A Convenient Synthesis of Dicarboxylic Monoesters using Isopropenyl Esters: Synthesis of Oxaunomycin Derivatives

Yasuyuki Kita,* Hiroshi Maeda, Fumie Takahashi and Seiji Fukui

Faculty of Pharmaceutical Sciences, Osaka University, 1–6 Yamada-oka, Suita, Osaka 565, Japan

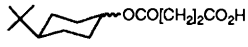
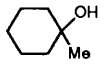
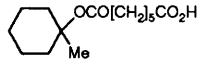
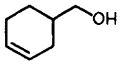
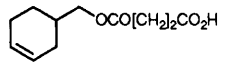
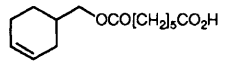
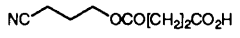
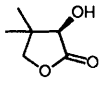
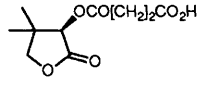
Reaction of various types of alcohols with a novel type of acylating agent, the isopropenyl esters **2a–e** in the presence of a catalytic amount of conc. sulfuric acid or toluene-*p*-sulfonic acid followed by selective deprotection of the terminal ester gives the monoesters **5a–i** in good yields.

Dicarboxylic monoesters are useful water-soluble prodrugs of steroids,[1] tocopherols,[2] anthracycline[3] and taxol,[4] and have been prepared by (*i*) treatment of alcohols with cyclic anhydrides, (*ii*) treatment of alcohols with acid chlorides followed by deprotection of the terminal ester, or (*iii*) conversion of alcohols to halo compounds followed by substitution with carboxylate anion. These methods cannot be used generally, however; (*i*) medium to large unstable anhydrides[5] cannot be employed in the direct acylation of alcohols; (*ii*) bulky secondary or tertiary alcohols do not react easily with acid anhydrides or acid chlorides and (*iii*) the transformation of bulky alcohols into the halo compounds may be troublesome. We report here a novel, convenient method[6] for acylation of bulky alcohols using isopropenyl

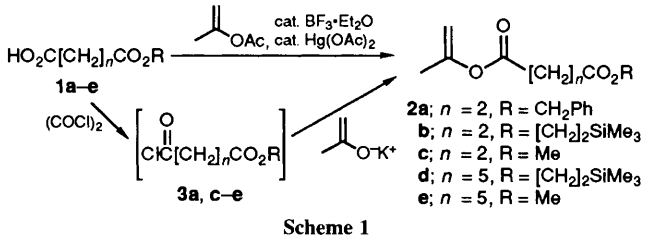
Table 1. Acylation of alcohols with reagents **2a–e** and deprotection of diesters **4a–k** to monoesters **5a–i**

$$R^2OH \xrightarrow{\textbf{2a–e}} R^2OCO[CH_2]_nCO_2R^1 \xrightarrow[\text{method } A–C]{\text{deprotection}} R^2OCO[CH_2]_nCO_2H$$

4a–k **5a–i**

Run	Alcohol	Conditions[a]	Yield[b] of 4(R)[c] (%)		Method[d]	Monoester	Yield[b] of 5(%)
1		**2a**, 6 h	**a** (Bn)	(86)	*A*	$PhCH_2CMe_2OCO[CH_2]_2CO_2H$	**a** (97)
2	$PhCH_2CMe_2OH$	**2b**, 40 °C, 13 h	**b** (TMSE)	(73)	*B*		**a** (88)
3		**2c**, 3 h	**c** (Me)	(70)	*C*	$PhCH_2CMe_2OCO[CH_2]_5CO_2H$	**a** (85)
4		**2e**, 3 h	**d** (Me)	(75)	*C*		**b** (81)
5		**2a**, 9 h	**e** (Bn)	(70)	*A*		**c** (78)
6		**2e**, 4 h	**f** (Me)	(79)	*C*		**d** (92)
7		**2b**, 40 °C, 8 h	**g** (TMSE)	(65)	*B*		**e** (85)
8		**2d**, 1 h	**h** (TMSE)	(92)	*B*		**f** (85)
9		**2b**, 40 °C, 8 h	**i** (TMSE)	(65)	*B*		**g** (82)
10		**2a**, 4 h	**j** (Bn)	(94)	*A*		**h** (95)
11		**2a**, conc. H_2SO_4, 1 h	**j** (Bn)	(92)			
12	PhOH	**2a**, 3 h	**k** (Bn)	(82)	*A*	$PhOCO[CH_2]_2CO_2H$	**i** (84)
13		**2a**, conc. H_2SO_4, 2 h	**k** (Bn)	(81)			

[a] Acylations were carried out at room temp. in the presence of 0.2 equiv. of *p*-TsOH unless otherwise noted. [b] Isolated yields are given. [c] Bn = CH_2Ph, TMSE = $Me_3Si[CH_2]_2$. [d] Method *A*: H_2/Pd, dioxane; method *B*: Bu_4NF, dimethylformamide; method *C*: NaOH, aq. MeOH.



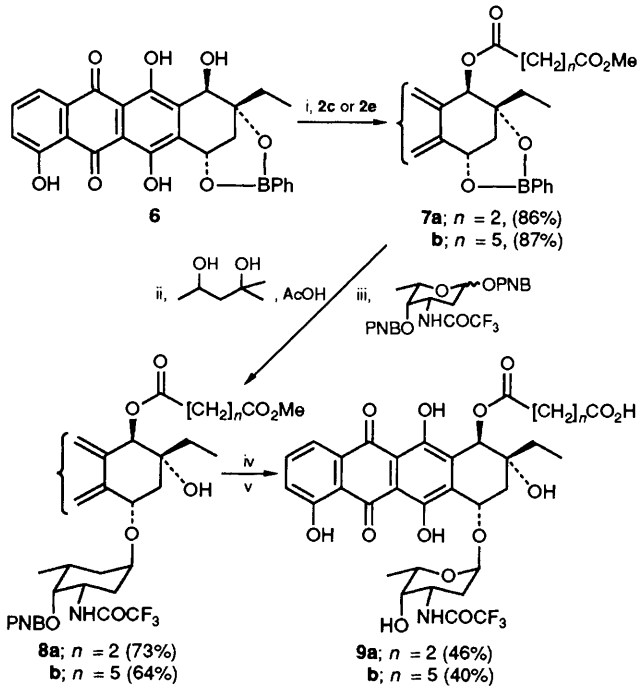
Scheme 1

esters **2a–e** and selective deprotection of the terminal ester leading to the monoesters.

The novel agents **2a–e**† could be prepared from the half esters **1a–e**‡ by treatment with isopropenyl acetate in the presence of a catalytic amount of BF_3·Et_2O and mercury(II) acetate[7] in fair yields, or by direct acylation of the potassium enolate generated from acetone and potassium hydride with acid chlorides **3a, c–e** (Scheme 1).

† **2a**, b.p. 165–168 °C at 2.0 mmHg; **2b**, b.p. 122–124 °C at 0.6 mmHg; **2c**, b.p. 104–106 °C at 14 mmHg; **2d**, b.p. 128 °C at 0.38 mmHg; **2e**, b.p. 121–123 °C at 2.5 mmHg.

‡ **1b** was prepared by heating a mixture of succinic anhydride and 2-(trimethylsilyl)ethanol in the presence of pyridine (77%), b.p. 132–133 °C at 0.6 mmHg. **1d** was prepared by treating the corresponding acid chloride, which was synthesized from benzyl hydrogen pimelate, with 2-(trimethylsilyl)ethanol in the presence of pyridine followed by catalytic hydrogenation of the benzyl ester (53%), b.p. 170–175 °C at 0.3 mmHg.



PNB = *p*-nitrobenzoyl

Scheme 2 *Reagents and conditions*: i, cat. conc. H_2SO_4, CH_2Cl_2; ii, acetone, CH_2Cl_2; iii, $CF_3SO_3SiMe_3$, 4 Å molecular sieve, CH_2Cl_2, Et_2O; iv, 0.1 mol dm^{-3} NaOH (1.2 equiv.), CH_2Cl_2, MeOH; v, 0.1 mol dm^{-3} NaOH (20 equiv.), $MeOCH_2CH_2OMe$

All acylation reactions of alcohols using **2a–e** were performed in the presence of a catalytic amount of acid to give high yields of diesters **4a–k**.§ Not only bulky alcohols such as tertiary alcohols and pantolactone, but also phenol were acylated smoothly in good yields. Furthermore, olefin, nitrile and lactone moieties were not affected under these reaction conditions (runs 7–11). The terminal ester of the dicarboxylic esters was removed selectively by the following three methods: (*i*) catalytic hydrogenation of the benzyl ester (method *A*), (*ii*) desilylative fragmentation of the 2-(trimethylsilyl)ethyl ester by treatment with fluoride anion[8] (method *B*) and (*iii*) selective saponification of the methyl ester by alkali treatment (method *C*). High yields (78–97%) of the half esters **5** were obtained in every case (Table 1). Methods *A* and *B* gave satisfactory results for primary and secondary alcohols and method *C* is suitable for deprotection of the terminal esters derived from tertiary alcohols. Method *B* is best for esters bearing an olefin or a nitrile unit (runs 7–9).

Finally, we applied this method to the half esterification of the anthracycline antibiotic, oxaunomycin,[9] which was found to be about 100-fold more active than adriamycin against leukaemic L-1210 cultures. The reagents **2c, e** smoothly reacted with 7,9-*O*-phenylboronyl-β-rhodomycinone **6**[10] to afford otherwise unavailable 10-*O*-acylated products **7a, b** in good yields, which were converted to the desired water-soluble half esters **9a, b** *via* the glycoside ester **8a, b** (Scheme 2).

§ A mixture of the alcohol (1.25 mmol) and **2** (2.5 mmol) in the presence of a catalytic amount of toluene-*p*-sulfonic acid (*p*-TsOH) (0.25 mmol) or conc. sulfuric acid (2 drops) in methylene chloride (10 ml) was stirred under the conditions indicated in Table 1, concentrated under reduced pressure and acidified with conc. hydrochloric acid (5 drops) in acetonitrile (0.1 ml). The mixture was stirred for 30 min and partitioned with ethyl acetate (20 ml) and saturated aqueous sodium hydrogen carbonate (10 ml). The organic layer was dried over magnesium sulfate and evaporated to yield a residue, which was purified by column chromatography on silica gel (ethyl acetate–n-hexane) to give pure **4**.

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