The Use of t-Butyl Acetothioacetate as a Route to Bis-β-ketomacrolides

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Dianions from t-butyl acetothioacetate may be alkylated at the γ-carbon atom with suitably protected iodoalkanols to afford useful precursors for dimerisation to novel bis-β-ketomacrolides in the presence of copper(I) trifluoroacetate.

Recently we showed that t-butyl acetothioacetate (**1**) could function as a synthetic equivalent to diketene and further, could be used for the rapid preparation of acyl tetronic acid derivatives, some of which are natural products.[1] We now show that this versatile reagent may also be transformed to a range of novel bis-β-ketomacrolides.

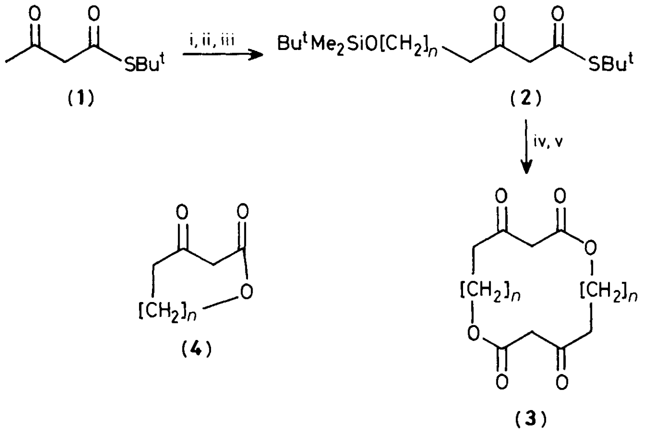
This dianion from t-butyl acetothioacetate was generated by treatment with 1 equiv. of sodium hydride at −20 °C followed by reaction with 1 equiv. of n-butyl-lithium at −40 °C in dimethoxyethane (DME) solution.

The dianion was then treated with a range of t-butyldimethylsilyl-protected iodoalkanols to give the γ-alkylated products (**2**) in reasonable yields (Table 1). These products were deprotected with 5% aqueous HF[2] in essentially quantitative yield to the corresponding alcohol. Subsequent treatment with copper(I) trifluoroacetate (5 equiv.) in dichloromethane solution, containing a sodium hydrogen phosphate buffer, over 15 min gave either the dimeric bis-β-ketomacrolide (**3**) or the monomeric β-ketomacrolide (**4**)

Table 1. Yields in the reaction of (**1**) with iodoalkanols.

Iodide *n*	% Yield (**2**)	% Yield (**3**)[a] (Ring-size)	% Yield (**4**) (Ring-size)
4	60	38 (18)	—
5	59	49 (20)	—
6	59	42 (22)	—
8	39	42 (26)	12 (13)
11	67	8[b] (32)	72 (16)
		16[c] (32)	62 (16)

[a] In all cases the final concentration of (**2**) in CH_2Cl_2 was 0.02 M. [b] Addition of (**2**) as 0.06 M in CH_2Cl_2. [c] Addition of (**2**) as 0.19 M in CH_2Cl_2.



Reagents: i, NaH, DME; ii, Bu^nLi; iii, $I[CH_2]_nOSiMe_2Bu^t$; iv, HF; v, $CuOCOCF_3$, CH_2Cl_2.

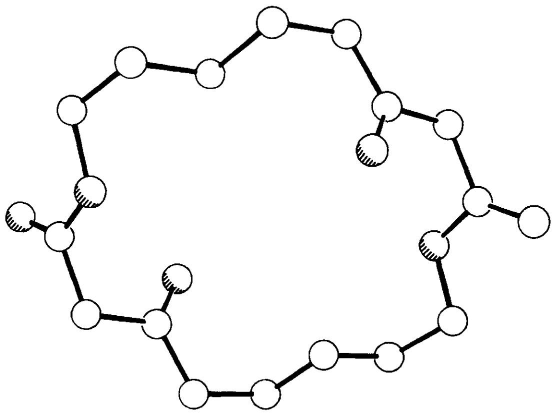


Figure 1. The molecular structure of $C_{16}H_{24}O_6$. *Crystal data:*† monoclinic, a = 10.486(4), b = 5.000(1), c = 16.630(4) Å, β = 102.12(3)°, U = 853 Å^3, space group $P2_1/n$, Z = 2, M = 312.4, D_c = 1.22 g cm^{-3}.

depending upon the chain length (Table 1). The choice of copper(I) trifluoroacetate as the transesterification catalyst in these examples was noticeably superior to either $Hg(CF_3CO_2)_2$ or $Ag(CF_3CO_2)$, which had been recommended[3] in other systems, and may reflect an improved templating ability of Cu^I.

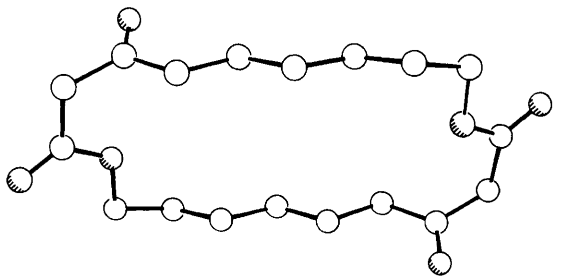


Figure 2. The molecular structure of $C_{18}H_{28}O_6$. *Crystal data:*† monoclinic, a = 4.671(2), b = 24.095(9), c = 8.344(3) Å, β = 103.78(3)°, U = 912 Å^3, space group $P2_1/c$, Z = 2, M = 340.4, D_c = 1.24 g cm^{-3}.

While t-butyl thioesters have been used previously with great success in macrolide synthesis,[4] they had not previously been used to prepare bis-macrolide species where the preferred methods were either the Mitsunobu coupling,[5] imidazole active ester,[6] or tin-mediated esterification[7] methods.

Since a number of the bis-β-ketomacrolides were crystalline we have also studied their crystal structures. Interestingly while the 18-membered ring adopts a very open cyclic arrangement (Figure 1), the larger ring analogues, 20- and 22-membered rings, prefer an arrangement in which the lipophilic hydrocarbon linking chains are closely stacked (*e.g.* Figure 2).

We are presently investigating systems where there is additional oxygen functionality in these linking chains with the aim of producing unusual speciation compounds. Also this dimerisation methodology should allow the preparation of natural bis-macrolides which is an area of growing interest.[8]

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† For the 22-membered ring compound $C_{20}H_{32}O_6$. *Crystal data:* triclinic, a = 5.521(1), b = 8.249(2), c = 11.822(3) Å, α = 95.55(2), β = 101.63(2), γ = 106.21(2)°, U = 500 Å^3, space group $P\bar{1}$, Z = 1, M = 368.4, D_c = 1.23 g cm^{-3}. Data for all compounds were measured on a Nicolet R3m diffractometer with graphite monochromated Cu-K_α radiation using ω-scans. All structures were solved by direct methods and refined anisotropically giving for each structure respectively R = 0.050, R_w = 0.073 for 1112 independent observed reflections [$|F_o| > \sigma(|F_o|)$, θ ≤ 58°] (Figure 1); R = 0.051, R_w = 0.057 for 859 independent observed reflections [θ ≤ 50°] (Figure 2), and R = 0.040, R_w = 0.051 for 1199 independent observed reflections [θ ≤ 58°] for the 22-membered ring compound. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.