Repetitive Template-Directed Acyl Transfer to Mimic Steps in the Biosynthesis of Polyketides and Fatty Acids

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Efficient condensations between two acyl groups attached to a tetramethylglycoluril template provide a repetitive sequence for efficient construction of fatty acids and polyketide-like natural products in a biomimetic fashion.

The assembly of acyl units by sequential Claisen-type condensations to form a polyketide or fatty acid chain is quite general in biosynthesis.[1] Mimicking this efficient natural process with a molecular model may provide a synthetically useful method; however, little attention has been paid to this area.[2] Although Scott and coworkers reported in 1975 that the acetate–malonate diester of catechol is converted by base to the acetoacetate ester in 30% yield,[3] no subsequent biomimetic steps have been reported. We have recently demonstrated that sequential double acylation of glycoluril **1** gives derivatives **2**, which in turn undergo efficient condensations, resulting in β-keto compounds **3** in very good yields and with fair regioselectivity when the two acyl units are nonequivalent (Scheme 1).[4] We now report on the use of tetramethylglycoluril **1** as a template which allows *repetitive* Claisen-type condensations in a controlled manner, while the growing carbon chain remains attached to the template.

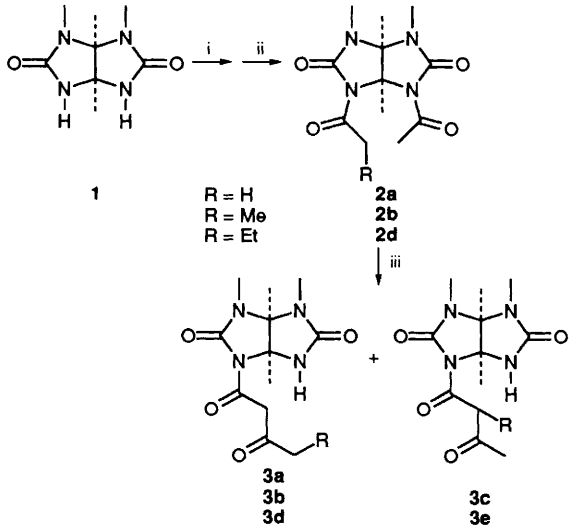
Initially, we focused our efforts on functional group transformations of **3a** analogous to the sequence of events that occurs on the fatty acid synthase: namely reduction of the ketone to the β-hydroxyacyl enzyme, elimination of water, and conjugate reduction to form the chain-extended acyl enzyme.[1] Thus, reduction of **3a** under appropriate conditions ($NaBH_4$, MeOH, then AcOH) provides **4**†[5] (Scheme 2). It was found that work-up by addition of glacial acetic acid is necessary as soon as the reduction of **3a** is complete to prevent cleavage of the side chain from the glycoluril template to produce methyl β-hydroxybutanoate. When other solvents such as THF, AcOH or EtOH were used for the reduction, compound **3a** was only partially converted, and most of the starting material was recovered. Elimination of water from **4** proceeds smoothly (TFAA, Et_3N)[6] to give **5**‡ ($E:Z$ = 98:2), which undergoes conjugate addition of hydride to give saturated butanoyl derivative **6**.

To demonstrate the feasibility of removing the synthesized acyl moiety from the template, **6** was treated with lithium benzalkoxide. Benzyl butanoate (80%) and the recovered glycoluril **1** (92%) were produced. The template may be recycled for further acylation and condensation reactions.

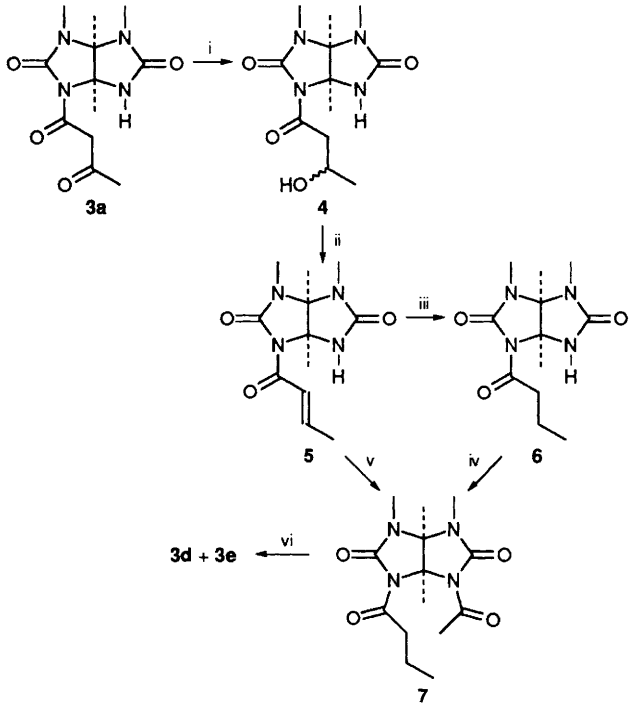
Compound **6** has previously been shown to undergo a second round of acylation to afford **7**.[4] An improved overall yield of **7** can be obtained by reduction of **5** with L-Selectride (1 equiv.) followed by quenching with acetyl chloride. Therefore, the NH proton in **5** can be transferred to the enolate of the acyl chain which is generated by hydride conjugate addition onto the double bond. Since the condensation of **7** was also previously reported to give hexanoyl derivative **3d** as the major product,[4] this process constitutes to our knowledge the first example of the biomimetic formation of a fatty-acid-like carbon chain by using a template-directed approach to repetitively add acyl units.

To test the generality of this process, we next investigated the chain extension of the crotonate derivative **5**. Acetylation of **5** gives **8** (62%). Treatment with Bu^{t}OLi affords compound **9** (60%) with a six-carbon chain (Scheme 3). Interestingly, this condensation proceeded exclusively with the regiochemistry shown. The reduction of **9** is more challenging due to its more stable enol form: **10** was obtained in 44% yield (plus 35% recovered **9**). Elimination of water from **10** is similar to that from compound **4** yielding **11** (86%), but the next round of acetylation gives **12** in only 38% yield (45% of **11** recovered). The third round of condensation gives **13** with an eight-carbon chain in 60% yield.

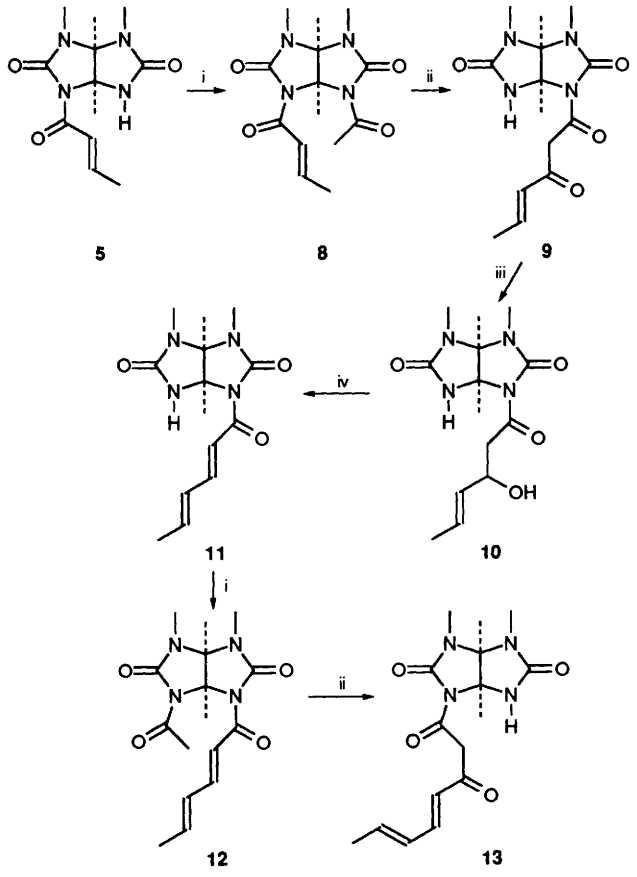
The products from efficient condensations of two acyl units bound to the bifunctional template **1** can be transformed to



Scheme 1 *Reagents and conditions*: i, Ac_2O, reflux, neat; ii, LDA, RCH_2COCl; iii, Bu^{t}OLi, then NH_4HCO_3



Scheme 2 *Reagents and conditions*: i, $NaBH_4$ (1.5 equiv.), MeOH, 0 °C, 10 min, then $MeCO_2H$ (10 equiv.), 93%; ii, TFAA, Et_3N, THF, 86%; iii, L-Selectride, THF, −78 °C to room temp., 2 h, 74%; iv, LDA, AcCl; v, L-Selectride, THF, −78 °C to room temp., 2 h, then AcCl, 63%; vi, see ref. 4



Scheme 3 *Reagents and conditions*: i, LDA, THF, 0 °C, then AcCl; ii, Bu^{t}OLi, THF, 0–25 °C, 20 min; iii, $NaBH_4$ (1.8 equiv.), MeOH, 0 °C, 10 min, then $MeCO_2H$; iv, TFAA, Et_3N, THF. See text for yields.

allow further acylation, regioselective condensation and other transformations, mimicking the head-to-tail assembly of acyl units in the biosynthesis of fatty acids and polyketide-type natural products. This approach is being used in our laboratory to make isotopically labelled compounds as precursors in biosynthetic studies, and may prove to be of use in synthesis when selective crossed-Claisen condensations could lead to useful intermediates.

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Footnotes

† Yields are unoptimized; all new compounds were analysed by ^1H and ^{13}C NMR, IR and gave satisfactory results for either elemental analysis or high resolution MS.

‡ Compound **5** can also be made directly by heating **1** with BuLi in THF for 1 h at reflux, and then adding crotonyl chloride. Material prepared in this way had $E:Z$ ratio of 94:6. All other spectroscopic data are identical.

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