Novel Efficient Synthesis of 1-Ethoxyvinyl Esters Using Ruthenium Catalysts and Their Use in Acylation of Amines and Alcohols: Synthesis of Hydrophilic 3'-*N*-Acylated Oxaunomycin Derivatives

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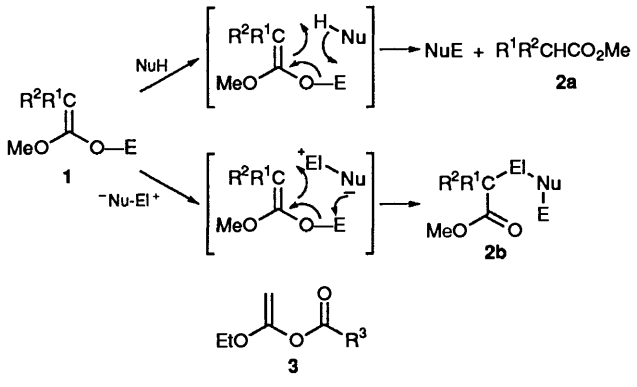
A novel and efficient synthesis of 1-ethoxyvinyl esters **3a–i** from carboxylic acids **4a–i** and ethoxyacetylene **5** by using a catalytic amount of ruthenium complex [{$RuCl_2$(*p*-cymene)}$_2$] **6f** has been developed. These reagents reacted smoothly with amines and alcohols to give the corresponding *N*- and *O*-acylated compounds in excellent yields. This acylation method has been applied to the synthesis of hydrophilic 3'-*N*-acylated oxaunomycin derivatives **13a, b**.

In organic synthesis, reagents are required which are able under neutral or nearly neutral conditions to bring about the desired reactions in high yields with easy isolation of the products; this is especially important for the synthesis of complicated compounds having multifunctional groups such as natural products. For this purpose, we have introduced the use of ketene acetal derivatives **1** as reagents for alkoxy (aryloxy) carbonylation,[1] acylation,[2] silylation,[3] silylenation,[4] Semmler–Wolff aromatization,[5] Pummerer-type rearrangement,[6] silyl-transfer aldol reaction,[7] silyl-transfer Michael addition,[8] silyl-transfer 1,3-addition of nitrones[9] and Pummerer-type cyclization.[10] The reactions using these reagents were generally carried out in an inert solvent such as dichloromethane, chloroform, tetrahydrofuran (THF) or acetonitrile and usually brought to completion at low temperature over a short period to give the desired products **2** in high yields.

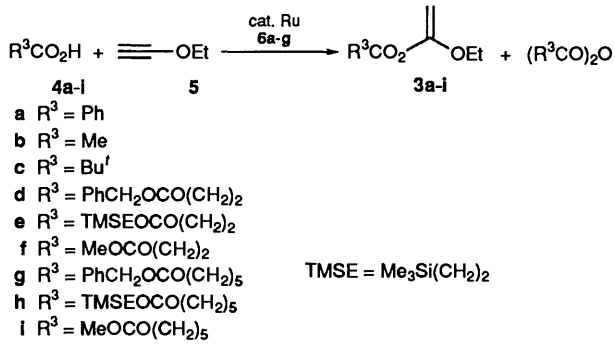


Scheme 1

In connection with this study, we have recently reported both a novel and efficient synthesis of 1-ethoxyvinyl esters **3** by using ruthenium-catalysed addition of carboxylic acids to ethoxyacetylene and their use in the acylation of amines and alcohols.[11] We now give a full account of the synthesis of 1-ethoxyvinyl esters and a useful application to the synthesis of the hydrophilic 3'-*N*-acylated oxaunomycin derivatives.

Results and Discussion

1-Alkoxyvinyl esters are known to be efficient reagents for acylation.[2a,b,12] They can react with amines and alcohols under neutral or nearly neutral conditions and release a neutral and stable ester to afford the corresponding *N*- and *O*-acylated products in high yields. These types of reagents have been prepared by mercury(II)-catalysed addition of carboxylic acid to alkoxyacetylene[12] or (trimethylsilyl)ethoxyacetylene.[2a,b] The toxicities of mercury salts strongly restrict the use of these reagents in organic synthesis, especially in the field of medicine. A further limitation is that a considerable quantity of acid anhydride was produced as a by-product. Recently, an efficient synthesis of the enol esters has been developed which involves the addition of carboxylic acids to terminal alkynes in the presence of ruthenium complexes.[13] The work described here examines this catalytic method for the preparation of the 1-ethoxyvinyl esters (Scheme 2 and Table 1).



Scheme 2

At first, blank experiments for the preparation of 1-ethoxyvinyl benzoate **3a** were carried out by the reaction of benzoic acid **4a** and ethoxyacetylene **5** in toluene without ruthenium catalyst. The desired **3a** was generated at a higher temperature, but the yields were low and a large amount of benzoic anhydride was produced accompanied by recovered **4a** (runs 1 and 2). Next, various types of ruthenium salts **6a–g** were investigated. Although the use of [$RuCl_2(PR_3)$(arene)] **6d, e**[13f–i] gave a good result for the formation of the enol esters, they were inadequate for the case of the 1-ethoxyvinyl esters (runs 6 and 7). The use of [{$RuCl_2$(*p*-cymene)}$_2$] **6f** in toluene was found to give the best result (run 8). Other solvents such as benzene, dichloromethane and THF gave lower yields (runs 9–11). In a typical experiment, a solution of **5** (1.25 equiv.) in dry toluene was added dropwise to a solution of **4a** (1.0 equiv.) and **6f** (0.005 equiv.) in toluene at 0 °C and the brown mixture was stirred at 40 °C for 15 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by short column chromatography on silica gel to give **3a** and benzoic anhydride in 80 and 5% yields, respectively. Similarly, various types of 1-ethoxyvinyl esters **3b–i** were prepared under the same conditions in good yields (Table 2). Exceptionally, **3b** was prepared in THF as solvent because of convenient isolation by direct distillation from the reaction mixture. The known reagents **3a, b** were identified by comparison with authentic

Table 1 Ruthenium catalysed addition of benzoic acid **4a** to ethoxyacetylene **5**

Run	Catalyst[a] (mol%)	Solvent	Yield (%) **3a**	Yield (%) $(PhCO)_2O$
1	No catalyst	toluene	3	2[c]
2	No catalyst[b]	toluene	20	27[d]
3	$[Ru_3(CO)_{12}]$ **6a** (1)	toluene	53	13
4	$RuCl_3 \cdot 3H_2O$ **6b** (1)	toluene	31	14
5	$[RuCl_2(PPh_3)_3]$ **6c** (1)	toluene	66	10
6	$[RuCl_2(PPh_3)(p\text{-cymene})]$ **6d** (1)	toluene	51	7
7	$[RuCl_2(PBu_3)(p\text{-cymene})]$ **6e** (1)	toluene	6	8
8	$[\{RuCl_2(p\text{-cymene})\}_2]$ **6f** (0.5)	toluene	80	5
9	**6f** (0.5)	benzene	78	4
10	**6f** (0.5)	CH_2Cl_2	61	3
11	**6f** (0.5)	THF	16	22
12	$[\{RuCl_2(benzene)\}_2]$ **6g** (0.5)	toluene	17	17

[a] The reaction was carried out at 40 °C for 15 min unless otherwise noted. [b] The reaction was carried out at 70 °C for 10 h. [c] **4a** (82%) was also recovered. [d] **4a** (23%) was also recovered.

Table 2 1-Ethoxyvinyl esters **3b–i**

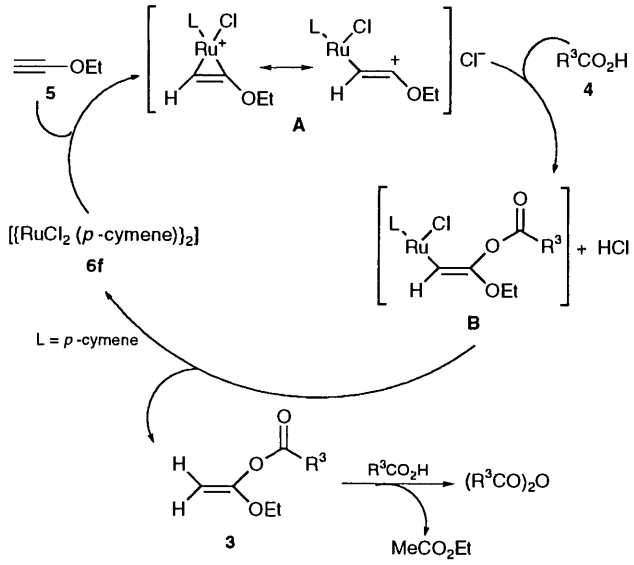
Compd.	R^3	Yield (%)
3b	Me[a]	65
3c	Bu[t]	66
3d	$PhCH_2OCO[CH_2]_2$	60
3e	$TMSEOCO[CH_2]_2$	74
3f	$MeOCO[CH_2]_2$	76
3g	$PhCH_2OCO[CH_2]_5$	84
3h	$TMSEOCO[CH_2]_5$	79
3i	$MeOCO[CH_2]_5$	73

[a] Carried out in THF.

samples[12b] and the structures of unknown reagents **3c–i** were proved by microanalyses and IR and ^1H NMR spectral data (Table 3).* The predominant formation of the 1-ethoxyvinyl esters **3** in this ruthenium-catalysed reaction is explained as follows. It is presumed that the catalytic cycle through intermediates **A** and **B** may be faster than the condensation of **3** with the starting carboxylic acids leading to acid anhydrides (Scheme 3).

The reaction of **3a–i** with primary amines **7a, b, d** was generally carried out by using equivalent amounts of **3** and **7** in dichloromethane at room temperature (runs 1,2,4–10 and 12) and with secondary amines **7c, e** proceeded at higher temperature (runs 11 and 13). Evaporation of the reaction mixture gave almost pure *N*-acylated compounds **8a–m**. All results of these reactions and physical data of amides **8** are summarized in Tables 4 and 5, respectively.

The acylation reaction of alcohols **9a–g** with **3a–j** was performed in the presence of a catalytic amount of acid to give high yields of the esters **10a–q**. When conc. H_2SO_4 was used as a catalyst, the reaction was furnished in a short time through the use of a slight excess of the reagents (runs 1, 3, 5 and 7). Employment of toluene-*p*-sulfonic acid (*p*-TsOH) as catalyst afforded better results (runs 2, 4, 6 and 8). The degree of racemization during the acylation is quite low (<0.9%) as shown by optical rotations (run 9). This acylation method is quite useful not only for the bulky alcohol **9d** (runs 10–18) but also for phenol **9g** (runs 23 and 24). Furthermore, olefin and nitrile groups were not affected under these reaction conditions



Scheme 3 Catalytic mechanisms for the formation of the 1-ethoxyvinyl esters **3**

(runs 19–22). In the work-up of the reaction, an excess of acylating reagent was quenched with water at room temperature. All the results of acylation reactions are summarized in Table 6. Compounds **10a, b, d, i–k, n, o, q** were identical with authentic samples.[2c] Physical data of **10c, e–h, l, m, p** are shown in Table 7.

Finally, we applied this method to the 3′-*N*-acylation of oxaunomycin **11**.[14] The reagents **3f, i** reacted smoothly with **11** in dry 1,2-dichloroethane to afford otherwise hardly obtainable† 3′-*N*-acylated products **12a** and **12b** in 92 and 96% yields, respectively. These were then saponified with aqueous 0.1 mol dm^{-3} NaOH to give the hydrophilic oxaunomycin derivatives **13a** and **13b** in high yields as shown in Scheme 4.

The preparation of other 3′-*N*-acylated oxaunomycin derivatives by this method and biological testing for activities against tumour cells are in progress.

Experimental

All boiling and melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using a 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer. ^1H NMR spectra were measured on Varian VXR-200 (200 MHz), Hitachi R-250HT (250 MHz), JEOL JNM-EX 270 (270 MHz) and JEOL JNM-GX 500 (500 MHz) spectrometers with Me_4Si as an internal standard and *J* values are given in Hz. Mass spectra (MS) were obtained on a JEOL JMS-D300 [for the electron impact (EI) MS] or a JEOL HX-100 [for fast atom bombardment (FAB) MS] mass spectrometer. E. Merck silica gel 60 (70–230 mesh ASTM) was used for column chromatography and E. Merck pre-coated thin-layer chromatography plates, silica gel 60 F_{254} were used for preparative thin-layer chromatography (prep. TLC).

General Procedure for 1-*Ethoxyvinyl Ester* **3** *Formation Utilizing Ethoxyacetylene* **5**.—1-*Ethoxyvinyl benzoate* **3a**. Typically, to a solution of **4a** (122 mg, 1.0 mmol) and **6f** (3.1 mg, 0.005 mmol) in dry toluene (1.5 cm^3) was added dropwise a

* These reagents are very soluble in common organic solvents, stable to purification by column chromatography on silica gel, and can be allowed either to stand at room temperature for a few weeks or to be stored in the refrigerator for more than several months under nitrogen.

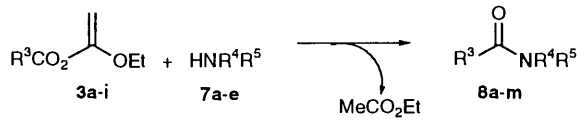
† The standard acylation methods using acid chlorides or acid anhydrides/base did not give any acylated products **12a, b**. Acylation using isopropenyl ester developed by us[2c] afforded **12a, b** but in low yields.

Table 3 Physical data of 1-ethoxyvinyl esters **3**

Compd.	$\nu_{max}(CHCl_3)/cm^{-1}$ C=O	C=C	$\delta_H(CDCl_3)$	Formula	Found (%) (Required) C	H
3a[a]	1746	1674	1.37 (3 H, t, *J* 6.9), 3.88 (1 H, d, *J* 3.6), 3.95 (2 H, q, *J* 6.9), 3.96 (1 H, d, *J* 3.6), 7.4–7.55 (2 H, m), 7.55–7.65 (1 H, m), 8.05–8.15 (2 H, m)	$C_{11}H_{12}O_3$	68.65 (68.73)	6.35 (6.29)
3b[b]	1771	1674	1.33 (3 H, t, *J* 7.0), 2.16 (3 H, s), 3.76 (1 H, d, *J* 3.6), 3.83 (1 H, d, *J* 3.6), 3.87 (2 H, q, *J* 7.0)	$C_6H_{10}O_3$	55.25 (55.37)	7.6 (7.75)
3c[c]	1759	1674	1.27 (9 H, s), 1.33 (3 H, t, *J* 6.9), 3.75 (1 H, d, *J* 3.4), 3.77 (1 H, d, *J* 3.4), 3.87 (2 H, q, *J* 6.9)	$C_9H_{16}O_3$	62.8 (62.76)	9.4 (9.36)
3d	1771, 1736	1674	1.33 (3 H, t, *J* 6.9), 2.6–2.9 (4 H, m), 3.75 (1 H, d, *J* 3.7), 3.82 (1 H, d, *J* 3.7), 3.86 (2 H, q, *J* 6.9), 5.14 (2 H, s), 7.2–7.5 (5 H, m)	$C_{15}H_{18}O_5$	64.6 (64.73)	6.55 (6.52)
3e	1771, 1728	1676	0.04 (9 H, s), 0.9–1.1 (2 H, m), 1.33 (3 H, t, *J* 7.0), 2.55–2.80 (4 H, m), 3.76 (1 H, d, *J* 3.7), 3.84 (1 H, d, *J* 3.7), 3.87 (2 H, q, *J* 7.0), 4.1–4.3 (2 H, m)	$C_{13}H_{24}O_5Si$	54.0) (54.14)	8.3 (8.39)
3f	1769, 1736	1676	1.33 (3 H, t, *J* 6.9), 2.6–2.85 (4 H, m), 3.71 (3 H, s), 3.77 (1 H, d, *J* 3.6), 3.85 (1 H, d, *J* 3.6), 3.87 (2 H, q, *J* 6.9)	$C_9H_{14}O_5$	53.35 (53.46)	6.95 (6.98)
3g	1767, 1732	1674	1.33 (3 H, t, *J* 7.0), 1.2–1.5 (2 H, m), 1.5–1.8 (4 H, m), 2.37 (2 H, t, *J* 7.6), 2.41 (2 H, t, *J* 7.6), 3.75 (1 H, d, *J* 3.6), 3.80 (1 H, d, *J* 3.6), 3.86 (2 H, q, *J* 7.0), 5.11 (2 H, s), 7.35 (5 H, s)	$C_{18}H_{24}O_5$	67.2 (67.48)	7.45 (7.55)
3h	1767, 1725	1674	0.04 (9 H, s), 0.9–1.1 (2 H, m), 1.33 (3 H, t, *J* 7.0), 1.2–1.5 (2 H, m), 1.5–1.8 (4 H, m), 2.29 (2 H, t, *J* 7.6), 2.42 (2 H, t, *J* 7.6), 3.75 (1 H, d, *J* 3.8), 3.80 (1 H, d, *J* 3.8), 3.86 (2 H, q, *J* 7.0), 4.05–4.25 (2 H, m)	$C_{16}H_{30}O_5Si$	57.85 (58.14)	9.1 (9.15)
3i	1767, 1732	1674	1.33 (3 H, t, *J* 7.0), 1.2–1.5 (2 H, m), 1.5–1.8 (4 H, m), 2.32 (2 H, t, *J* 7.4), 2.43 (2 H, t, *J* 7.4), 3.67 (3 H, s), 3.75 (1 H, d, *J* 3.6), 3.81 (1 H, d, *J* 3.6), 3.86 (2 H, q, *J* 7.0)	$C_{12}H_{20}O_5$	244.1294[d] (244.1309)	

[a] B.p. 95–105 °C/0.50 mmHg (bath temperature) (lit.,[12b] b.p. 99–100 °C/1.6 mmHg). [b] B.p. 61–62 °C/29 mmHg, (lit.,[12b] b.p. 50 °C/12 mmHg). [c] B.p. 52–55 °C/35 mmHg. [d] High resolution (EI) MS data.

Table 4 Acylation of the amines **7** with reagents **3**



Run	Amine	Reagent	Conditions[a] *T*/°C	*t*/h	Amide	Yield	(%)
1	$PhCH_2NH_2$ **7a**	**3a**	30	48	$PhCH_2NHCOR^3$ R^3=Ph	**8a**	87
2		**3b**	30	13	R^3=Me	**8b**	86
3		**3c**	83	24	R^3=Bu^t	**8c**	80
4		**3d**	30	12	R^3=$[CH_2]_2CO_2CH_2Ph$	**8d**	80
5		**3e**	30	17	R^3=$[CH_2]_2CO_2TMSE$	**8e**	90
6		**3f**	30	12	R^3=$[CH_2]_2CO_2Me$	**8f**	84
7		**3g**	30	12	R^3=$[CH_2]_5CO_2CH_2Ph$	**8g**	93
8		**3h**	30	12	R^3=$[CH_2]_5CO_2TMSE$	**8h**	86
9		**3i**	30	15	R^3=$[CH_2]_5CO_2Me$	**8i**	88
10	(*S*)-$PhCHMeNH_2$ **7b**	**3b**	30	12	(*S*)-PhCHMeNHCOMe	**8j**	95
11	$PhCH_2NHMe$ **7c**	**3f**	83	10	$PhCH_2N(Me)CO[CH_2]_2CO_2Me$	**8k**	76
12	$PhNH_2$ **7d**	**3f**	30	36	$PhNHCO[CH_2]_2CO_2Me$	**8l**	80
13	PhNHMe **7e**	**3f**	83	12[b]	$PhN(Me)CO[CH_2]_2CO_2Me$	**8m**	78

[a] The reaction was carried out in CH_2Cl_2 unless otherwise noted. [b] The reaction was carried out in $Cl[CH_2]_2Cl$.

solution of **5** (88 mg, 1.25 mmol) in dry toluene (1.5 cm^3) at 0 °C. The resulting solution was stirred at 40 °C for 15 min. After concentration of the reaction mixture under reduced pressure, the brown residue was purified by short column chromatography on silica gel (hexane–EtOAc, 95:5) to give the *title ester* **3a** (154 mg, 80%) as a colourless oil. Exceptionally, **3b** was prepared in dry THF and purified by direct distillation from the reaction mixture. Compounds **3c–i** were purified by column chromatography on silica gel [**3c** (hexane–EtOAc, 95:5), **3d, f, g, h, i** (hexane–EtOAc, 85:15), **3e** (hexane–EtOAc, 9:1)] compounds **3d–i** were partially decomposed by distillation.

The physical data of **3a–i** are summarized in Table 3.

General Procedure for Amide **8** *Formation from* 1-*Ethoxyvinyl Esters* **3** *and Amines* **7**.—N-*Benzylbenzamide* **8a**. Typically, to a solution of **7a** (220 mg, 1.14 mmol) in dry CH_2Cl_2 (3 cm^3) was added **3a** (122.6 mg, 1.14 mmol) in dry CH_2Cl_2 (3 cm^3), and the mixture was stirred at room temperature for 48 h. After concentration of the reaction mixture under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane–EtOAc, 1:1) to give the *title amide* **8a** (209 mg, 87%) as colourless crystals. Reaction conditions for the synthesis of **8a–m** are shown in Table 4. Compounds **8b–m** were purified by column chromatography on silica gel [**8b** (hexane–EtOAc, 1:3), **8c, e** (hexane–EtOAc, 2:1), **8d, h, l, m** (hexane–EtOAc, 1:1), **8f** (hexane-Et_2O, 3:2), **8g** (hexane–EtOAc, 2:3), **8i, j, k** (hexane–EtOAc, 1:2)].

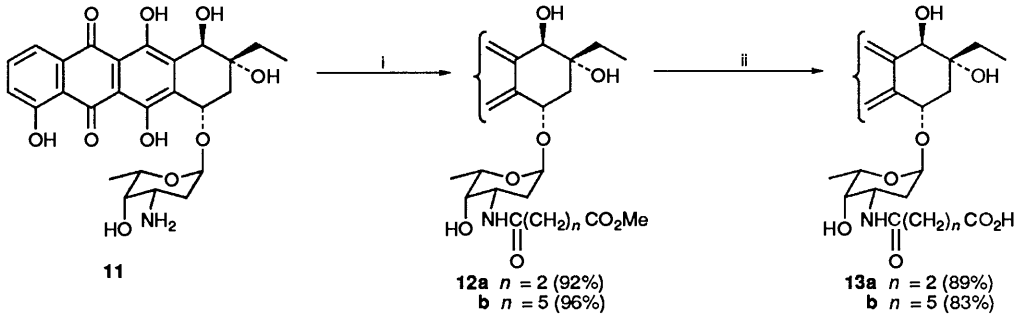
The physical data of **8a–m** are summarized in Table 5.

General Procedures for Acylating Reactions: (A) *Using a Catalytic Amount of conc.* H_2SO_4.—*Benzyl phenethyl pimelate* **10a**. Typically, a drop of conc. H_2SO_4 (*d* 1.84 g cm^{-3}) was added

Table 5 Physical data of amides **8**

Compd.	M.p./(°C) Recryst. solvent	$\nu_{max}(CHCl_3)$/ cm^{-1} NH	C=C	$\delta_H(CDCl_3)$	Formula	Found (%) (Required) C	H	N
8a	104–105[a] EtOAc–hexane	3450	1659	4.65 (1 H, d, *J* 5.8), 6.3–6.6 (1 H, br), 7.2–7.6 (8 H, m), 7.7–7.9 (2 H, m)	$C_{14}H_{13}NO$			
8b	59–61[b] EtOAc–hexane	3449	1671	2.00 (3 H, s), 4.41 (2 H, d, *J* 5.6), 5.8–6.2 (1 H, br), 7.15–7.45 (5 H, m)	$C_9H_{11}NO$			
8c	82–83[c] EtOAc–hexane	3467	1655	1.23 (9 H, s), 4.44 (2 H, d, *J* 5.6), 5.8–6.0 (1 H, br), 7.2–7.4 (5 H, m)	$C_{12}H_{17}NO$	75.15 (75.35)	8.9 (8.96)	7.3 (7.32)
8d	83–84 EtOAc–hexane	3445	1732 1673	2.25 (2 H, t, *J* 6.6), 2.76 (2 H, t, *J* 6.6), 4.42 (2 H, d, *J* 5.6), 5.12 (2 H, s), 5.8–6.1 (1 H, br), 7.2–7.4 (10 H, m)	$C_{18}H_{19}NO_3$	72.55 (72.70)	6.5 (6.44)	4.7 (4.71)
8e	Oil[d]	3445	1725 1673	0.04 (9 H, s), 0.9–1.1 (2 H, m), 2.51 (2 H, t, *J* 6.6), 2.68 (2 H, t, *J* 6.6), 4.1–4.25 (2 H, m), 4.44 (2 H, d, *J* 5.6), 5.9–6.1 (1 H, br), 7.2–7.4 (5 H, m)	$C_{16}H_{25}NO_3Si$	307.1601[e] (307.1601)		
8f	57–58[f] Et_2O-hexane	3445	1732 1673	2.52 (2 H, t *J* 6.5), 2.71 (2 H, t, *J* 6.5), 3.68 (3 H, s), 4.44 (2 H, d, *J* 5.8), 5.8–6.1 (1 H, br), 7.1–7.5 (5 H, m)	$C_{12}H_{15}NO_3$	65.15 (65.14)	6.8 (6.83)	6.3 (6.33)
8g	57–58 Et_2O	3447	1732 1667	1.2–1.5 (2 H, m), 1.5–1.8 (4 H, m), 2.20 (2 H, t, *J* 7.4), 2.36 (2 H, t, *J* 7.4), 4.43 (2 H, d, *J* 5.9), 5.10 (2 H, s), 5.6–5.8 (1 H, br), 7.2–7.5 (10 H, m)	$C_{21}H_{25}NO_3$	74.35 (74.31)	7.5 (7.42)	4.1 (4.13)
8h	Oil[g]	3447	1723 1665	0.04 (9 H, s), 0.9–1.05 (2 H, m), 1.25–1.5 (2 H, m), 1.5–1.9 (4 H, m), 2.22 (2 H, t, *J* 7.4), 2.28 (2 H, t, *J* 7.4), 4.05–4.25 (2 H, m), 4.44 (2 H, d, *J* 5.8), 5.7–5.9 (1 H, br), 7.2–7.4 (5 H, m)	$C_{19}H_{31}NO_3Si$	349.2066[e] (349.2071)		
8i	49–50 Et_2O–hexane	3447	1732 1665	1.3–1.5 (2 H, m), 1.5–1.8 (4 H, m), 2.22 (2 H, t, *J* 7.4), 2.31 (2 H, t, *J* 7.4), 3.65 (3 H, s), 4.43 (2 H, d, *J* 5.6), 5.6–5.9 (1 H, br), 7.2–7.4 (5 H, m)	$C_{15}H_{21}NO_3$	68.25 (68.41)	8.0 (8.04)	5.35 (5.32)
8j[h]	102–103[i] $CHCl_2$-hexane	3441	1665	1.58 (3 H, d, *J* 6.8), 1.98 (3 H, s), 5.05–5.2 (1 H, m), 5.6–5.9 (1 H, br), 7.2–7.4 (5 H, m)	$C_{10}H_{13}NO$			
8k	Oil[j]		1734 1643	2.65–2.75 (4 H, m), 2.94 (3 H × 7/10, s), 2.95 (3 H × 3/10, s), 3.70 (3 H × 3/10, s), 3.71 (3 H × 7/10, s), 4.57 (2 H × 3/10, s), 4.60 (2 H × 7/10, s), 7.15–7.45 (5 H, m)	$C_{13}H_{17}NO_3$	235.1216[e] (235.1209)		
8l	94–95[k] EtOAc-hexane	3432	1732 1690	2.6–2.8 (4 H, m), 3.71 (3 H, s), 7.0–7.55 (5 H, m), 7.55–7.7 (1 H, br)	$C_{11}H_{13}NO_3$			
8m	37–38 hexane		1732 1647	2.36 (2 H, t, *J* 8.0), 2.59 (2 H, t, *J* 8.0), 3.28 (3 H, s), 3.66 (3 H, s), 7.2–7.5 (5 H, m)	$C_{12}H_{15}NO_3$	65.1 (65.14)	6.85 (6.83)	6.3 (6.33)

[a] Lit.,[12a] m.p. 105.8–106.2 °C. [b] Lit.,[2a] m.p. 61–62 °C. [c] Lit.,[2a] m.p. 82–83 °C. [d] B.p. 180–190 °C/0.40 mmHg (bath temperature). [e] High resolution (EI) MS data. [f] Lit., [15] m.p. 61–64 °C. [g] B.p. 220–230 °C/0.20 mmHg (bath temperature). [h] $[\alpha]_D^{22}$ − 156.2 (*c* 1.9, benzene) {lit.,[16] $[\alpha]_D^{22}$ − 154.4 (*c* 2.7–3.0, benzene. [i] Lit.,[16] m.p. 102–103.5 °C. [j] B.p. 165–180 °C/0.40 mmHg (bath temperature). [k] Lit.,[17] m.p. 94–94.5 °C.



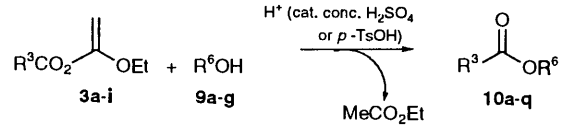
Scheme 4 *Reagents and conditions:* i, **3f** or **3i**, $Cl[CH_2]_2Cl$, 83 °C, 1 h; ii, 0.1 mol dm^{-3} NaOH, MeOH

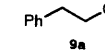
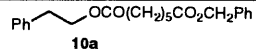
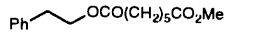
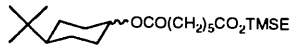
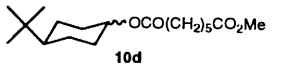
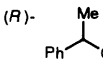
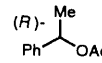
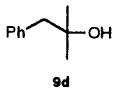
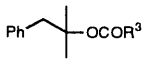
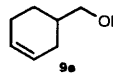
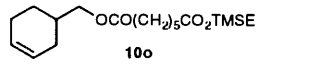
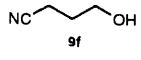
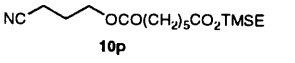
to a solution of **3g** (150 mg, 0.47 mmol) and **9a** (47.7 mg, 0.39 mmol) in dry CH_2Cl_2 (3.6 cm^3), and the mixture stirred at room temperature for 5 min. After the solvent had been removed under reduced pressure, water (2 drops) was added to the residue. The mixture was stirred for 5 min and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$) and evaporated to give a residue, which was purified by column chromatography on silica gel (hexane–Et_2O, 3:2) to afford the *title diester* **10a** (109 mg, 79%) as a colourless oil.

(B) *Using a Catalytic Amount of* p-TsOH.—*Methyl phenethyl pimelate* **10b**. Typically, anhydrous *p*-TsOH (21 mg, 0.12 mmol) was added to a solution of **3i** (180 mg, 0.74 mmol) and **9a** (75.0 mg, 0.61 mmol) in dry CH_2Cl_2 (5.5 cm^3), and the mixture was stirred at room temperature for 30 min. After the solvent had been removed under reduced pressure, water (2 drops) was added to the residue. The mixture was stirred for 10 min and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$) and evaporated to give a residue, which was purified by column chromatography on silica gel (hexane–Et_2O, 3:2) to afford the *title diester* **10b** (150 mg, 88%) as a colourless oil.

Reaction conditions for the synthesis of **10a–q** are shown in Table 6. Compounds **10c–q** were purified by column chromatography on silica gel [**10c** (hexane–Et_2O, 5:1), **10d**, **j**, **k** (hexane–Et_2O, 3:1), **10e**, **q** (hexane–EtOAc, 9:1), **10f** (hexane–Et_2O, 3:2), **10g** (hexane–EtOAc, 20:1), **10h** (hexane–Et_2O, 14:1), **10i**, **l**, **o** (hexane–Et_2O, 4:1), **10m** (hexane–Et_2O, 7:1), **10n** (hexane–Et_2O, 2:1), **10p** (hexane–Et_2O, 1:2)]. **10a**, **b**, **d**, **i–k**, **n**, **o**,

Table 6 Acylation of alcohols **9** with Reagents **3**



Run	Alcohol **9**	Conditions: **3** (equiv.)	Catalyst	Time	Ester **10**		Yield (%)
1	 **9a**	**3g** (1.2)	c.H_2SO_4	5 min	 **10a**		79
2		**3g** (1.2)	*p*-TsOH	30 min			92
3		**3i** (1.2)	c.H_2SO_4	5 min	 **10b**		79
4		**3i** (1.2)	*p*-TsOH	30 min			88
5	 **9b**	**3h** (1.5)	c.H_2SO_4	5 min	 **10c**		88
6		**3h** (1.5)	*p*-TsOH	15 min			91
7		**3i** (1.5)	c.H_2SO_4	20 min	 **10d**		84
8		**3i** (1.5)	*p*-TsOH	1 h			98
9	 **9c**	**3b** (1.5)	*p*-TsOH	45 min	 **10e**		83
10	 **9d**	**3a** (1.5)	*p*-TsOH	40 h		**10f**	52
11		**3b** (1.5)	*p*-TsOH	5 h		**10f**	85
12		**3c** (1.5)	*p*-TsOH	5 h	R^3 = Me	**10g**	92
13		**3d** (1.5)	*p*-TsOH	3.5 h	R^3 = Bu^t	**10h**	80
14		**3e** (1.5)	*p*-TsOH	3 h	R^3 = $PhCH_2OCO(CH_2)_2$	**10i**	73
15		**3f** (1.5)	*p*-TsOH	3 h	R^3 = $TMSEOCO(CH_2)_2$	**10j**	75
16		**3g** (1.5)	*p*-TsOH	2 h	R^3 = $MeOCO(CH_2)_2$	**10k**	90
17		**3h** (1.5)	*p*-TsOH	1 h	R^3 = $PhCH_2OCO(CH_2)_5$	**10l**	99
18		**3i** (1.5)	*p*-TsOH	2 h	R^3 = $TMSEOCO(CH_2)_5$	**10m**	98
					R^3 = $MeOCO(CH_2)_5$	**10n**	
19	 **9e**	**3h** (1.2)	c.H_2SO_4	5 min	 **10o**		85
20		**3h** (1.2)	*p*-TsOH	10 min			99
21	 **9f**	**3h** (1.5)	c.H_2SO_4	5 min	 **10p**		62
22		**3h** (1.5)	*p*-TsOH	30 min			71
23	PhOH **9g**	**3d** (1.5)	c.H_2SO_4	5 min	$PhOCO(CH_2)_2CO_2CH_2Ph$ **10q**		95
23		**3d** (1.5)	*p*-TsOH	1 h			96

q were identical with authentic samples.[2c] Physical data of **10c**, **e**–**h**, **l**, **m**, **p** are summarized in Table 7.

3′-N-(3-*Methoxycarbonyl*-1-*oxopropyl*)*oxaunomycin* **12a**.—A mixture of **11** (20.0 mg, 0.039 mmol) and **3f** (8.0 mg, 0.040 mmol) in 1,2-dichloroethane (20 cm^3) was heated under reflux for 1 h. After concentration of the reaction mixture under reduced pressure, the residue was purified by prep. TLC (CH_2Cl_2–MeOH, 9:1) to give the *title compound* **12a** (22.5 mg, 92%) as red crystals, m.p. 148–151 °C ($CHCl_3$–Et_2O); $[\alpha]_D^{25}$ +253 (*c* 0.092, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400, 1736 and 1655; δ_H[500 MHz; $(CD_3)_2SO$] 0.98 (3 H, t, *J* 7.3, 14-H_{x3}), 1.13 (3 H, d, *J* 6.7, 6′-H_{x3}), 1.41 (1 H, dd, *J* 12.8 and 3.7, 2′-H), 1.55–1.70 (2 H, m, 13-H_{x2}), 1.84 (1 H, dt, *J* 12.8 and 3.7, 2′-H), 2.06 (2 H, br t, *J* 2.4, 8-H_{x2}), 2.25–2.50 (4 H, m, 2 × CH_2), 3.53 (3 H, s, CH_3), 3.80–3.92 (1 H, m, 3′-H), 4.14 (1 H, q, *J* 6.7, 5′-H), 4.60 (1 H, br s, 10-H), 4.7–4.8 (1 H, br, 4′-OH), 4.92 (1 H, br t, *J* 2.4, 7-H), 5.24 (1 H, d, *J* 3.7, 1′-H), 5.5–5.65 (1 H, br, 10-OH), 7.41 (1 H, d, *J* 7.3, 3-H), 7.57 (1 H, d, *J* 7.9, 3′-NH), 7.8–7.95 (2 H, m, 1-H and 2-H), 12.01 (1 H, s, 4-OH), 12.84 (1 H, s, 6-OH) and 13.58 (1 H, s, 11-OH) [Found: M^- (FAB, negative), 629.2146. $C_{31}H_{35}NO_{13}$ requires, *M*, 629.2109].

3′-N-(6-*Methoxycarbonyl*-1-*oxohexyl*)*oxaunomycin* **12b**.—This compound was prepared from **11** (20.0 mg, 0.039 mmol) and **3i** (10.0 mg, 0.041 mmol) by the same procedure as described for the preparation of **12a**. The crude product was purified by prep. TLC (CH_2Cl_2–MeOH, 9:1) to give the *title compound* **12b** (25.0 mg, 96%) as red crystals, m.p. 130–133 °C ($CHCl_3$–Et_2O); $[\alpha]_D^{25}$ +221 (*c* 0.078, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400, 1736, 1649 and 1601; δ_H[500 MHz; $(CD_3)_2SO$] 0.98 (3 H, t, *J* 7.3, 14-H_{x3}), 1.13 (3 H, d, *J* 6.7, 6′-H_{x3}), 1.05–1.25 (2 H, m, CH_2), 1.30–1.55 (5 H, m, 2′-H and 2 × CH_2), 1.55–1.70 (2 H, m, 13-H_{x2}), 1.83 (1 H, dt, *J* 12.8, 3.7, 2′-H), 1.95–2.10 (2 H, m, CH_2), 2.07 (2 H, br d, *J* 2.6, 8-H_{x2}), 2.23 (2 H, t, *J* 7.6, CH_2), 3.54 (3 H, s, CH_3), 3.56 (1 H, s, 9-OH), 3.8–3.95 (1 H, m, 3′-H), 4.14 (1 H, q, *J* 6.7, 5′-H), 4.60 (1 H, br d, *J* 5.5, 10-H), 4.71–4.77 (1 H, br, 4′-OH), 4.92 (1 H, br t, *J* 2.6, 7-H), 5.24 (1 H, br d, *J* 3.7, 1′-H), 5.58 (1 H, br d, *J* 5.5, 10-OH), 7.42 (1 H, d, *J* 7.3, 3-H), 7.45 (1 H, d, *J* 8.6, 3′-NH), 7.8–7.95 (2 H, m, 1-H and 2-H), 12.01 (1 H, s, 4-OH), 12.85 (1 H, s, 6-OH) and 13.59 (1 H, s, 11-OH) [Found: M^- (FAB, negative), 671.2552. $C_{34}H_{41}NO_{13}$ requires, *M*, 671.2578].

3′-N-(3-*Carboxy*-1-*oxopropyl*)*oxaunomycin* **13a**.—To a solution of **12a** (17.0 mg, 0.027 mmol) in MeOH (1.5 cm^3) was added NaOH (1 mol dm^{-3}; 0.54 cm^3, 0.54 mmol) at 10 °C and the mixture was stirred at room temperature for 1 h. After the mixture had been quenched with 10% aqueous HCl, EtOAc and water were added to it with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc. The extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by prep. TLC (CH_2Cl_2–MeOH, 87:13) to

Table 7 Physical data of diesters **10c**, **e–h**, **l**, **m**, **p**

Compound	B.p.(°C)[a] (mmHg)	$\nu_{max}(CHCl_3)/cm^{-1}$ C=O	$\delta_H(CDCl_3)$	Formula	Found (%) (Required) C	H
10c	190–200 (0.45)	1721	0.04 (9 H, s), 0.85 (5/7 × 9 H, s), 0.86 (2/7 × 9 H, s), 0.9–2.4 (21 H, m), 4.05–4.25 (2 H, m), 4.5–4.8 (5/7 H, m), 4.9–5.1 (2/7 H, m)	$C_{22}H_{42}O_4Si$	66.1 (66.28)	10.5 (10.62)
10e[b]	90–100 (0.25)	1725	1.54 (3 H, d, *J* 6.8), 2.07 (3 H, s), 5.94 (1 H, q, *J* 6.6) 7.2–7.4 (5 H, m)	$C_{10}H_{12}O_2$		
10f	140–150 (0.20)	1707	1.59 (6 H, s), 3.22 (2 H, s), 7.1–7.35 (5 H, m), 7.35–7.6 (3 H, m), 7.9–8.0 (2 H, m)	$C_{17}H_{18}O_2$	80.25 (80.28)	7.3 (7.13)
10g	105–110[c] (15)	1721	1.44 (6 H, s), 1.98 (3 H, s), 3.06 (2 H, s), 7.15–7.35 (5 H, m)	$C_{12}H_{16}O_2$	74.95 (74.97)	8.35 (8.39)
10h	190–205 (0.30)	1715	1.13 (9 H, s), 1.44 (6 H, 2), 3.05 (2 H, s), 7.15–7.35 (5 H,m)	$C_{15}H_{22}O_2$	76.55 (76.87)	9.6 (9.46)
10l	200–210 (0.25)	1725	1.2–1.5 (2 H, m), 1.44 (6 H, s), 1.5–1.8 (4 H, m), 2.20 (2 H, t, *J* 7.6), 2.35 (2 H, t, *J* 7.6), 3.04 (2 H, s), 5.11 (2 H, s), 7.1–7.4 (10 H, m)	$C_{24}H_{30}O_4$	75.3 (75.36)	7.95 (7.91)
10m	160–175 (0.25)	1721	0.04 (9 H, s), 0.9–1.05 (2 H, m), 1.2–1.4 (2 H, m), 1.44 (6 H, s), 1.5–1.7 (4 H, m), 2.21 (2 H, t, *J* 7.2), 2.27 (2 H, t, *J* 7.2) 3.05 (2 H, s), 4.1–4.25 (2 H, m), 7.15–7.3 (5 H, m)	$C_{22}H_{36}O_4Si$	67.05 (67.29)	9.2 (9.24)
10p	*d*	1728	0.04 (9 H, s), 0.9–1.05 (2 H, m), 1.2–1.5 (2 H, m), 1.5–1.8 (4 H, m), 1.9–2.1 (2 H, m), 2.2–2.4 (4 H, m), 2.46 (2 H, t, *J* 7.0), 4.1–4.25 (2 H, m), 4.19 (2 H, t, *J* 5.8)	$C_{16}H_{29}NO_4Si$	327.7.1868[e] (327.1866)	

[a] Bath temperature. [b] $[\alpha]_D^{24}$ + 99.5 (*c*, 1.5, cyclopentane) {lit.,[18] $[\alpha]_D^{24}$ + 101.2 (*c*, 1.5, cyclopentane}. [c] Lit.,[19] b.p. 102–103 °C/10 mmHg. [d] Oil. Partial decomposition was occurred on distillation. [e] High resolution (EJ) MS data.

give the *title compound* **13a** (14.8 mg, 89%) as red crystals, m.p. 173–177 °C ($CHCl_3$–Et_2O); $[\alpha]_D^{25}$ +449 (*c* 0.022, 1,4-dioxane); ν_{max}(KBr)/cm^{-1} 3400, 1717, 1653 and 1603; δ_H [500 MHz; $(CD_3)_2SO$] 0.98 (3 H, t, *J* 7.3, 14-H_{x3}), 1.13 (3 H, d, *J* 6.7, 6'-H_{x3}), 1.42 (1 H, dd, *J* 12.8 and 4.3, 2'-H), 1.55–1.60 (2 H, m, 13-H_{x2}), 1.83 (1 H, dt, *J* 12.8 and 3.7, 2'-H), 2.06 (2 H, br d, *J* 2.5, 8-H_{x2}), 2.20–2.40 (4 H, m, 2 × CH_2), 3.85 (1 H, s, 9-OH), 4.14 (1 H, q, *J* 6.7, 5'-H), 4.60 (1 H, d, *J* 7.3, 10-H), 4.74 (1 H, d, *J* 5.5, 4'-OH), 4.92 (1 H, br t, *J* 2.5, 7-H), 5.24 (1 H, d, *J* 3.7, 1'-H), 5.58 (1 H, d, *J* 7.3, 10-OH), 7.42 (1 H, d, *J* 7.9, 3-H), 7.54 (1 H, d, *J* 7.9, 3'-NH), 7.80–7.95 (2 H, m, 1-H and 2-H), 11.85–12.05 (1 H, br, CO_2H), 12.01 (1 H, br s, 4-OH), 12.85 (1 H, br s, 6-OH) and 13.58 (1 H, br s, 11-OH); [Found: M^- (FAB, negative), 615.1968. $C_{30}H_{33}NO_{13}$ requires *M*, 615.1952].

3'-N-(6-*Carboxy*-1-*oxohexyl*)*oxaunomycin* **13b**.—This compound was prepared from **12b** (20.0 mg, 0.030 mmol) and aqueous NaOH (1 mol dm^{-3}; 0.60 cm^3, 0.60 mmol) by the same procedure as for the preparation of **13a**. The crude product was purified by prep. TLC (CH_2Cl_2–MeOH, 85:15) to give the *title compound* **13b** (16.3 mg, 83%) as red crystals, m.p. 188–192 °C ($CHCl_3$–Et_2O); $[\alpha]_D^{25}$ +351 (*c* 0.020, 1,4-dioxane); ν_{max}(KBr)/cm^{-1} 3315, 1717, 1664 and 1599; δ_H[500 MHz; $(CD_3)_2SO$] 0.98 (3 H, t, *J* 7.3, 14-H_{x3}), 1.13 (3 H, d, *J* 6.7, 6'-H_{x3}), 1.1–1.3 (2 H, m, CH_2), 1.35–1.55 (5 H, m, 2'-H and 2 × CH_2), 1.55–1.75 (2 H, m, 13-H_{x2}), 1.83 (1 H, dt, *J* 12.8 and 3.7, 2'-H), 2.03 (2 H, t, *J* 7.6, CH_2), 2.07 (2 H, s, 8-H_{x2}), 2.14 (2 H, t, *J* 7.3, CH_2), 3.8–3.95 (2 H, m, 9-OH and 3'-H), 4.14 (1 H, q, *J* 6.7, 5'-H), 4.61 (1 H, d, *J* 6.1, 10-H), 4.75 (1 H, br s, 4'-OH), 4.92 (1 H, d, *J* 2.1, 7-H), 5.25 (1 H, br s, 1'-H), 5.59 (1 H, d, *J* 6.1, 10-OH), 7.40–7.55 (2 H, m, 3-H and 3'-NH), 7.8–7.95 (2 H, m, 1-H and 2-H), 11.89 (1 H, br, CO_2H), 12.01 (1 H, s, 4-OH), 12.84 (1 H, s, 6-OH) and 13.58 (1 H, s, 11-OH) [Found: M^- (FAB, negative), 657.2402. $C_{33}H_{39}NO_{13}$ requires *M*, 657.2422].

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