A Novel Transacylation Method for the Synthesis of α-*N*-Acyl-β-lactones; Application to (±)-Diacetylobafluorin and (+)-SQ 26,517†

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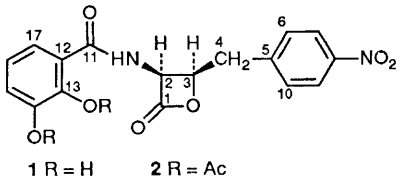
Stereoselective synthesis of (±)-diacetylobafluorin and (+)-SQ 26,517 has been accomplished *via* transacylation of α-*N*-(2-nitrophenyl)sulphenyl-β-lactones with 2-acylmercaptobenzothiazoles.

As part of a research programme directed toward the synthesis of obafluorin **1**, a β-lactone antibiotic with unprecedented biological activity,[1] we required a mild and convenient procedure for the synthesis of α-*N*-acyl-β-lactones. Although several methods are reported for the synthesis of β-lactones, none of them have been found to be suitable for the β-substituted-β-lactone antibiotics such as obafluorin **1** and SQ 26,517 **3**.[2,3] Recently Vederas and co-workers,[4] reported the synthesis of SQ 26,517. In this communication we describe a novel transacylation method for α-*N*-acyl-β-lactones. Further, its application to the first stereoselective synthesis of diacetylobafluorin **2** and SQ 26,517 **3** is also delineated. Since the presence of both the β-lactone affecting unprotected amino- and mercapto-nucleophiles are avoided and almost neutral conditions are used, the scope of this transacylation reaction is significantly extended.

Our earlier attempts to synthesise the β-hydroxy-α-amino ester **7** (Scheme 1) from a glycine Schiff base derivative resulted in unusual *N*-acylation leading to the formation of *N*-acylaziridines.[5] We have now chosen ethyl isocyanoacetate **4** as a glycine synthetic equivalent because it not only provides the required *threo* isomer stereoselectively[6] but also effects an aldol type condensation under mild basic conditions, which



1 R = H **2** R = Ac **3**

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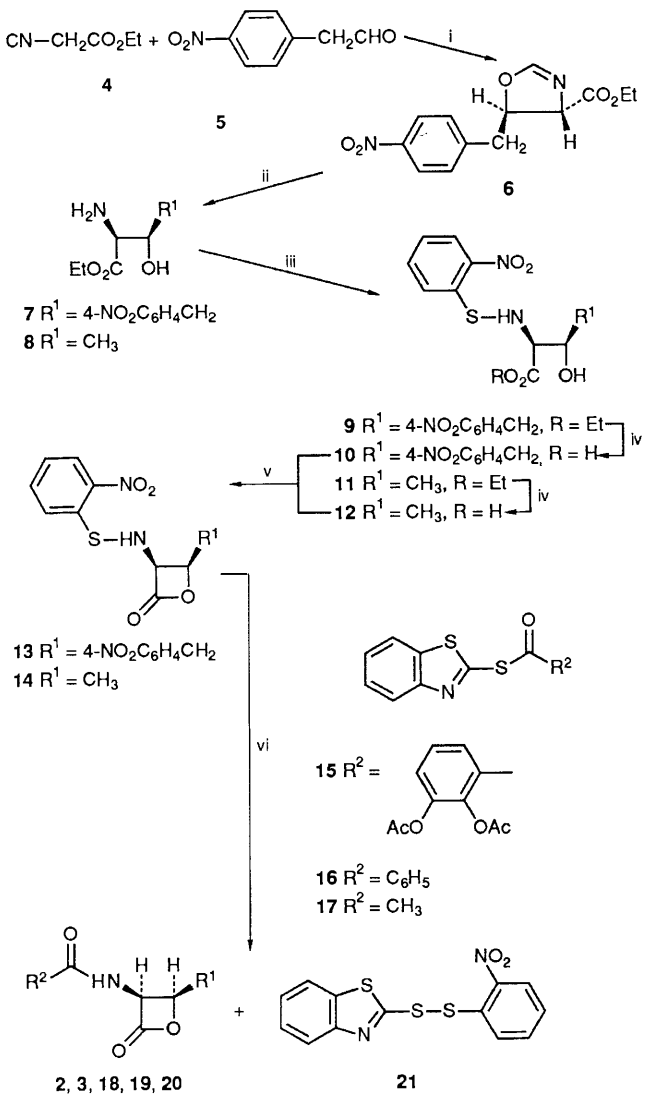

Scheme 1 *Reagents and conditions*: i, NaCN, EtOH, room temp.; ii, conc. HCl, MeOH, 50 °C; iii, 2-$NO_2C_6H_4SCl$, Et_3N, CH_2Cl_2, room temp.; iv, aq. NaOH, tetrahydrofuran, room temp.; v, $PhSO_2Cl$, pyridine, 0 °C; vi, PPTS, CH_2Cl_2, room temp.

are suitable for the enolizable aldehyde **5**. Thus, treatment of **4** with aldehyde **5** (NaCN, ethanol) afforded *trans*-oxazoline **6** as the only product in 74% yield with no detectable *cis*-isomer. It is interesting to note the stereoselective formation of **6**. A literature report[6] as well as our own observation indicated the formation of 95:5 *trans*- and *cis*-diastereoisomers in the reaction of **4** with benzaldehyde under similar conditions. Hydrolysis of **6** with conc. HCl in methanol gave *threo*-hydroxy-amino ester **7** (64%). The methyl ester analogue of **7**, a possible transesterification product, was not observed in the reaction mixture. The protection of the amino group with 2-nitrophenylsulphenyl chloride as described,[7] produced the ester **9**, which was hydrolysed to afford the acid **10**. Cyclization of the β-hydroxyamino acid **10** to the β-lactone **13** was effected with benzenesuphonyl chloride in pyridine (62%). Transacylation of the lactone **13** with 2-acylmercaptobenzothiazole **15** in the presence of pyridinium toluene-*p*-sulphonate (PPTS) in dichloromethane afforded diacetylobafluorin **2** (76%, entry 1, Table 1). The spectral data of **2**‡ are comparable with the reported values of diacetylobafluorin prepared from **1**.[1] Under similar conditions reaction of **13** with 2-benzoylmercaptobenzothiazole **16** gave 13,14-didehydroxy-obafluorin **18** (entry 2) indicating little effect of the substituents in the aryl group R^2 on transacylation.

Table 1 Synthesis of α-*N*-acyl-β-lactones[a]

Entry	Substrate	Reagent	Product	M.p./°C	Yield (%)
1	**13**	**15**	**2**	152–54	76
2	**13**	**16**	**18**	160–61	80
3	**14**	**17**	**3**	96–98	52
4	**14**	**16**	**19**	156–58	78
5	**14**	**15**	**20**	130–31	70

[a] All compounds showed consistent ^1H NMR, IR and mass spectral data with the assigned structures and gave satisfactory elemental analysis. The unoptimized yields refer to isolated products.

In order to synthesise SQ 26,517 and thus ascertain the generality of this transacylation protocol the reactions of the L-threonine-β-lactone derivative **14** were examined. The results are summarized in Table 1. The β-lactone **14** was prepared from L-threonine ethyl ester **8** by a reaction sequence as depicted in Scheme 1 and described above. Thus, treatment of **14** with 2-acetylmercaptobenzothiazole **17** gave SQ 26,517 **3**, $[\alpha]_D^{26}$ + 57.3 (*c* 0.1, H_2O), in 52% yield (entry 3). The lower yield of **3** compared to α-*N*-benzoyl-β-lactones **19** and **20** (entries 4 and 5) may be due to the stability of the acetyl derivative **17** being lower than that of the benzoyl derivatives **15** and **16**, which was observed during their preparation. The formation of (+)-SQ 26,517 **3** from L-threonine derivative **8** without epimerisation further extends the scope of this method for the synthesis of optically active α-*N*-acyl-β-lactones.

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‡ *Selected spectroscopic data* for: **2** IR ($CHCl_3$) 3260, 1840, 1770, 1700, 1650, 1610, 1550, 1520 and 1350 cm^{-1}; ^1H NMR ($CDCl_3$–CD_3COCD_3, 90 MHz) δ 2.31 (s, 6H), 3.41 (dd, *J* 6, 15 Hz, 2H, CH_2-4), 5.11 (m, 1H, H-3), 6.00 (dd, *J* 6, 8 Hz, 1H, H-2), 7.35 (d, *J* 9 Hz, 1H, H-15), 7.55 (d, *J* 9 Hz, 2H, H-6 and H-10), 7.91 (m, 2H, H-16 and H-17), 8.24 (d, *J* 9 Hz, 2H, H-7 and H-9), 9.00 (br, d, 1H, N*H*). Mass *m/z* (%) 442 (M^+, 0.4), 427 (0.5), 401 (0.4), 277 (2.2), 247 (0.9), 238 (1.8), 221 (1.5), 196 (7.1), 179 (3.4), 167 (18.8), 137 (7.1), 105 (100.0).