Tri-n-butyltin Hydride assisted Highly Stereoselective Lactonisation of Homoallylic Xanthates

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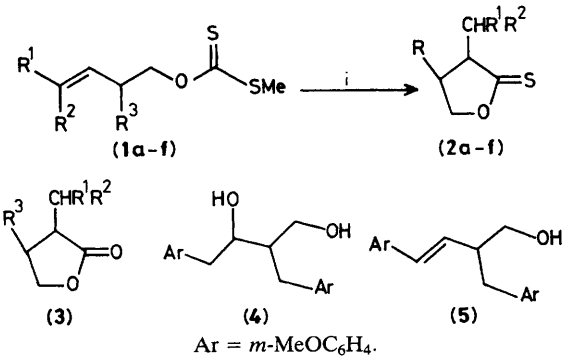
A highly stereo- and regio-selective radical cyclisation of homoallylic xanthate esters is presented and the reaction is applied to the synthesis of some ring fused lactones.

Radical–initiated cyclisation[1] is one of the most attractive routes to the synthesis of mono-,[2] fused-,[3] and tandem[4] cyclised systems; it is compatible with unprotected functional groups and relatively insensitive to steric hindrance, although the selectivity is not satisfactorily high.[5]

Recently, Bachi and Bosch reported[6] that a xanthate ester could be a latent precursor of a lactone in a radical cyclisation reaction, but the stereoselectivity of the cyclisation was not revealed. We report here an independent investigation on a highly stereoselective xanthate ester cyclisation assisted by tri-n-butyltin hydride.

Homoallylic xanthate (**1**) and tri-n-butyltin hydride (1.2



Scheme 1. *Reagents and conditions*: i, Bu_3SnH–AIBN, toluene, 80 °C.

equiv.) in dry toluene were heated 80 °C for 2 h with portionwise addition of 10% AIBN (azoisobutyronitrile) under an argon atmosphere (Scheme 1). The cyclisation was regiospecific to afford the 5-*exo*-*trig* thionolactone (**2c**) with high diastereoselectivity. Thionolactone (**2c**) was easily converted to the corresponding lactone (**3c**) (66%) by oxidation with *m*-chloroperbenzoic acid (1.3 equiv.) in CH_2Cl_2 at room temperature for 3 h. Its configuration was difficult to determine from spectral data. In order to determine the stereochemistry of the predominant diastereoisomer, we attempted synthesis of a known natural product 'enterolactone dimethyl ether,' (**2e**),[7] whose configuration was *anti*.† The diol (**4**) was obtained from *m*-methoxyphenylacetic acid

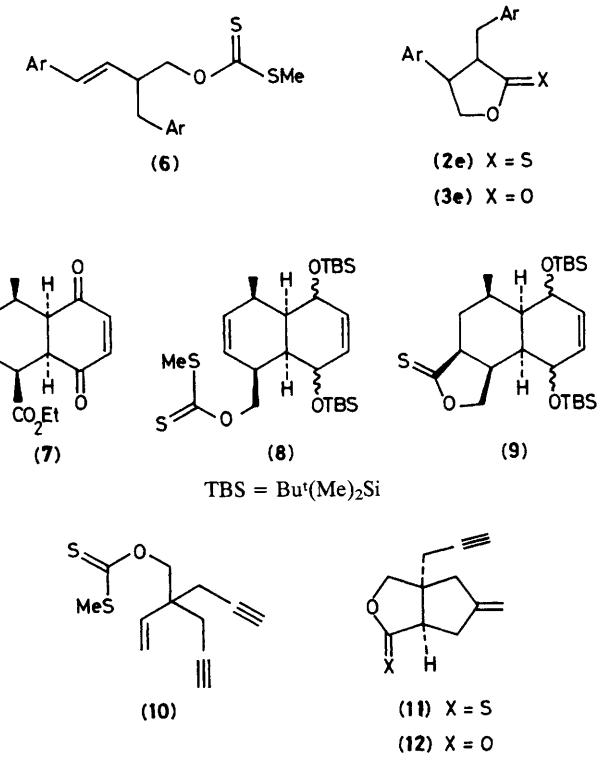


Table 1. Radical cyclisation of xanthate ester (**1**) to thionolactone (**2**).

	R^1	R^2	R^3	Yield[a] of (**2**)/%	*syn* : *anti*	
a	H	Et	H	50 (83)[b]	—	—
b	Et	H	H	72 (94)[b]	—	—
c	Me	H	Et	80	4	96
d	Et	H	Et	77	4	96
e	*m*-MeO–C_6H_4–	H	*m*-MeO–$C_6H_4CH_2$–	75	10	90
f	H		–$(CH_2)_3$–	71	99	1

[a] Isolated yields. [b] Conversion yields.

in several steps‡ and was selectively silylated at the primary hydroxy group, followed by tosylation of the secondary hydroxy group, detosylation {1,8-diazabicyclo[5.4.0]undec-7-ene, refluxing in tetrahydrofuran (THF)}, and then desilylation (HCl–MeOH) to give the *trans*-homoallyl alcohol (**5**). Xanthate ester (**6**), prepared by treating (**5**) with KH in THF/CS_2 followed by methyl iodide, was subjected to tributyltin hydride (1.2 equiv.) assisted cyclisation in toluene at 80 °C using 10% AIBN to give thionolactone (**2e**) (75%) in a diastereoisomer ratio 10 : 90 (Table 1).

This mixture was treated with *m*-chloroperbenzoic acid in CH_2Cl_2 to give the corresponding lactone (**3e**) (66%) in a *syn*/*anti* ratio of 8 : 92. The major compound was separated by repeated h.p.l.c.§ and identified as the *anti* stereoisomer by comparison of its spectral data with those of an authentic sample.[7] From the similar reaction features, it is presumed that the thionolactones (**2c**) and (**2d**) also have the *anti*

† *Spectroscopic data*. *syn*-(**3e**): ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 2.335 (t, 1H, *J* 13, 13 Hz), 2.70 (m, 1H), 2.812 (dd, 1H, *J* 11, 15 Hz), 2.971 (dd, 1H, *J* 4, 13 Hz), 3.117 (ddd, 1H, *J* 5, 71 Hz), 3.316 (dd, 1H, *J* 5, 15 Hz), 3.796 (s, 3H), 3.820 (s, 3H), 4.016 (ddd, 1H, *J* 1, 5, 9.5 Hz), 4.058 (dd, 1H, *J* 1.5, 9.5 Hz), 6.57—7.29 (m, 8H); ^{13}C n.m.r. (100 MHz, $CDCl_3$) δ 30.88 (t), 32.97 (t), 39.80 (d), 45.17 (d), 55.17 (q), 55.22 (q), 69.48 (t), 111.77 (d), 111.82 (d), 114.32 (d), 114.85 (d), 120.68 (d), 121.27 (d), 129.75 (d), 140.10 (s), 140.20 (s), 159.84 (s), 159.95 (s), 177.87 (s); M^+, found *m*/*z* 326.1518, calcd. for $C_{20}H_{22}O_4$ 326.1516. *anti*-(**3e**): ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 2.470 (dd, 1H, *J* 9,13 Hz), 2.52 (m, 1H), 2.61 (m, 2H), 2.915 (dd, 1H, *J* 7, 14 Hz), 3.063 (dd, 1H, *J* 5, 14 Hz), 3.767 (s, 3H), 3.781 (s, 3H), 3.861 (dd, 1H, *J* 8, 9 Hz), 6.52—7.23 (m, 8H); ^{13}C n.m.r. (100 MHz, $CDCl_3$) δ 35.15 (t), 38.58 (t), 41.26 (d), 46.35 (d), 55.13 (q), 55.17 (q), 71.68 (t), 111.86 (d), 112.37 (d), 114.51 (d), 114.84 (d), 120.91 (d), 121.59 (d), 129.66 (d), 129.72 (d), 139.30 (s), 139.55 (s), 159.82 (s), 159.86 (s), 178.47 (s); M^+, found *m*/*z* 326.2526, calcd. for $C_{20}H_{22}O_4$ 326.1516. *trans*=(**2e**): ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 2.453 (dd, 1H, *J* 9, 13.5 Hz), 2.526 (dd, 1H, *J* 6, 13.5 Hz), 2.56 (m, 1H), 2.905 (dd, 1H, *J* 9, 14 Hz), 2.977 (dddd, 1H, *J* 5, 6, 9 Hz), 3.363 (dd, 1H, *J* 5, 14 Hz), 3.751 (s, BH), 3.773 (s, 3H), 4.409 (dd, 1H, *J* 7, 10 Hz), 4.254 (dd, 1H, *J* 6, 10 Hz), 6.46—7.22 (m, 8H); ^{13}C n.m.r. (100 MHz, CDCl) δ 38.54 (t), 39.26 (t), 42.66 (d), 55.11 (q), 55.17 (q), 60.47 (d), 79.28 (t), 111.89 (d), 112.40 (d), 114.41 (d), 114.73 (d), 120.86 (d), 121.49 (d), 129.63 (d), 129.70 (d), 139.49 (s), 139.67 (s), 159.80 (s), 159.84 (s), 225.37 (s); M^+, found *m*/*z* 342.1285, calcd. for $C_{20}H_{22}O_3S$ 342.1287. *cis*-(**2e**): ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 2.236 (t, 1H, *J* 13, 13 Hz), 2.71 (m, 1H), 2.808 (dd, 1H, *J* 11, 15 Hz), 2.938 (dd, 1H, *J* 4, 13 Hz), 3.274 (ddd, 1H, J 4, 6, 11 Hz), 3.664 (dd, 1H, *J* 4, 15 Hz), 3.754 (s, 3H), 3.823 (s, 3H), 4.294 (ddd, 1H, *J* 1, 5, 9.5 Hz), ~6.51—7.30 (m, 8H). (**11**): ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 2.011 (m, 1H), ~2.35—2.45 (m, 4H), 2.912 (br.s, 2H), 3.159 (dd, 1H), *J* 0.6, 0.6 Hz), 4.415 (d, 1H, *J* 1 Hz), 4.603 (d, 1H, 1 Hz), 4.934 (br.s, 2H); ^{13}C n.m.r. (100 MHz, $CDCl_3$) δ 25.651 (t), 38.238 (t), 43.064 (t), 51.387 (s), 62.933 (d), 71.444 (s), 79.716 (d), 82.905 (t), 101.221 (t), 146.861 (s), 222.543 (s); i.r. (neat) 3375, 2900, 1660, 1245, 1170 cm^{-1} cm^{-1}; M^+, found *m*/*z*; 192.0613, calcd. for $C_{11}H_{12}OS$ 192.0608. (**12**): ^{1}H n,m.r. (60 MHz, CCl_4) δ 2.150 (m, 1H), 2.50 (m, 1H), 2.50 (m, 5H), 2.750 (m, 2H), 4.17 (br.s, 1H), 4.25 (br.s, 1H), 4.925 (br.s, 2H); i.r. (neat) 3325, 1790, 1645, 1230, 1175 cm^{-1}; M$^+$, *m*/*z* found 176.0847, calcd. for $C_{11}H_{12}O_2$ 176.0837.

‡ Diol (**4**) was prepared in the following way in 50% total yield: treatment of *m*-methoxyphenylacetic acid with i, $(COCl)_2/CH_2Cl_2$, ii, Merudrum acid/pyridine, iii, EtOH, reflux, iv, NaH/*m*-methoxybenzyl chloride/benzene, reflux, v, $LiAlH_4/Et_2O$.

§ The determination of the ratio and the separation of the diastereoisomers was carried out with Hitach L-6000 h.p.l.c. system using a 250 × 10 mm column packed with Merk LiChrosorb Si 60.

configuration.¶ On the contrary, the configuration of (**2f**) (a five-membered ring fused bicyclic thionolactone) was assigned as *syn*, especially in view of the considerable ring strain inherent in the corresponding *anti*-fused thionolactone.[8]

Bicyclic homoallylic xanthate ester (**8**) was prepared as follows: treatment of the Diels–Alder adduct (**7**) with (i) $NaBH_4$/MeOH, (ii) t-butyldimethylsilyl chloride/imidazole, (iii) $LiAlH_4$/THF, and (iv) NaH/CS_2/MeI. The product was successfully converted to the tricyclic thionolactone (**9**) (70%).

A tandem version of this cyclisation was also successfully performed. Acyclic xanthate ester (**10**) was treated in the standard manner as described to give (**11**) (40%), which in turn was oxidized to the corresponding lactone (**12**) (80%). The progress of the tandem cyclisation will be published elsewhere.

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¶ All new compounds gave satisfactory analytical and spectroscopic data.

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