolved in CH_2Cl_2 (20 mL), and pyridine (3.2 mL) and ethyl chloroformate (4.5 mL, 19.6 mmol) were added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. Workup and column chromatography (silica gel, CH_2Cl_2–EtOAc, 95:5) provided **22**; yield: 4.4 g (10.7 mmol, 87%); yellow solid; mp 55–56 °C; R_f = 0.42 (CH_2Cl_2–EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 6 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.28 (d, *J* = 5.0 Hz, 2 H), 4.47 (s, 2 H), 4.75 (d, *J* = 5.3 Hz, 2 H), 5.86 (dtt, *J* = 11.3, 5.3, 2.5 Hz, 2 H), 6.17 (s, 1 H), 6.46 (d, *J* = 2.5 Hz, 1 H), 6.60 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.57 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 14.3, 44.8 (2 t), 58.1, 63.2, 64.2, 65.6, 80.8, 96.1, 97.4, 107.8, 108.8, 111.9 (d) 127.3, 127.5, 130.1, 136.6, 151.0, 155.0, 156.2, 161.4.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{23}H_{27}NO_6$: 413.1832; found: 413.1847.

UV (DMSO): λ_{max} (abs) = 396 nm; λ_{max} (em) = 478 nm.

Anal. Calcd for $C_{23}H_{27}NO_6$ (413.46): C, 66.81; H, 6.58; N, 3.39. found: C, 67.11; H, 6.61; N, 3.13.

Palladium-Catalyzed Allylic Alkylations of Chelated Glycine Ester Enolate; General Procedure

At –20 °C, a solution of LHMDS was prepared from HMDS (111 mg, 0.69 mmol) and 1.6 M BuLi (0.39 mL, 0.625 mmol) in THF (1 mL). This solution was cooled to –78 °C and added to a solution of the protected amino acid ester (0.25 mmol) in THF (1 mL). After 20 min at –78 °C, a solution of $ZnCl_2$ (38 mg, 0.275 mmol) in THF (1 mL) was added under vigorous stirring. After an additional 30 min, a solution of $[allylPdCl]_2$ (1 mg, 2.5 µmol, 1 mol%), PPh_3 (3 mg, 11.3 µmol, 4.5 mol%), and the corresponding allylic ester (0.5 mmol) in THF (3 mL) was added. The solution was stirred and warmed up to r.t. in the cooling bath overnight. Subsequently, the solution was diluted with Et_2O and hydrolyzed with aq 1 N $KHSO_4$. The aqueous phase was extracted with Et_2O (2 ×) and the combined organic phases were dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by silica gel column chromatography.

tert-Butyl (*E*)-5-(7-Methoxy-2-oxo-2*H*-chromen-4-yl)-2-(2,2,2-trifluoroacetamido)pent-4-enoate (23)

According to the general procedure for allylic alkylations, **23** was obtained from TFA-protected *tert*-butyl glycinate (64 mg, 0.28 mmol) and carbonate **3** (76 mg, 0.25 mmol) after flash chromatography (Reveleris, Gradient PE–EtOAc, 9:1 to EtOAc); yield: 75 mg (0.17 mmol, 68%); yellow oil; R_f = 0.31 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 2.81 (m, 1 H), 3.00 (m, 1 H), 3.86 (s, 3 H), 4.65 (m, 1 H), 6.22 (s, 1 H), 6.28 (dt, *J* = 15.7, 7.4 Hz, 1 H), 6.70 (d, *J* = 15.7 Hz, 1 H), 6.80–6.85 (m, 2 H), 7.20 (d, *J* = 6.8 Hz, 1 H), 7.49 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (3 q), 35.5, 55.7, 60.4, 84.1, 101.2, 108.3, 111.8, 112.4, 125.5, 127.5, 132.6, 149.9, 155.6, 161.5, 162.9, 168.8, signals of the TFA group could not be detected.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{21}H_{22}F_3NO_6$: 441.1393; found: 441.1412.

tert-Butyl (*E*)-5-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]-2-(2,2,2-trifluoroacetamido)pent-4-enoate (24)

According to the general procedure for allylic alkylations, **24** was obtained from TFA-protected *tert*-butyl glycinate (81 mg, 0.36 mmol) and carbonate **17** (76 mg, 0.25 mmol) after flash chromatography (PE–EtOAc, 7:3); yield: 86.9 mg (0.18 mmol, 72%); yellow oil; R_f = 0.25 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H), 1.49 (s, 9 H), 2.82 (m, 1 H), 2.95 (m, 1 H), 3.40 (q, *J* = 7.1 Hz, 4 H), 4.64 (dd, *J* = 12.4, 5.7 Hz, 1 H), 6.03 (s, 1 H), 6.24 (dt, *J* = 15.1, 7.4 Hz, 1 H), 6.49 (d, *J* = 2.5 Hz, 1 H), 6.55 (dd, *J* = 9.0, 2.6 Hz, 1 H), 6.68 (d, *J* = 15.6 Hz, 1 H), 7.14 (d, *J* = 6.7 Hz, 1 H), 7.37 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (2 q), 27.8 (3 q), 35.5, 44.7 (2 t), 52.7, 84.1, 97.9, 104.6, 107.2, 108.5, 114.2, 125.3, 128.1, 131.5, 149.9, 150.7, 156.5, 162.4, 162.5, 168.9.

HRMS (CI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{30}F_3N_2O_5$: 483.2101; found: 483.2101.

UV (DMSO): λ_{max} (abs) = 380 nm; λ_{max} (em) = 443 nm.

tert-Butyl 5-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]-2-(2,2,2-trifluoroacetamido)pentanoate (24′)

To a solution of alkene **24** (20.0 mg, 41.1 µmol) in MeOH was added 10% Pd/C (2 mg). The mixture was stirred for 2 h under H_2 atmosphere and the solvent was removed in vacuo after TLC proved full conversion. The residue was subjected to flash chromatography (PE–EtOAc, 7:3); yield: 12.0 mg (27.7 µmol, 60%); yellow oil, R_f = 0.21 (PE–EtOAc, 7:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H), 1.44 (s, 9 H), 1.64 (m, 1 H), 1.76 (m, 1 H), 1.86 (m, 1 H), 2.04 (m, 1 H), 2.66 (m, 1 H), 2.76 (m, 1 H), 3.40 (q, *J* = 7.1 Hz, 4 H), 4.52 (dt, *J* = 6.4 Hz, 6.3 Hz, 6 H), 5.90 (s, 1 H), 6.50 (d, *J* = 2.5 Hz, 1 H), 6.57 (dd, *J* = 9.0 Hz, 2.5 Hz, 1 H), 6.99 (d, *J* = 7.23 Hz, 1 H), 7.35 (*J* = 9.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 23.7, 27.9, 31.0, 31.6, 44.8, 52.7, 83.7, 97.9, 107.7, 108.5, 115.6 (q, *J* = 287.7 Hz), 125.1, 150.5, 155.5, 156.3, 156.7 (q, *J* = 37.6 Hz), 162.2, 168.7.

HRMS (CI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{32}F_3N_2O_5$: 485.2258; found: 485.2261.

UV (DMSO): λ_{max} (abs) = 380 nm; λ_{max} (em) = 441 nm.

tert-Butyl (*E*)-5-(7-Methoxy-2-oxo-2*H*-chromen-4-yl)-3-methyl-2-(2,2,2-trifluoroacetamido)pent-4-enoate (25)

According to the general procedure for allylic alkylations, **25** was obtained from TFA-protected *tert*-butyl glycinate (64 mg, 0.28 mmol) and carbonate **6** (80 mg, 0.25 mmol) after flash chromatography (Reveleris, Gradient PE–EtOAc, 9:1 to EtOAc); yield: 72 mg (0.16 mmol, 63%); yellow oil; R_f = 0.40 (PE–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer, 66%) = 1.22 (d, *J* = 6.7 Hz, 3 H), 1.49 (s, 9 H), 3.09 (m, 1 H), 3.87 (s, 3 H), 4.63 (dd, *J* = 7.8, 4.6 Hz, 1 H), 6.26 (s, 1 H), 6.38 (dd, *J* = 15.6, 7.8 Hz, 1 H), 6.71 (d, *J* = 15.6 Hz, 1 H), 6.82–6.91 (m, 2 H), 7.01 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.7 Hz, 1 H); δ (minor diastereomer, 34%, selected signals) = 1.50 (s, 9 H), 3.88 (s, 3 H), 4.11 (m, 1 H), 4.21 (dd, *J* = 7.8, 4.6 Hz, 1 H), 6.25 (s, 1 H), 6.64 (d, *J* = 15.6 Hz, 1 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 7.69 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer, 66%) = 15.5, 28.1 (3 q), 40.3, 55.8, 59.9, 84.1, 101.2, 108.2, 112.4, 112.5, 124.9, 125.3, 139.0, 150.1, 155.7, 161.5, 162.9, 168.4; signals of the TFA group could not be detected; δ (minor diastereomer, 34%, selected signals) = 15.2, 28.0 (3 q), 35.9, 56.5, 60.4, 73.7, 100.9, 111.8, 137.5.

HRMS (CI): *m*/*z* (M + H)$^+$ calcd for $C_{22}H_{25}F_3NO_6$: 456.1628; found: 456.1607.

tert-Butyl (*E*)-7-(11-Oxo-2,3,6,7-tetrahydro-1*H*,5*H*,11*H*-pyrano[2,3-*f*]pyrido[3,2,1-*ij*]quinolin-9-yl)-2-(2,2,2-trifluoroacetamido)hept-4-enoate (26a) and *tert*-Butyl 3-[2-(11-Oxo-2,3,6,7-tetrahydro-1*H*,5*H*,11*H*-pyrano[2,3-*f*]pyrido[3,2,1-*ij*]quinolin-9-yl)ethyl]-2-(2,2,2-trifluoroacetamido)pent-4-enoate (26b)

According to the general procedure for allylic alkylations, the amino acid derivatives **26a**,**b** were obtained from TFA-protected *tert*-butyl glycinate (64 mg, 0.28 mmol) and carbonate **11** (99 mg, 0.25 mmol) after flash chromatography (Reveleris, Gradient PE–EtOAc, 9:1 to EtOAc); yield: 111 mg (0.20 mmol, 80%); yellow oil; R_f (**26a**/**b**) = 0.20 (PE–EtOAc, 7:3).

26a (60%)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.94–1.97 (m, 4 H), 2.35 (td, *J* = 15.1, 7.1 Hz, 2 H), 2.49 (m, 1 H), 2.62–2.70 (m, 3 H), 2.76 (t, *J* = 6.1 Hz, 2 H), 2.87 (t, *J* = 6.5 Hz, 2 H), 3.21–3.27 (m, 4 H), 4.50 (m, 1 H), 5.34 (m, 1 H), 5.61 (dt, *J* = 15.4, 6.4 Hz, 1 H), 5.86 (s, 1 H), 6.94–6.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 20.6, 21.5, 27.7, 27.9 (3 q), 31.2 (2 t), 35.0, 49.5, 49.9, 52.7, 83.5, 107.0, 107.0, 107.9, 118.0, 121.2, 124.0, 134.1, 145.7, 151.3, 155.8, 162.6, 169.3; signals of the TFA group could not be detected.

26b (40%)

^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer, 70%) = 1.47 (s, 9 H), 1.95–2.00 (m, 4 H), 2.35 (td, *J* = 15.1, 7.1 Hz, 2 H), 2.68–2.78 (m, 4 H), 2.85 (t, *J* = 6.5 Hz, 2 H), 3.22–3.27 (m, 4 H), 4.20 (m, 1 H) 4.61 (m, 1 H), 5.28 (m, 2 H), 5.60 (m, 1 H), 5.86 (s, 1 H), 6.95 (s, 1 H), 6.77 (d, *J* = 7.9 Hz, 1 H), 6.95 (s, 1 H); δ (minor diastereomer, 30%, selected signals) = 1.46 (s, 9 H), 6.96 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer, 70%) = 20.4, 20.6, 21.5, 27.7, 27.9 (3 q), 31.2 (2t), 46.3, 49.5, 49.9, 55.4, 83.6, 107.1, 107.2, 107.9, 118.0, 120.1, 123.2, 132.7, 145.7, 151.2, 155.7, 162.5, 168.6; signals of the TFA group could not be detected.

HRMS (CI): *m*/*z* (M)$^+$ calcd for $C_{28}H_{33}F_3N_2O_5$: 534.2336; found: 534.2336.

UV (DMSO): λ_{max} (abs) = 385 nm; λ_{max} (em) = 455 nm.

tert-Butyl (*E*)-7-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]-2-(2,2,2-trifluoro-acetamido)hept-4-enoate (27a) and *tert*-Butyl 3-[2-(7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl)ethyl]-2-(2,2,2-trifluoroacetamido)pent-4-enoate (27b)

According to the general procedure for allylic alkylations, the amino acid derivatives **27a**/**b** were obtained from TFA-protected *tert*-butyl glycinate (134 mg, 0.59 mmol) and carbonate **20** (154 mg, 0.41 mmol) after flash chromatography (PE–EtOAc, 7:3) as an inseparable mixture of regio- and stereoisomers; yield: 170 mg (0.32 mmol, 80%); yellow oil; R_f (**27a**/**b**) = 0.23 (PE–EtOAc, 7:3).

27a

^{1}H NMR (400 MHz, $CDCl_3$): δ (major rotamer, 82%) = 1.19 (t, *J* = 7.1 Hz, 6 H), 1.46 (s, 9 H), 2.31–2.41 (m, 2 H), 2.49 (m, 1 H), 2.61–2.76 (m, 3 H), 3.39 (q, *J* = 7.1 Hz, 4 H), 4.50 (m, 1 H), 7.56 (dt, *J* = 15.3, 7.6 Hz, 1 H), 5.60 (dt, *J* = 15.3, 6.9 Hz, 1 H), 5.88 (s, 1 H), 6.47 (d, *J* = 2.5 Hz, 1 H), 6.56 (m, 1 H), 6.98 (d, *J* = 7.3 Hz, 1 H), 7.34 (d, *J* = 9.0 Hz); δ (minor rotamer, selected signals): 1.45 (s, 9 H), 7.03 (d, *J* = 7.0 Hz, 1 H).

27b

^{1}H NMR (400 MHz, $CDCl_3$): δ (minor rotamer, 18%, selected signals) = 1.45 (s, 9 H), 4.61 (dd, *J* = 8.7, 4.4 Hz, 1 H), 5.21 (d, *J* = 17.1 Hz, 1 H), 5.29 (d, *J* = 10.9 Hz, 1 H), 5.62 (m, 1 H), 5.89 (s, 1 H), 6.83 (d, *J* = 8.6 Hz, 1 H), 7.36 (d, *J* = 8.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (isomeric mixture) = 12.3, 20.0, 24.2, 26.0, 27.8, 27.8, 29.1, 29.3, 29.5, 31.1, 31.1, 31.2, 32.9, 33.5, 34.8, 44.6, 46.2, 51.4, 51.5, 52.6, 52.6, 55.4, 82.3, 83.4, 83.6, 97.7, 107.4, 107.6, 107.7, 107.8, 108.8, 107.9, 108.4, 108.5, 115.5 (q, *J* = 287.6 Hz), 115.6 (q, *J* = 287.7 Hz) 120.0, 123.4, 124.2, 125.0, 125.1, 132.4, 133.7, 134.7, 150.4, 150.4, 155.5, 155.6, 155.7, 156.2, 156.3, 156.4 (q, *J* = 33.5 Hz), 156.2 (q, *J* = 32.2 Hz), 162.1, 162.1, 162.2, 168.5, 169.2, 173.3, 173.6.

HRMS (CI): *m*/*z* $(M)^+$ calcd for $C_{26}H_{33}F_3N_2O_5$: 510.2342; found: 510.2338.

UV (DMSO): λ_{max} (abs) = 364 nm; λ_{max} (em) = 420 nm.

***tert*-Butyl 6-({3-[7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl]prop-2-yn-1-yl}oxy)-2-(2,2,2-trifluoroacetamido)hex-4-enoate (28)**

According to the general procedure for allylic alkylations, **28** was obtained from TFA-protected *tert*-butyl glycinate (227 mg, 1.0 mmol) and carbonate **22** (206 mg, 0.5 mmol) after flash chromatography (CH_2Cl_2–EtOAc, 95:5, 9:1) as a 7:3 *E*/*Z*-mixture; yield: 189 mg (0.34 mmol, 69%); yellow oil; R_f = 0.41 (CH_2Cl_2–EtOAc, 95:5).

(*E*)-**28** (70%)

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.20 (t, *J* = 7.1 Hz, 6 H), 1.48 (s, 9 H), 2.55 (m, 1 H), 2.72 (m, 1 H), 3.40 (q, *J* = 7.1 Hz, 4 H), 3.83 (s, 2 H), 3.99 (d, *J* = 4.9 Hz, 2 H), 4.55 (m, 1 H), 5.54–5.70 (m, 2 H), 5.98 (s, 1 H), 6.49 (d, *J* = 2.5 Hz, 1 H), 6.56 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.09 (d, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 1 H).

(*Z*)-**28** (30%)

^{1}H NMR (400 MHz, $CDCl_3$): δ (selected signals) = 1.47 (s, 9 H), 3.80 (s, 2 H), 4.17 (d, *J* = 2.59 Hz, 2 H), 4.78 (m, 1 H), 5.80 (m, 1 H), 7.41 (d, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*E*/*Z* mixture) = 12.4 (2 q), 28.0, 34.7, 43.0, 44.8 (2 t), 52.6, 71.4, 74.5, 83.7, 97.7, 108.0, 108.7, 110.0, 110.4, 125.8, 127.5, 130.5, 148.4, 150.8 (2 s), 156.4, 156.8, 161.8, 169.1, 203.6.

HRMS (CI): *m*/*z* $(M + H)^+$ calcd for $C_{28}H_{34}F_3N_2O_6$: 551.2363; found: 551.2340.

UV (DMSO): λ_{max} (abs) = 372 nm; λ_{max} (em) = 446 nm.

Acknowledgment

Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Supporting Information

Supporting information for this article (copies of NMR spectra) is available online at http://dx.doi.org/10.1055/s-0035-1561628.

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