Glycoluril† as an efficient molecular template for intramolecular Claisen-type condensations

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The readily prepared 3,4,7,8-tetramethylglycoluril 1 acts as a template to promote efficient intramolecular Claisen-like condensations between two acyl groups which are attached to the *N*-1 and *N*-6 positions. Thus, two sequential acylations of 1 give symmetric or unsymmetric diacylglycolurils 9–18 in good yield. Treatment of 9–18 with lithium *tert*-alkoxides furnishes *N*-(β-ketoacyl)glycolurils 19–27 under mild conditions and in high yields; rate-limiting deprotonation, predominantly on the least substituted of the two acyl groups, precedes a fast intramolecular Claisen-type condensation. Reduction of the keto group in 19 and 26, followed by elimination of water gives alk-2-enoylglycolurils 6 and 7; conjugate hydride addition (L-Selectride) then gives alkanoylglycoluril 5. Compounds 5–7 undergo further rounds of *N*-acylation then intramolecular condensation. Linear chains can thus be constructed on 1 by repetitive sequences of acylation–condensation–functional group transformation. N^1-Alk-2-enoyl-N^6-alkanoylglycolurils 14–17 also afford condensation products with high selectivity upon treatment with L-Selectride, effecting a method for net reversal of the regioselectivity observed in the base-promoted rearrangement. The synthesized chains can be readily removed from the template, regenerating 1. The efficiency of the condensation reaction, the sequence of transformations and the ability to grow linear carbon chains in a repetitive manner mimic these aspects of the catalytic cycle of fatty acid synthases and polyketide synthases.

Introduction

An array of natural products are derived *in vivo* from multiple Claisen-like 'head-to-tail' condensations of acyl units which are provided as coenzyme A thioesters.[1,2] In comparison with the highly efficient biosynthetic process occurring on the surface of the fatty acid synthases (FAS),[2,3] polyketide synthases (PKS),[2–4] and thiolases[3] which catalyze the assembly of these metabolites, the chemical synthesis of these fatty acids and polyketides poses a considerable challenge to the organic chemist. The preparation of small di-, tri- and oligo-ketides in isotopically labeled form for biosynthetic incorporation experiments has also proved demanding.[5] The desire for an efficient synthetic method for the preparation of these classes of compound led us to investigate a biomimetic approach[6] to the sequential assembly of acyl moieties.[7]

In 1975, Scott *et al*. illustrated that catechol acetate malonate undergoes intramolecular decarboxylative condensation to give acetoacetylcatechol.[8] Thus catechol provides a template effect to mimic that present in FAS and PKS, where two active site sulfhydryl groups hold the acetate and malonate units from acetyl-coenzyme A (Ac-CoA) and malonyl-CoA through covalent attachment prior to decarboxylative condensation. In both enzymes, as well as in the catechol derivative, the two acyl moieties are thus presumably oriented so that, after decarboxylation of the malonyl entity, the resulting formal acetyl enolate nucleophile is trapped by the electrophilic acetyl group to give the acetoacetyl derivative.

An analogous template-directed intramolecular Claisen-type condensation, in which two acyl groups undergo reaction, can effect the same *net* transformation as occurs *in vivo*, since the malonyl units required for the enzymic chain extension are derived directly from AcCoA by carboxylation using the biotin-dependent AcCoA carboxylase.[9] This Claisen-like approach could prove useful in synthesis if it were extended to mimic the repetitive 'head-to-tail' addition of acetyl or propanoyl units which occurs on FAS and PKS.[1–4] Thus a growing linear chain would be generated which is extended by two carbon atoms each cycle. Further, the full array of oxidation states found at C-1 of each unit within the growing chain in different metabolites should be accessible; these include β-keto groups generated in the condensation steps, as well as β-hydroxy, enoyl and saturated units which are formed by functional group manipulations on the surface of the synthases prior to addition of the next acyl unit.[1,2] Finally, the newly synthesized chain would be released from the template.

Modeling of all of the aspects of the reactions which are catalyzed by these multi-functional enzyme complexes presents a substantial challenge. We have chosen to focus on developing a bifunctional template approach to mimic some aspects of FAS and PKS, specifically: (a) the efficiency of the condensation between acyl units; (b) the ability to grow acyl chains by a repetitive sequence of acyl addition then C–C bond formation between acyl units, without the growing chain leaving the template surface; and (c) the control of regioselectivity that occurs during incorporation of alkanoates into polyketides. In addition we wished to develop chemical reactions which parallel the biochemical functional group transformations which occur within each cycle of FAS, with the aim of developing this approach as synthetically useful methodology. We have previously reported that 3,4,7,8-tetramethylglycoluril **1** provides a template effect to promote intramolecular Claisen-type condensations between two acyl units attached to the two NH sites, and that this approach can be used in an iterative manner for the synthesis of natural products.[7] Herein, we report in detail on these results, as well as on studies of the mechanism of the condensation step and a novel method for reversing the regiochemistry obtained in the crossed-Claisen approach.

Results and discussion

Preparation and acylation of 3,4,7,8-tetramethylglycoluril 1

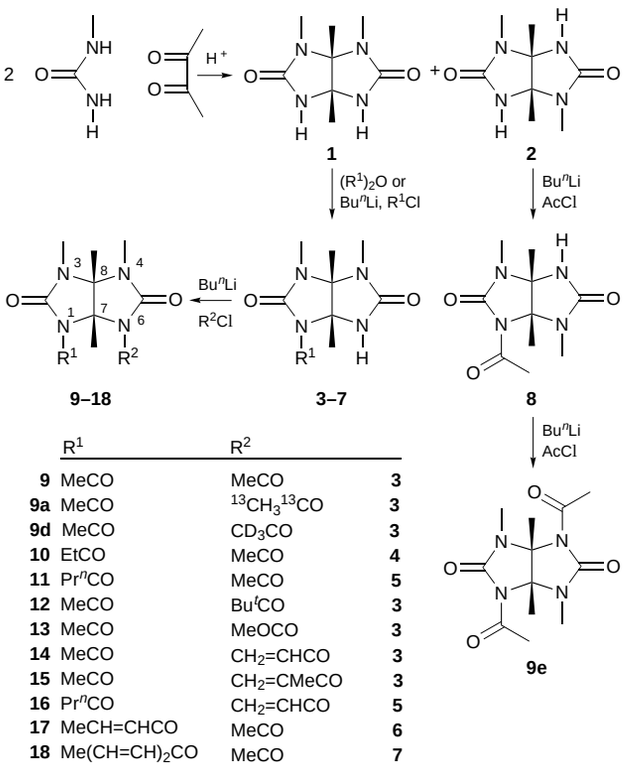
Tetramethylglycoluril **1** is readily prepared according to the

† IUPAC name: perhydroimidazo[4,5-*d*]imidazole-2,5-dione.

Table 1 Yields for the preparation of monoacylglycolurils **3**–**7** from **1**[a]

Entry	Product	R[1][b]	Method[c]	Yield (%)	Yield of by-product (%)[d]
1	**3**	MeCO	A	78	1
2	**3**	MeCO	B	89	ND[e]
3	**4**	EtCO	A	83	9
4	**5**	Pr^{n}CO	A	70	3
5	**6**	MeCH=CHCO[f]	B	68	ND[e]
6	**7**	Me(CH=CH)$_2$CO[g]	B	15	ND[e]

[a] All yields are for products after purification by column chromatography. [b] See Scheme 1. [c] See text. [d] The by-products are the symmetric diacylglycoluril in each case. [e] ND: none detected. [f] *E*. [g] *E*, *E*.



	R[1]	R[2]	
9	MeCO	MeCO	**3**
9a	MeCO	$^{13}CH_3{}^{13}CO$	**3**
9d	MeCO	CD_3CO	**3**
10	EtCO	MeCO	**4**
11	Pr^{n}CO	MeCO	**5**
12	MeCO	Bu^{t}CO	**3**
13	MeCO	MeOCO	**3**
14	MeCO	CH_2=CHCO	**3**
15	MeCO	CH_2=CMeCO	**3**
16	Pr^{n}CO	CH_2=CHCO	**5**
17	MeCH=CHCO	MeCO	**6**
18	Me(CH=CH)$_2$CO	MeCO	**7**

Scheme 1

method of Biltz (Scheme 1).[10] Thus, reaction of monomethylurea with butane-2,3-dione in ethanol in the presence of catalytic aqueous HCl affords a mixture of isomers **1** and **2**, which can be either used directly (see below), or separated by recrystallization to afford pure **1**. Compound **1** is thus available in one step from readily available starting materials, allowing preparation in hundred-gram quantities.

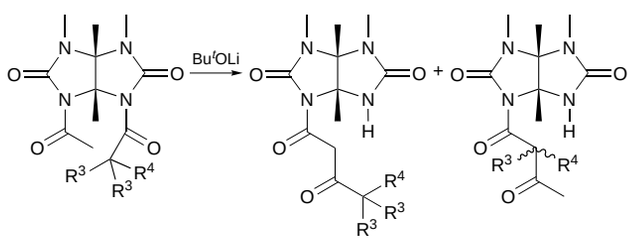
Selective monoacylation of the glycoluril **1** with a variety of acylating agents can be accomplished in one of two ways (Scheme 1). In method A, the glycoluril is heated to reflux in neat alkanoic anhydride, following the procedure of Biltz.[10] In this way, pure **1** affords the mono-acetyl, -propanoyl, and -butanoyl derivatives **3**, **4** and **5**, respectively in good yields (Table 1). Alternatively, the mixture of isomers **1** and **2** gives the desired acyl derivatives by method A, along with recovered **2**, which does not react under these conditions. Acetylglycoluril **3** was conveniently prepared on a large scale in this manner. Only small amounts of diacyl derivatives, which are readily removed by column chromatography, are formed in this method: presumably, steric hindrance by the first acyl unit reduces the rate of acylation at the second site. Method A is convenient for large-scale synthesis of the monoacyl derivatives when a large excess of the anhydride can be used.

In method B, pure **1** was treated with either Bu^{n}Li or LDA (1 equiv.) and heated at reflux; treatment of the resulting suspension with an acyl chloride then work-up gives the monoacyl derivatives. Compounds **3**, **6** and **7** were prepared in this way. This method provides a marginally better yield than method A for **3** (Table 1), and requires only a slight excess of acylating agent. Again, little or no diacyl products were obtained. Treatment of a mixture of **1** and **2** using acetyl chloride and method B gives a mixture of monoacetyl derivatives **3** and **8** which are readily separable by column chromatography. Together, these results show that monoacylation at one of the two NH groups of **1** can be easily accomplished; the method chosen for a given acyl group depends on availability of the respective activated acyl derivatives.

The monoacyl derivatives are readily converted to diacylglycolurils under more forcing conditions by treatment with base (Bu^{n}Li or LDA, 1 equiv.), followed by an acyl halide (Scheme 1). Table 2 gives the yields of the diacyl derivatives **9**–**18** prepared in this way. Thus, the glycoluril **1** lends itself to the preparation of both symmetric and asymmetric diacyl derivatives. This is an ideal situation for setting up the proposed crossed-Claisen-like condensation reaction.

Condensation reactions of diacetylglycolurils

In early experiments on this system, the diacetylglycoluril **9** was treated with LDA or Bu^{n}Li in THF. Although the desired condensation product **19** is obtained under these conditions the yields are low (Table 3 and Scheme 2). Subsequently, it was



	R[3]	R[4]		
9	H	H	**19**	**19**
9d	D	D	**19d**	**19e**
10	H	Me	**20**	**21ab**
11	H	Et	**22**	**23ab**
12	Me	Me	**24**	–

Scheme 2

shown that treatment of **9** with lithium *tert*-butoxide in THF results in superior yields. In this case, the reaction is observed by TLC to proceed to completion within 20 min at 0 °C. Work-up under non-buffered aqueous conditions, however, results in a yield that is well below quantitative. Further investigations showed that **19** undergoes decomposition during aqueous work-up; however, the use of solid ammonium hydrogen carbonate, or aqueous sodium hydrogen sulfate to quench the reaction mixture avoids this decomposition. All subsequent experiments have used one of these methods of work-up. Compound **19** can thus be prepared from **9** and is obtained in quantitative yield as an apparently pure solid by NMR after removal of solvent. In order to ensure complete purity, and the absence of lithium ion in the product (which potentially could act as a lithium ion chelant), **19** was subjected to column chromatography, giving an isolated yield of 93%.

Table 2 Yields for the preparation of diacylglycolurils from **3**–**7**[a]

Entry	Starting Material	Product	R^1[b]	R^2[b]	Yield[a] (%)
1	**3**	**9**	MeCO	MeCO	78
2	**3**	**9a**	MeCO	$^{13}CH_3{}^{13}CO$	80
3	**3**	**9d**	MeCO	CD_3CO	68
4	**4**	**10**	EtCO	MeCO	54
5	**5**	**11**	Pr^{n}CO	MeCO	61
6	**3**	**12**	MeCO	Bu^{t}CO	52
7	**3**	**13**	MeCO	MeOCO	84
8	**3**	**14**	MeCO	CH_2=CHCO	41
9	**3**	**15**	MeCO	CH_2CMeCO	36
10	**5**	**16**	Pr^{n}CO	CH_2=CHCO	36
11	**6**	**17**	MeCH=CHCO[c]	MeCO	62
12	**7**	**18**	$Me(CH=CH)_2CO$[d]	MeCO	38

[a] All yields are for products after purification by column chromatography. [b] See Scheme 1. [c] *E*. [d] *E*, *E*.

Table 3 Yields[a] and isomer ratios[b] for the condensation of diacylglycolurils **9**–**18**

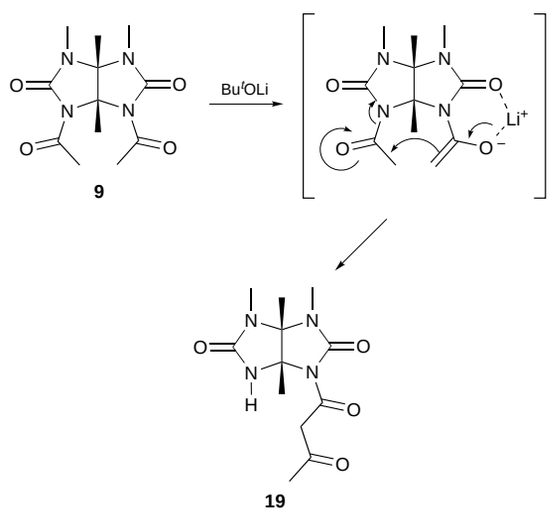
Entry	Starting material	Base	Product(s)	R^3[c]	R^4[c]	R^5[d]	Yield[a] (%)	Ratio[b]
1	**9**	LDA	**19**	H	H	—	43	—
2	**9**	Bu^{t}OLi	**19**	H	H	—	93	—
3	**9d**	Bu^{t}OLi	**19d** **19**	D	D	—	80	83:17
4	**10**	Bu^{t}OLi	**20** **21ab**	H	Me	—	81	83:17
5	**11**	Bu^{t}OLi	**22** **23ab**	H	Et	—	88	81:19
6	**11**	Bu^{t}ONa	**22** **23ab**	H	Et	—	56	60:40
7	**11**	Bu^{t}OK–18-crown-6	**22** **23ab**	H	Et	—	80	67:33
8	**11**	Bu^{t}OLi–12-crown-4	**22** **23ab**	H	Et	—	80	75:25
9	**11**	$EtC(Me)_2OLi$	**22** **23ab**	H	Et	—	80	86:14
10	**12**	Bu^{t}OLi	**24**	Me	Me	—	79	—
11	**13**	Bu^{t}OLi	**25**	—	—	OMe	82	—
12	**13**	$EtC(Me)_2OLi$	**25**	—	—	OMe	85	—
13	**13**	LiHMDS	**25**	—	—	OMe	63	—
14	**17**	Bu^{t}OLi	**26**	—	—	MeCH=CH[e]	60	—
15	**18**	Bu^{t}OLi	**27**	—	—	$Me(CH=CH)_2$[f]	60	—

[a] All yields are for products after purification by column chromatography. [b] Determined by integration of the proton NMR spectrum. [c] See Scheme 2. [d] See Scheme 5. [e] *E*. [f] *E*, *E*.

In contrast with **9**, derivative **9e** (Scheme 1), which was prepared from **8** using Bu^{n}Li then AcCl, and in which the two acetyl units are located on opposite sides of the glycoluril template, fails to give any condensation product under the reaction conditions. Instead, the acyl groups are slowly cleaved to give monoacetyl derivative **8** and ultimately recovered **2**.

Comparison of these two very different outcomes suggests that the enhanced efficiency in **9** is the result of an intramolecular condensation. Deprotonation of one acetyl group would generate an enolate which can be oriented appropriately for nucleophilic attack at the electrophilic carbonyl of the other, 'acceptor' acetyl moiety (Scheme 3).

There are, of course, numerous examples of efficient intermolecular Claisen-like condensations where an enolate is pregenerated with a strong base prior to addition of an acyl donor. However, the appropriate comparison in the current case is with addition of a weak base to a carbonyl compound followed by intermolecular condensation. Such classical Claisen condensations generally proceed much more slowly under similar conditions, usually requiring elevated temperature and longer reaction times.[11] Comparison may also be drawn with intermolecular acylations of the enolates derived from *N*-acyloxazolidones, although these enolates are usually generated with strong bases at low temperature.[12,13] Glycoluril **1** may be viewed as a bifunctional variant of these oxazolidones, where an *N*-CH_3 group replaces the ring oxygen. Another analogous



Scheme 3 Proposed mechanism for the intramolecular Claisen-like condensation of diacetylglycoluril **9** to give **19**

system is the use of catechol by Scott *et al*. as a template in the conversion of catechol acetate malonate to acetoacetylcatechol, which proceeded in 30% yield.[8] The superior yield and milder conditions for condensation of diacetylglycoluril compared

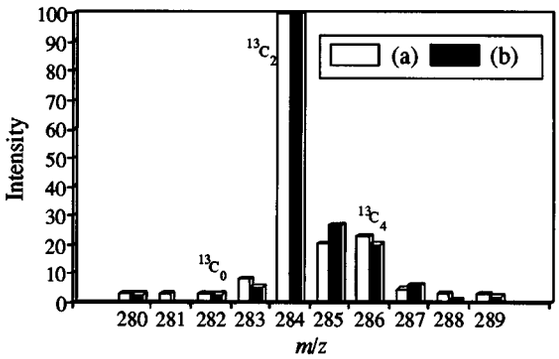


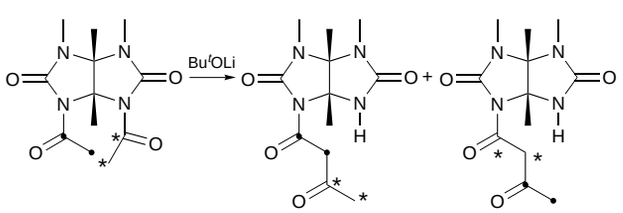
Fig. 1 Molecular ion region of the mass spectrum of (a) **9a** and (b) **19** derived from **9a**, corrected to 100%. The ratio of [$^{13}C_0$]-, [$^{13}C_2$]- and [$^{13}C_4$]-isotopomers (*m*/*z* 282, 284 and 286, respectively) remains unchanged during the reaction. The data were corrected for the relative abundance of ions in unlabeled **9** and **19** to obtain percentages of each isotopomer in the mixtures.

with the catechol case suggest that the six-membered cyclic transition state which would be formed on the glycoluril is more readily achieved than the seven-membered ring in the catechol. Alternatively, or as well, the number of available conformations of the enolate from **9**, which is probably restricted due to orbital overlap requirements,[13,14] compared to that for the catechol enolate, could explain the efficiency of the former process. However, Scott's study did not reveal which step is rate-limiting for the catechol derivative; thus, these comparisons remain tenuous. The reaction may also be assisted by the relatively high electrophilic reactivity of the acyl group of glycolurils, compared to normal amides, as has been demonstrated by Tice and Ganem.[15]

The lack of any evidence for formation of the *O*-acetyl-enol ether, which could be formed by nucleophilic attack of the oxygen of the ambident enolate on the acceptor carbonyl, also suggests that the condensation reaction proceeds through an oriented enolate. Chelation of the lithium counter-ion by the enolate and urea oxygens, a process well-documented by Evans and co-workers in the *N*-acyloxazolidone enolates,[12–14,16] could explain this result, since this effect would enforce an orientation in which intramolecular condensation could occur only by carbon attack.

With these considerations in mind, further investigations of the mechanism of this condensation reaction were undertaken. Isotopically labeled diacetylglycolurils **9a** and **9d** were prepared from **3** as described above, using [$^{13}C_2$]acetyl chloride and [$^2H_3$]acetyl chloride, respectively. For **9a**, mass spectrometry as well as proton and carbon-13 NMR revealed that the sample contained 84% of the desired [$^{13}C_2$]-isotopomer, as well as 16% of the unexpected [$^{13}C_4$]-isotopomer **9b**. However, the amount of the [$^{12}C_4$]-isotopomer **9c** was below the limits of detection [Fig. 1 (a)]. The slow exchange of acyl groups which must lead to **9b** has not been observed in any of the other acylation reactions described herein, and remains anomalous.

Treatment of the mixture of **9a** and **9b** with Bu^{t}OLi as above gives labeled **19** (Scheme 4). The mass spectrum of the resulting



Scheme 4

sample is shown in Fig. 1 (b); the results show that the product is comprised of a mixture of the two [$^{13}C_2$]-isotopomers **19a**, as well as 14% of [$^{13}C_4$]-isotopomer **19b**, but no [$^{12}C_4$]-isotopomer **19c**. The ratio of **19a**:**19b** in the product is identical within experimental error to the ratio of **9a**:**9b** in the starting material. Hence, the condensation is entirely intramolecular within the limits of detection (*ca.* 3%), since any intermolecular reaction, or indeed acyl group exchange between molecules of **9a**, would result in some [$^{12}C_4$]-product, as well as a change in distribution of [$^{13}C_2$]- and [$^{13}C_4$]-isotopomers.

Rearrangement of **9d** gives a mixture of **19** and **19d** as the sole product isotopomers within limits of detection (Scheme 2). In this case, product **19e** which results from deprotonation at the [$^2H_3$]acetyl group, exchanges the remaining two deuterons during work-up to give **19** (also see below). The ratio of **19**:**19d** was determined to be 1:4.6 by MS and by NMR spectral integration. This reaction therefore exhibits a primary kinetic isotope effect of 4.6, favoring deprotonation over deuterium loss. The distribution of isotopomers (*i.e.* only [$^2H_0$] and [$^2H_3$]) is consistent with rate-limiting deprotonation followed by efficient internal trapping of the resulting enolate, which out-competes enolate proton exchange by either intermolecular or intramolecular pathways. This exchange can occur in this experiment since the *tert*-butoxide was generated from Bu^{n}Li and *excess tert*-butyl alcohol.

Crossed-Claisen condensations

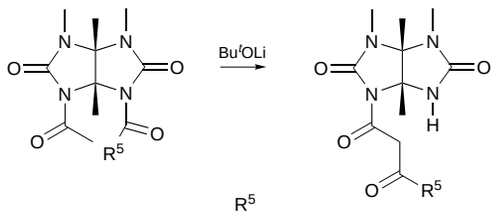
Treatment of the asymmetric acetyl propanoyl and acetyl butanoyl glycolurils **10** and **11** with Bu^{t}OLi under similar conditions efficiently affords mixtures of the regioisomeric condensation products **20/21** and **22/23** respectively (Scheme 2). The yield and ratio of products, determined by NMR, is given for each case in Table 3. None of the putative products from condensation between two acetyl, or between two alkanoyl moieties was observed in any of these reactions, again showing the reaction to be entirely intramolecular within the limits of detection. There was no evidence for formation of *O*-acyl enol ethers. Therefore the condensation process is of general utility; however the yields fall somewhat as the size of either of the acyl units increases, probably reflecting increased difficulty for approach of the base. Of the two possible regioisomers, the major results from enolate formation on the less hindered acyl group, consistent with the rate-limiting step involving deprotonation as is the case for **9**. In both these cases, the minor regioisomer is produced as a mixture of two diastereomers **21ab** and **23ab**, which were distinguishable in the proton NMR spectrum. One diastereomer was observed to be major; however, the ratios were not determined accurately due to the small amounts present in the mixture (see below for further discussion). While the formation of the minor regioisomer reduces the yield of this reaction from a synthetic standpoint, the results compare favorably with the mixture of four regioisomers expected for an intermolecular crossed-Claisen condensation.

For the acetyl butanoyl derivative **11**, the presence of complexing agents such as a crown ether, or the use of sodium or potassium as counter-ion, had relatively little influence on either the yield or the ratio of products (Table 3). From the mechanistic standpoint, these marginal effects reveal little. The somewhat enhanced yield for lithium as opposed to sodium or potassium bases is suggestive of some role for the counter-ion in the reaction. Whether this effect involves chelation (see above) remains an open question. However, a significant and consistent improvement was observed by using the more hindered base, lithium 1,1-dimethylpropoxide: the ratio of regioisomers **22**:**23** was increased to 6:1 in this case.

Acetyl pivaloyl derivative **12** gives the expected **24** as sole product; however, a reaction time of 5 h was required. Thus bulky substituents do not prevent the condensation process. It is unclear whether the reduced rate in this case reflects increased

steric hindrance for approach of the base, or involvement of the pivaloyl group in the rate-limiting step.

In order to test the feasibility of using glycoluril **1** to promote decarboxylative condensation, hence more closely resembling the process in FAS and PKS, a malonate derivative of **1** was prepared. Since direct reaction of **1** with malonyl chlorides failed to provide any identifiable products, an indirect approach was used. The glycoluril **13**, bearing a methoxycarbonyl- and an acetyl-group readily undergoes deprotonation by Bu′OLi followed by transfer of the methoxycarbonyl group to give malonate derivative **25** (Scheme 5). The influence of reaction



	R^5	
13	OMe	**25**
17	MeCH=CH	**26**
18	$Me(CH=CH)_2$	**27**

Scheme 5

conditions was also investigated for this conversion; the results are given in Table 3. Again, there was little effect on the reaction as a result of additives or changing counter-ion. This intramolecular condensation is reminiscent of the reaction of bound acetyl-CoA with carboxybiotin in the active site of acetyl-CoA carboxylase,[9] and provides an interesting model of this process. Indeed, glycoluril has been compared with biotin; both molecules have similar ureido rings.[17] *N*-Acylation of these malonyl derivatives is currently being investigated.

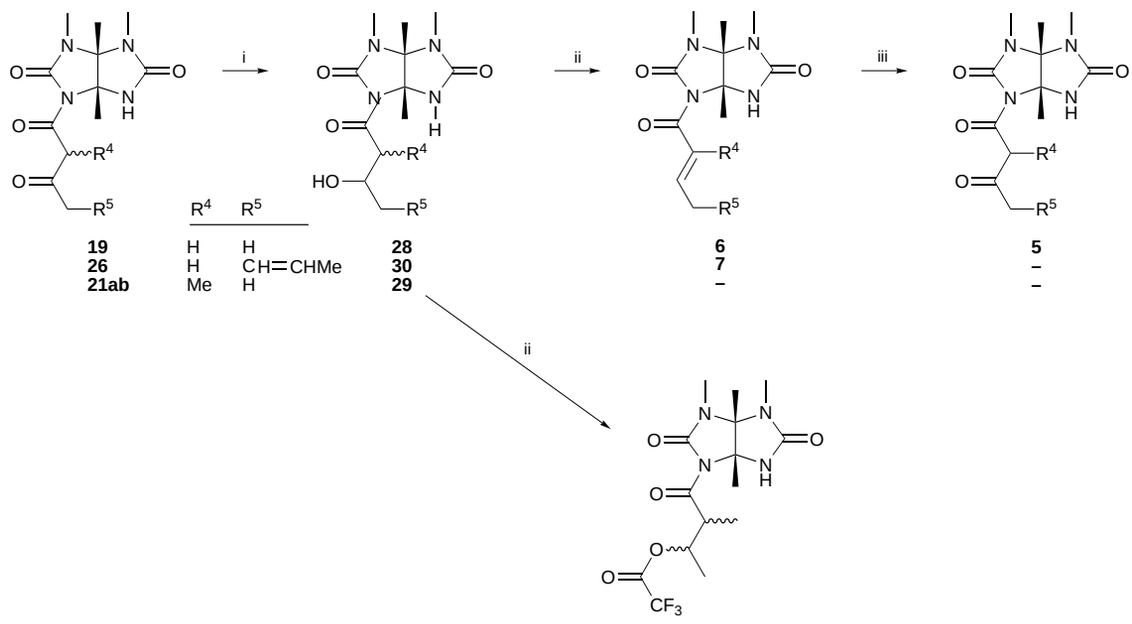
Compounds **17** and **18** containing α,β-unsaturated acyl groups were treated with Bu′OLi to test their capability to undergo intramolecular Claisen condensations. Compounds **26** and **27** were the sole products, resulting from deprotonation at the saturated acyl group to give the products of linear chain growth. The potential product derived from deprotonation at the γ-position of the α,β-unsaturated moiety, followed by nucleophilic attack on the acetyl group, was not detected. Nor was there any conjugate addition of the acetyl enolate to the α,β-unsaturated moiety, a process which occurs readily in corresponding oxazolidone cases.[18] Thus, this system should be of use for effecting selective 1,2-additions of enolates to unsaturated acyl moieties.

Taken together, the above results demonstrate a highly efficient process in which two acyl groups attached to the glycoluril template **1** undergo rate-limiting deprotonation by weak bases, followed by a facile intramolecular Claisen-like condensation which out-competes the many potential side-reactions, resulting in high product yield. Deprotonation occurs at the smaller, least hindered acyl group, while a range of acyl groups including alkanoyl, alk-2-enoyl and methoxycarbonyl can act as the electrophilic moiety.

Functional group manipulations on β-ketoacylglycolurils

In order to achieve a chemical reaction sequence that parallels the events that occur on FAS, namely the net reduction of the β-carbonyl group to methylene, the following manipulations were carried out. Treatment of the β-ketoalkanoyl derivatives **19**, **21ab** and **26** with sodium borohydride in methanol furnishes β-hydroxyalkanoyl derivatives **28** (93%), **29** (77%) and **30** (44% plus 51% recovered **26**), respectively (Scheme 6).[19] It was found that work-up with glacial acetic acid immediately after completion of the reaction was necessary, otherwise loss of acyl groups occurred: methyl β-hydroxybutanoate was formed from **19**. For **28** and **30**, ^{1}H and ^{13}C NMR showed a *ca.* 1:1 ratio of two diastereomers, while **29** is comprised of all four possible diastereomers in approximately equal proportions. Due to extensive overlap of resonances, accurate ratios were not determined. Thus little diastereoselectivity is observed in these reductions. Stereoselective reductions are under active investigation; however, sodium borohydride remains the most effective agent to date in terms of yield. The issue of stereoselectivity in this reduction is of course moot when the products are to be dehydrated as described below.

Elimination of water from the β-hydroxyalkanoyl derivatives **28** and **30** yields the alk-2-enoyl derivatives **6** (83%) and **7** (86%) respectively (Scheme 6). A variety of conditions were investigated for this reaction. In the event, use of TFAA and Et_3N proved to give the best yields.[20] For **6**, the *E*:*Z* ratio was 98:2 (by ^{1}H NMR spectroscopy), while for **7**, the *E*,*E* isomer was the only product observed. In each case, the products had spectroscopic properties that were identical to material prepared directly from **1** and the appropriate acylating agent, except that **6** prepared in the latter manner had an *E*:*Z* ratio of 93:7. The



	R^4	R^5			
19	H	H	**28**	**6**	**5**
26	H	CH=CHMe	**30**	**7**	–
21ab	Me	H	**29**	–	–

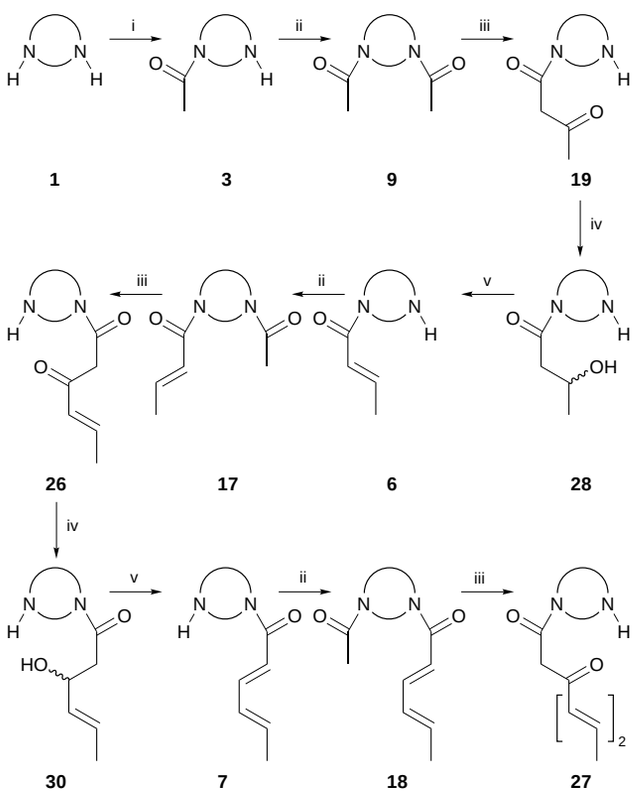
31

Scheme 6 *Reagents and conditions*: i, $NaBH_4$, MeOH, 10 min, then AcOH; ii, TFAA, Et_3N, CH_2Cl_2, 20 min; iii, L-Selectride, THF, −78 to 0 °C, 2 h, NH_4HCO_3

same conditions on **29** give only the trifluoromethyl ester **31**. This observation suggests that in this case **31** cannot attain a suitable conformation for elimination; this is in accord with observations on *N*-(α-alkyl-β-ketoacyl)oxazolidones, which show low acidity at the α-position,[12–14] as well as results with (α-alkyl-β-ketoacyl)glycolurils (see below).

A variety of reducing agents was investigated for effecting conjugate addition of hydride to the alk-2-enoyl derivatives. In our hands, use of L-Selectride in THF proved most satisfactory; under these conditions, followed by quenching with NH_4HCO_3, **6** furnished the saturated compound **5** (74%) (Scheme 6). The product had spectroscopic properties that were identical to **5** prepared directly from **1** and butanoic anhydride. Alternatively, the crude mixture from the L-Selectride reduction was quenched with acetyl chloride prior to work-up, resulting in **11** directly without the requirement for isolation of **5**. This process is useful in reducing the number of steps to be performed when a series of condensation–functional group manipulation–acylation sequences are to be strung together (see below).

The results demonstrate that transformations equivalent to each of the steps in the FAS cycle can be effected on the glycoluril. Since **5**, **6** and **7** can undergo further acetylation then condensation (see above), these processes constitute the first examples to our knowledge of growth of a linear fatty acid chain by a repetitive biomimetic sequence while the growing chain remains attached to the template.[7] Scheme 7 illustrates an



Scheme 7 *Reagents and conditions*: i, Ac_2O, neat, reflux, 20 h; ii, Bu^{n}Li, THF, 1 h, then AcCl; iii, Bu^{t}OLi, THF, 0 °C, 20 min; iv, $NaBH_4$, MeOH, 10 min, then AcOH; v, TFAA, Et_3N, CH_2Cl_2, 20 min. The stylised circle represents the glycoluril template.

example in which an eight-carbon polyketide chain containing C=C bonds is assembled from four acetate units, using reactions described above. The creation of chains adorned with hydroxy groups and poly-β-keto acids using this methodology is currently under investigation.

Cleavage of acyl groups from the glycoluril template

Treatment of butanoyl derivative **5** with lithium benzalkoxide (C_6H_5-CH_2OLi) in THF, using the method developed by Evans and co-workers for *N*-acyloxazolidones,[14,16] gives benzyl butanoate (83%) and recovered **1** (92%). The corresponding reaction with but-2-enoyl derivative **6** gives recovered **1** (86%) and benzyl but-2-enoate (55%). The reaction regenerates the glycoluril in high yield, ready for recycling. Reasonable to good yields of the benzyl esters are obtained. As well, the observation of formation of methyl β-hydroxybutanoate from **19** when treatment with $NaBH_4$ is not followed by quenching with AcOH shows that methoxide can also be used as a nucleophile to cleave β-hydroxyacyl chains. These methods allow completion of the glycoluril 'cycle,' and mimic the role of thioesterases which cleave fatty acyl and in some cases polyketide chains from the FAS/PKS surface to regenerate the free enzyme.[1,2]

Table 4 Yields[a] and isomer ratios[b] for the L-Selectride-induced condensation of *N*-(alk-2′-enoyl)-*N*′-acylglycolurils **14**–**17**

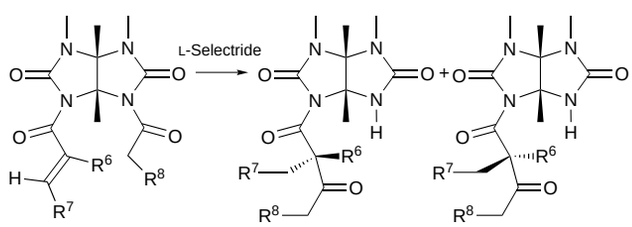
Entry	Starting material	Product	R^6[c]	R^7[c]	R^8[c]	Yield[a] (%)	Ratio[b]
1	**14**	**21ab**	H	H	H	60	2.1:1
2	**15**	**32**	Me	H	H	68	—
3	**16**	**33ab**	H	H	Et	66	2.2:1
4	**17**	**23ab**	H	Me	H	52	1.5:1

[a] All yields are for products after purification by column chromatography. [b] Determined by integration of the proton NMR spectrum. [c] See Scheme 8.

Hydride addition to alkenoyl-alkanoylglycolurils and reversal of regiochemistry

While the above reactions present many facets for continued development, which are currently being investigated further, we initially focussed on the question of regiochemistry in the condensation reaction. Thus, while condensation reactions of diacylglycolurils proceed with high efficiency and moderate regioselectivity favoring deprotonation at the less hindered of the two possible α-positions, we wished to develop a process in which reversal of the regiochemical outcome was obtained, resulting in the nett equivalent of deprotonation at the more hindered acyl moiety.

Reaction of the *N*-alk-2-enoyl *N*′-alkanoylglycolurils **14**, **15**, **16** and **17** with L-Selectride in THF gives **21ab**, **32**, **33ab** and **23ab**, respectively (Scheme 8). Yields and diastereomer ratios



	R^6	R^7	R^8		
14	H	H	H	**21a**	**21b**
15	Me	H	H	**32**	**32**
16	H	H	Et	**33a**	**33b**
17	H	Me	H	**23a**	**23b**

Scheme 8

are given in Table 4. For **14** and **17**, minor side-products which were separated and characterized include the saturated compounds **10** (3%) and **11** (19%), respectively, as well as **3** (6% and 9%, respectively) from loss of one acyl group. The major products are consistent with the conjugate addition of hydride to the alk-2-enoyl group, generating enolates as intermediates. The enolates then undergo nucleophilic attack on the alkanoyl moiety. These enolates correspond to deprotonation at the more hindered of two acyl groups, a process which is difficult to achieve by other methods. Compound **15** gives the enolate of 2-methylpropanoylglycoluril. The corresponding *N*-(2-methylpropanoyl)oxazolidone failed to undergo deprotonation even under forcing conditions.[14] No products derived from intra- or

inter-molecular proton transfer from the more acidic alkanoyl group to the presumed transient enolate followed by condensation were detected in any of the cases investigated, providing further evidence of the efficiency with which the carbon–carbon bond forming step takes place. Since neither proton transfer process occurs, it is likely that the small amounts of **10** and **11** observed as products are formed during work-up, where residual reducing agent remains and the medium provides an efficient proton trap for the enolates.

For **21ab**, **33ab** and **23ab**, the mixtures of diastereomeric α-epimers are separable by flash chromatography. While treatment of **19** with D_2O results in slow exchange of the hydrogens at C-2 of the acyl chain, the mixture **21ab** fails to undergo H–D exchange during 2 weeks under these conditions. The observed low kinetic acidity in these H–D exchange experiments resembles that for (α-alkyl-β-ketoalkanoyl)oxazolidone derivatives which was reported by Evans and co-workers,[12–14] again emphasizing the similarities between the two systems. However, the pure diastereomers, **21a** and **21b**, and **23a** and **23b**, were converted upon treatment with Bu^{t}OK to a mixture with the same composition as for the products from the condensation reactions. This result suggests that the immediate product in the condensation reaction is the enolate of the β-ketoacyl group. The observed diastereomer ratio in the latter reaction is thus controlled by the enolate reprotonation step. Hence, any diastereoselectivity in the actual condensation step is masked.

In conclusion, the glycoluril template **1** provides a framework onto which two different acyl groups can be attached. Generation of an enolate at one acyl site allows efficient intramolecular Claisen-type condensation onto the other, mimicking the proposed process in FAS and PKS. The enolates may be generated directly by deprotonation, in which case asymmetrically substituted diacylglycolurils give predominantly the product from deprotonation at the least hindered position; alternatively, an indirect method of enolate generation by addition of hydride to α,β-unsaturated acyl groups can be used to effect net regiochemical reversal of the process. The resulting β-ketoacylglycolurils can be chemically modified in steps which parallel those in FAS and PKS to give *N*-alk-2-enoyl- and *N*-alkanoyl-glycolurils. As in FAS and PKS, these compounds can undergo further rounds of acylation, condensation and functional group manipulation to give extended carbon chains without the growing chain leaving the enzyme or template surface. The synthetic application of this methodology to products which can be derived from such a crossed-Claisen approach, as well as other aspects of this interesting system, are currently the subject of further investigations.

Experimental

General

All reactions were performed in flame-dried glassware, under a positive pressure of nitrogen, unless otherwise noted. Air- and moisture-sensitive compounds were transferred by syringe. Concentration of organic solutions was performed on the rotary evaporator (*ca*. 25 Torr), followed by evacuation to constant weight (<0.05 Torr). Flash column chromatography was performed on Kieselgel 60 (230–400 mesh ASTM) according to the method of Still *et al*.[21] THF was freshly distilled under nitrogen protection from potassium–benzophenone, diisopropylamine from calcium hydride and *tert*-butyl alcohol from sodium. *n*-Butyllithium (Bu^{n}Li) was titrated using 2,5-dimethoxybenzyl alcohol in THF.[22] All other reagents were used as purchased except where indicated.

Melting points are uncorrected. Proton and carbon-13 nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC 200, Bruker AC 300 or Bruker AC 500 NMR spectrometers. Proton chemical shifts (δ scale) refer to $SiMe_4$ and those of ^{13}C to $CDCl_3$. Data are given as chemical shift [integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (*J* in Hz), assignment]. Fourier transform (FT) infrared spectra were recorded on a Bio-Rad SPC 3200 spectrophotometer. Ultraviolet spectra were obtained on a Perkin-Elmer Lambda 9 UV–VIS–NIR spectrophotometer. Mass spectra were recorded on a VG analytical ZAB-E mass spectrometer using electron impact (EI). High resolution mass spectra were also recorded on the same spectrometer. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada.

3,4,7,8-Tetramethylglycoluril 1[10]

To a stirred suspension of monomethylurea (7.6 g, 103 mmol) in absolute ethanol (120 ml) was added concentrated hydrochloric acid (4 drops) and freshly distilled butane-2,3-dione (4.5 ml, 4.5 g, 52 mmol). The solution clarified as the exothermic reaction proceeded. Product appeared as a precipitate after *ca*. 15 min. The mixture was stirred for a further 30 min, then cooled to 0 °C for 1 h. The solid product was collected by vacuum filtration, washed with cooled ethanol (2 × 5 ml) then exhaustively with dichloromethane and dried to give 5.2 g (51%) of a 1:1 mixture of **1** and **2**. The crude product was recrystallized twice from ethanol (60 ml ethanol per 1 g solid). Compound **1** (2.1 g, 21%) was obtained as colorless crystals; mp >300 °C (lit.,[10] >300 °C); ν_{max}(FT, KBr pellet)/cm^{-1} 3282 (NH), 2920 (C–H), 1683 (C=O), 1506, 1441, 1414, 1389, 1263, 1230, 1120, 1087, 1003, 963, 768, 721; δ_H(200 MHz, CD_3OD) 2.77 (6H, s, NCH_3), 1.48 (3H, s, CH_3), 1.39 (3H, s, CH_3); δ_C(50 MHz, CD_3OD) 161.0 (*C*=O), 83.1 (*C*NN), 74.7 (*C*NN), 26.8 (N*C*H$_3$), 22.1 (*C*H$_3$), 15.9 (*C*H$_3$); *m*/*z* (EI) 198.1121 (M$^+$. $C_8H_{14}N_4O_2$ requires 198.1117), 183, 140, 126, 125, 111, 85, 65 (base).

1,4,7,8-Tetramethylglycoluril 2

A mixture of **1** and **2** (2.0 g, 1:1) was heated at reflux with acetic anhydride (20 ml) for 20 h. After cooling to room temperature, the solid material was collected and washed with $CHCl_3$, THF and cold ethanol, to give **2** (810 mg, 81% based on the amount of **2** present in the starting material); δ_H(200 MHz, CD_3OD) 2.61 (6H, s, NCH_3), 1.40 (6H, s, CH_3); *m*/*z* (EI) 198.1111 (M$^+$. $C_8H_{14}N_4O_2$ requires 198.1117).

General procedures for monoacylglycolurils 3–7

Method A. A mixture of **1** and the carboxylic anhydride (10 ml per g **1**) was heated at reflux for 20 h, at which point the starting material had completely dissolved. Most of the remaining anhydride was removed on the rotary evaporator. The residue was cooled and chloroform (10 ml per g **1**) was added. The mixture was filtered and the filtrate was concentrated. To the residue in a minimum amount of $CHCl_3$ was added ethyl acetate (10 ml per g **1**) and the mixture was cooled to 4 °C overnight. The crystals were collected, washed with diethyl ether and recrystallized or purified by flash chromatography.

Method B. To a stirred suspension of finely powdered glycoluril **1** in dry THF (200 ml per g **1**) at room temperature was added Bu^{n}Li (1.1 equiv.). The mixture was heated at reflux for 2 h. After cooling to room temperature, 1.5 equiv. of the acyl chloride was added. The resulting clear solution was heated at reflux for 30 min, cooled and filtered. The filtrate was concentrated to give crude product. Recrystallization or flash chromatography gave the pure products.

1-Acetyl-3,4,7,8-tetramethylglycoluril 3.[10] Glycoluril **1** (2 g, 10 mmol) was heated with acetic anhydride (20 ml) to give **3** (1.89 g, 78%) by method A. Glycoluril **1** (2 g, 10 mmol) in THF (200 ml) was treated with Bu^{n}Li (1.6 M, 7.0 ml, 11 mmol) then acetyl chloride (1.07 ml, 1.18 g, 15 mmol) according to method B to give **3** (2.15 g, 89%) as a white solid after recrystallization ($CHCl_3$–EtOAc); mp 178–180 °C (Found: C, 50.27; H, 6.85; N, 23.16. $C_{10}H_{16}N_4O_3$ requires C, 49.99; H, 6.71; N, 23.32%); ν_{max}(FT, KBr pellet)/cm^{-1} 3250 (NH), 2980 (CH), 2940 (CH), 1723 (C=O), 1689 (C=O), 1487, 1416, 1326, 1117, 943; δ_H(200

MHz, $CDCl_3$) 6.00 (1H, br s, NH), 3.02 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 2.48 (3H, s, $COCH_3$), 1.69 (3H, s, CH_3), 1.56 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 171.0 (MeC=O), 157.2 (NNC=O), 153.0 (NNC=O), 78.5 (CNN), 76.4 (CNN), 27.0, 26.3, 24.8, 19.5, 15.6; *m/z* (EI) 240.1231 (M^+. $C_{10}H_{16}N_4O_3$ requires 240.1222), 225, 210, 198, 183, 168, 156, 140, 125 (base).

1-Propanoyl-3,4,7,8-tetramethylglycoluril 4. Compound **1** (2 g, 10 mmol) was heated with propanoic anhydride (20 ml) according to method A. Purification by flash column chromatography (2% MeOH in $CHCl_3$) gave **4** (2.14 g, 83%) as a white solid; mp (from $CHCl_3$) 160–162 °C; ν_{max}(FT, KBr pellet)/cm^{-1} 3265 (NH), 3108, 3000, 2942, 1730 (C=O), 1718 (C=O), 1685 (C=O), 1461, 1411; δ_H(200 MHz, $CDCl_3$) 6.29 (1H, s, NH), 3.01 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 3.00–2.74 (2H, m, CH_2), 1.70 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.11 (3H, t, *J* 7.3, CH_3CH_2); δ_C(50 MHz, $CDCl_3$) 174.5, 157.0, 152.7, 78.4, 77.2, 29.6, 26.7, 26.1, 19.3, 15.4, 7.9; *m/z* 254.1370 (M^+. $C_{11}H_{18}N_4O_3$ requires 254.1379), 197, 180, 168, 156, 140, 125 (base).

1-Butanoyl-3,4,7,8-tetramethylglycoluril 5. Glycoluril **1** (2.6 g, 13 mmol) was heated with butanoic anhydride (20 ml) according to method A. Purification by flash column chromatography (2% MeOH in $CHCl_3$) gave **5** (2.48 g, 70%) as a white solid; mp (from $CHCl_3$) 125–126 °C (Found: C, 53.63; H, 7.22; N, 20.64. $C_{12}H_{20}N_4O_3$ requires C, 53.71; H, 7.51; N, 20.88%); ν_{max}(FT, KBr pellet)/cm^{-1} 3252 (NH), 2998, 2956, 2875, 1710 (C=O), 1689 (C=O), 1458, 1408; δ_H(200 MHz, $CDCl_3$) 6.01 (1H, s, NH), 3.01 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 2.96–2.75 (2H, m, CH_2CO), 1.68 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.70–1.50 (2H, m, CH_2CH_3), 0.96 (3H, t, *J* 7.4, CH_3CH_2); δ_C(50 MHz, $CDCl_3$) 174.1, 157.2, 153.0, 78.6, 76.5, 38.2, 27.1, 26.4, 19.6, 17.7, 15.7, 13.6; *m/z* (EI) 268.1526 (M^+. $C_{12}H_{20}N_4O_3$ requires 268.1535), 253, 240, 211, 199, 183, 168, 156, 141, 125 (base).

1-(But-2-enoyl)-3,4,7,8-tetramethylglycoluril 6 from 1. Glycoluril **1** (2.50 g, 12.6 mmol) in THF (100 ml) was treated with Bu″Li (1.8 M, 7 ml, 12.6 mmol) then but-2-enoic anhydride (3 ml, 3.1 g, 20 mmol) according to method B to give **6** (2.3 g, 68%) as a white solid after purification by flash column chromatography (2% MeOH in $CHCl_3$); mp 163–165 °C (Found: C, 53.92; H, 6.78; N, 20.79. $C_{12}H_{18}N_4O_3$ requires C, 54.12; H, 6.81; N, 21.04%); λ_{max}(CH_3OH)/nm 229 (ε/dm^3 mol^{-1} cm^{-1} 12 000); ν_{max}(FT, KBr pellet)/cm^{-1} 3310 (NH), 2990, 1722 (C=O), 1667 (C=O), 1627; δ_H(200 MHz, $CDCl_3$) 7.27 (1H, dq, *J* 15.2, 1.4, CH=CHMe), 7.08 (1H, dq, *J* 15.2, 6.4, MeCH=CH), 6.13 (1H, s, NH), 3.02 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 1.93 (3H, dd, *J* 6.5, 1.3, $CH=CHCH_3$), 1.71 (3H, s, CH_3), 1.57 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 165.2, 157.1, 152.6, 144.8, 123.0, 78.2, 76.2, 26.7, 26.0, 19.3, 18.0, 15.3; *m/z* (EI) 266 (M^+, base), 251, 192, 168, 142, 125.

1-(Hexa-2,4-dienoyl)-3,4,7,8-tetramethylglycoluril 7 from 1. Glycoluril **1** (2.0 g, 10 mmol) in THF (120 ml) was treated with Bu″Li (1.6 M, 7.9 ml, 11 mmol) then hexa-2,4-dienoyl chloride[23] (1.45 g, 11.1 mmol) according to method B to give **7** (320 mg, 15%) after purification by flash column chromatography (2% MeOH in $CHCl_3$) as a white solid (Found: C, 57.41; H, 6.98; N, 18.81. $C_{14}H_{20}N_4O_3$ requires C, 57.52; H, 6.90; N, 19.16%); λ_{max}(CH_3OH)/nm 319 (ε/dm^3 mol^{-1} cm^{-1} 26 000); ν_{max}(FT, KBr pellet)/cm^{-1} 3289, 3089, 2915, 1731, 1712, 1668, 1597; δ_H(200 MHz, CD_2Cl_2) 7.37 (1H, dd, *J* 15.3, 9.4, CH=CHCO), 7.23 (1H, d, *J* 15.3, CH=CHCO), 6.39–6.12 (2H, m, CH=CH), 2.99 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 1.86 (3H, d, *J* 5.6, CH_3CH=CH), 1.68 (3H, s, CH_3), 1.54 (3H, s, CH_3); δ_C(50 MHz, CD_2Cl_2) 166.4, 157.6, 153.3, 145.5, 140.4, 130.8, 120.4, 78.9, 77.1, 27.3, 26.5, 20.0, 18.9, 15.9; *m/z* (EI) 292 (M^+), 218, 168, 125 (base).

1-Acetyl-3,6,7,8-tetramethylglycoluril 8. Glycoluril **2** (510 mg, 2.57 mmol) in THF was treated with Bu″Li then acetyl chloride according to method B. Purification by flash column chromatography (1% MeOH in $CHCl_3$) gave **8** (310 mg, 50%) as a white solid; δ_H(200 MHz, $CDCl_3$) 6.19 (1H, s, NH), 2.98 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 2.51 (3H, s, $COCH_3$), 1.84 (3H, s, CH_3), 1.51 (3H, s, CH_3).

General procedure for preparation of diacylglycolurils 9–18

Either Bu″Li in hexane or freshly prepared LDA in THF (1 equiv.) was added to a stirred solution of the monoacylglycoluril **3**–**7** in THF (80 ml per g starting material) at 0 °C. After stirring for 30 min, the acyl chloride (1.2–1.5 equiv.) was added. After stirring for 1 h at room temperature, the resulting solution was concentrated to remove most of the THF. Chloroform (30 ml g^{-1}) was added to the residue, and the mixture was stirred, cooled and filtered. The filtrate was concentrated and separated by flash column chromatography (1% MeOH in $CHCl_3$) to give the pure diacylglycoluril and recovered starting material.

1,6-Diacetyl-3,4,7,8-tetramethylglycoluril 9. 1-Acetyl-3,4,7,8-tetramethylglycoluril **3** (910 mg, 3.79 mmol) was treated with Bu″Li (1.6 M, 2.5 ml, 4 mmol) followed by AcCl (0.4 ml, 5.6 mmol) to give recovered **3** (17%) and **9** (834 mg, 78%) as a white solid; mp 194–196 °C; ν_{max}(FT, KBr pellet)/cm^{-1} 2975, 2920, 1705 (C=O), 1688 (C=O), 1399, 1358, 1314, 1248, 1082, 1035, 994, 930, 869, 744, 696; δ_H(200 MHz, $CDCl_3$) 2.97 (6H, s, 2 NCH_3), 2.48 (6H, s, 2 $COCH_3$), 1.95 (3H, s, CH_3), 1.51 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 170.5 (MeC=O), 153.1 (NNC=O), 80.4 (NNC), 77.3 (NNC), 26.7, 26.0, 19.0, 14.5; *m/z* (EI) 282.1336 (M^+. $C_{12}H_{18}N_4O_4$ requires 282.1328), 240, 225, 210, 198, 183, 168, 156, 141, 125 (base).

1-([$^{13}C_2$]Acetyl)-6-acetyl-3,4,7,8-tetramethylglycoluril 9a. Compound **3** (1.53 g, 6.38 mmol) was treated with Bu″Li (1.49 M, 4.3 ml, 6.40 mmol) and then [$^{13}C_2$]acetyl chloride (0.6 g, 7.45 mmol) to give **9a** with some **9b** (1.44 g, 80%); δ_H(200 MHz, $CDCl_3$) 2.99 (6H, s, 2 NCH_3), 2.47 (6H, s and dd, *J* 130, 6.8; integration ratio of s:dd = 1:1.25, $COCH_3$ and $^{13}CO^{13}CH_3$), 1.95 (3H, s, CH_3), 1.55 (3H, s, CH_3); δ_C(200 MHz, $CDCl_3$) 170.0 (enhanced d, *J* 52.4, ^{13}C=O), 152.7, 80.0, 77.5, 25.7 (enhanced d, *J* 52.2), 18.6, 14.1; *m/z* (EI) 286 (3.2, [$^{13}C_4$]M^+ **9b**), 285 (4), 284.1385 (10.4, [$^{13}C_2$]M^+ **9a**. $C_{10}{}^{13}C_2H_{18}N_4O_4$ requires 284.1396), 242 (20.2), 240 (14.5), 198 (12.8), 168 (20), 156 (31.2), 141 (48), 125 (100).

1-([$^2H_3$]Acetyl)-6-acetyl-3,4,7,8-tetramethylglycoluril 9d. Compound **3** (1.18 g, 4.92 mmol) was treated with Bu″Li (1.6 M, 3.0 ml, 4.8 mmol) and then [$^2H_3$]acetyl chloride (0.35 ml, 4.72 mmol) to produce **9d** (0.948 g, 68%); δ_H(200 MHz, $CDCl_3$) identical to **9**, except δ 2.48 (3H, s, $COCH_3$); δ_D(77 MHz, $CHCl_3$, reference $CDCl_3$ δ 7.248) 2.43 (s); *m/z* 285.1515 (M^+. $C_{12}H_{15}D_3N_4O_4$ requires 285.1513), 267, 241, 213, 168, 156, 140, 125, 83 (base).

1-Propanoyl-6-acetyl-3,4,7,8-tetramethylglycoluril 10. 1-Propanoyl-3,4,7,8-tetramethylglycoluril **4** (2.52 g, 9.92 mmol) was treated with Bu″Li (1.3 M, 8.0 ml, 10.4 mmol) and then acetyl chloride (0.75 ml, 15.5 mmol) to produce recovered **4** (19%) and **10** (1.59 g, 54%); mp 180–182 °C (Found: C, 52.83; H, 6.60; N, 19.26. $C_{13}H_{20}N_4O_4$ requires C, 52.96; H, 6.80; N, 18.91%); ν_{max}(FT, KBr pellet)/cm^{-1} 2975, 2942, 1758 (C=O), 1722 (C=O), 1445, 1411; δ_H(200 MHz, $CDCl_3$) 3.08–2.70 (2H, m, CH_2), 2.99 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 2.47 (3H, s, CH_3), 1.95 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.13 (3H, t, *J* 7.3, CH_2CH_3); δ_C(50 MHz, $CDCl_3$) 174.1, 170.1, 152.8 (2 C=O), 80.2, 77.6, 30.8, 26.4 (2 CH_3–N), 25.8, 18.8, 14.2, 8.2; *m/z* (EI) 296.1497 (M^+. $C_{13}H_{20}N_4O_4$ requires 296.1484), 254, 241, 225, 199, 183, 168, 156, 141, 125 (base).

1-Butanoyl-6-acetyl-3,4,7,8-tetramethylglycoluril 11. 1-Butanoyl-3,4,7,8-tetramethylglycoluril **5** (1.20 g, 4.48 mmol) was treated with Bu″Li (2.8 ml, 4.48 mmol) and then acetyl chloride (0.5 ml, 7.6 mmol) to produce **12** (0.85 g, 61%) (with 20% recovered **9**); mp 130–132 °C (Found: C, 54.05; H, 7.07; N, 17.81. $C_{14}H_{22}N_4O_4$ requires C, 54.18; H, 7.15; N, 18.06%); ν_{max}(FT, KBr pellet)/cm^{-1} 2980, 2945, 1756, 1735, 1722, 1410; δ_H(200 MHz, $CDCl_3$) 2.99 (6H, s, 2 NCH_3), 2.97–2.66 (2H, m, CH_2CO), 2.47 (3H, s, CH_3CO), 1.95 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.75–1.59 (2H, m, CH_2CH_3), 0.95 (3H, t, *J* 7.4, CH_3CH_2); δ_C(50 MHz, $CDCl_3$) 173.1, 170.1, 152.71, 152.66, 80.1, 77.5, 39.1, 26.4, 26.3, 25.8, 18.7, 17.4, 14.1, 13.3; *m/z* (EI) 310.1633

(M^+. $C_{14}H_{22}N_4O_4$ requires 310.1641), 282, 268, 241, 199, 183, 168, 156, 141, 125 (base).

1-Trimethylacetyl-6-acetyl-3,4,7,8-tetramethylglycoluril 12. 1-Acetyl-3,4,7,8-tetramethylglycoluril **3** (550 mg, 2.3 mmol) was treated with Bu″Li (1.6 M, 1.5 ml, 2.4 mmol) and then trimethylacetyl chloride (0.350 ml, 2.8 mmol) to give **12** (273 mg, 52%); mp 180–182 °C; ν_{max}(FT, KBr pellet)/cm^{-1} 2985, 2924, 1748, 1733, 1710, 1690, 1449, 1411, 1386, 1327, 1274, 1229, 1113, 1093, 945, 886, 811, 760, 740, 683, 603, 587; δ_H(200 MHz, $CDCl_3$) 3.02 (3H, s, NCH_3), 2.90 (3H, s, NCH_3), 2.50 (3H, s, $COCH_3$), 1.91 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.32 [9H, s, $(CH_3)_3C$]; δ_C(50 MHz, $CDCl_3$) 183.3, 170.5, 153.6, 152.8, 80.5, 78.4, 43.7, 27.2, 27.0, 26.9, 25.2, 19.5, 15.4; *m*/*z* (EI) 325 (M^++1), 269, 211, 225, 198, 168, 141, 126 (base), 125.

1-Methoxycarbonyl-6-acetyl-3,4,7,8-tetramethylglycoluril 13. 1-Acetyl-3,4,7,8-tetramethylglycoluril **3** (715 mg, 2.97 mmol) in THF (28 ml) at 0 °C was treated with Bu″Li (1.5 M, 1.98 ml, 2.97 mmol) and then methyl chloroformate (0.30 ml, 3.9 mmol). The crude material was purified by MPLC using a 1 inch diameter silica LOBAR column, eluted with ethyl acetate at 4 ml min^{-1} to give **13** (758 mg, 84%); δ_H(200 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 2.98 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.44 (3H, s, $COCH_3$), 1.88 (3H, s, CH_3), 1.49 (3H, s, CH_3).

1-Propenoyl-6-acetyl-3,4,7,8-tetramethylglycoluril 14. 1-Acetyl-3,4,7,8-tetramethylglycoluril **3** (9.6 g, 40 mmol) was treated with Bu″Li (1.6 M, 25 ml, 40 mmol) and then propenoyl chloride (4.5 ml, 55 mmol) to give **14** (4.9 g, 41%) (Found: C, 53.14; H, 6.00; N, 19.10. $C_{13}H_{18}N_4O_4$ requires C, 53.05; H, 6.16; N, 19.04%); λ_{max}(CH_3OH)/nm 226 (ε/dm^3 mol^{-1} cm^{-1} 9930); ν_{max}(FT, KBr pellet)/cm^{-1} 3033, 2943, 1754, 1729, 1706, 1619, 1452, 1399, 1338; δ_H(200 MHz, $CDCl_3$) 7.23 (1H, dd, *J* 16.9, 10.3, C*H*=CH_2), 6.45 (1H, dd, *J* 17.0, 1.9, CH=C*H*H), 5.78 (1H, dd, *J* 10.3, 1.8, CH=C*H*H), 2.98 (6H, s, 2 NCH_3), 2.49 (3H, s, $COCH_3$), 1.99 (3H, s, CH_3), 1.53 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 170.4, 165.5, 153.0, 130.4, 129.7, 80.5, 77.9, 26.8, 26.7, 19.0, 14.6; *m*/*z* (EI) 294 (M^+), 252, 168, 125 (base).

1-(2-Methylpropenoyl)-6-acetyl-3,4,7,8-tetramethylglycoluril 15. 1-Acetyl-3,4,7,8-tetramethylglycoluril **3** (1.35 g, 5.6 mmol) was treated with Bu″Li (1.6 M, 3.5 ml, 5.6 mmol) and then 2-methylpropenoyl chloride (0.65 ml, 6.65 mmol) to give **15** (0.63 g, 36%); δ_H(200 MHz, $CDCl_3$) 5.40 (2H, s, C=CH_2), 3.00 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 2.44 (3H, s, $COCH_3$), 1.95 (3H, s, CH_3), 1.53 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 170.7, 169.8, 152.7, 152.4, 141.4, 121.7, 79.7, 77.9, 26.7, 26.5, 24.9, 18.8, 18.2, 14.9; *m*/*z* (EI) 308.1485 (M^+. $C_{14}H_{20}N_4O_4$ requires 308.1485), 266, 168, 142, 126 (base).

1-Butanoyl-6-propenoyl-3,4,7,8-tetramethylglycoluril 16. 1-Butanoyl-3,4,7,8-tetramethylglycoluril **5** (0.728 g, 2.72 mmol) was treated with Bu″Li (1.6 M, 1.7 ml, 2.72 mmol) and then propenoyl chloride (0.27 ml) to give **16** (0.312 g, 36%); mp 143–145 °C (Found: C, 56.00; H, 6.95; N, 17.43; $C_{15}H_{22}N_4O_4$ requires C, 55.88; H, 6.88; N, 17.38%); λ_{max}(CH_3OH)/nm 224 (ε/dm^3 mol^{-1} cm^{-1} 11 700); ν_{max}(FT, KBr pellet)/cm^{-1} 2965, 2935, 1754, 1731, 1706, 1401; δ_H(300 MHz, $CDCl_3$) 7.19 (1H, dd, *J* 17.0, 10.4, C*H*=CH_2), 6.44 (1H, dd, *J* 17.0, 1.8, CH=C*H*H), 5.76 (1H, dd, *J* 10.3, 1.8, CH=C*H*H), 2.98 (3H, s, NCH_3), 2.96 (3H, s, NCH_3), 3.01–2.71 (2H, m, CH_2CO), 1.99 (3H, s, CH_3), 1.70–1.60 (2H, m, CH_2CH_3), 1.51 (3H, s, CH_3), 0.95 (3H, t, *J* 7.4, CH_3CH_2); δ_C(75 MHz, $CDCl_3$) 173.6, 165.6, 153.1, 130.6, 129.6, 80.7, 78.0, 39.4, 26.8 (2 CH_3N), 19.2, 17.9, 14.7, 13.6; *m*/*z* (EI) 322 (M^+), 294, 253, 179, 125 (base).

1-(But-2-enoyl)-6-acetyl-3,4,7,8-tetramethylglycoluril 17. Compound **6** (700 mg, 2.63 mmol) was treated with Bu″Li (1.6 M, 1.5 ml, 2.4 mmol) and then acetyl chloride (0.3 ml). The crude product was purified by flash column chromatography ($CHCl_3$) to give **17** (502 mg, 62%, with 12% recovered **6**) (Found: C, 54.48; H, 6.88; N, 18.06. $C_{14}H_{20}N_4O_4$ requires C, 54.53; H, 6.54; N, 18.17%); λ_{max}(CH_3OH)/nm 206 (ε/dm^3 mol^{-1} cm^{-1} 11 000); ν_{max}(FT, KBr pellet)/cm^{-1} 2939, 1749 (C=O), 1722 (C=O), 1703 (C=O), 1637 (C=O), 1408, 1341; δ_H(500 MHz, $CDCl_3$) 7.09–7.02 (1H, m, C*H*=CHCO), 6.96 (1H, d, *J* 15.3, CH=C*H*), 2.95 (6H, s, 2 NCH_3), 2.48 (3H, s, $COCH_3$), 1.98 (3H, s, CH_3), 1.91 (3H, d, *J* 6.6, CH=CHCH_3), 1.47 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 170.5, 165.6, 153.2, 153.1, 144.6, 124.9, 80.5, 77.8, 26.7 (2 CH_3N), 26.0, 19.1, 18.3, 14.6; *m*/*z* (EI) 308 (M^+), 280, 241, 192, 167, 124, 125 (base).

1-(Hexa-2,4-dienoyl)-6-acetyl-3,4,7,8-tetramethylglycoluril 18. Compound **7** (160 mg, 0.54 mmol) in THF (30 ml) was treated with LDA (1.1 equiv.) and acetyl chloride (0.05 ml, 0.7 mmol) to give **18** (68 mg, 38%, with 45% recovered **7**); λ_{max}(CH_3OH)/nm 275 (ε/dm^3 mol^{-1} cm^{-1} 9300); ν_{max}(FT, KBr pellet)/cm^{-1} 2939, 1735 (C=O), 1702 (C=O); δ_H(500 MHz, $CDCl_3$) 7.37 (1H, dd, *J* 15.0, 10.9, C*H*=CH), 6.97 (1H, d, *J* 15.1, CH=C*H*CO), 6.26 (1H, dd, *J* 14.9, 11.4, C*H*=CH), 6.15 (1H, dq, *J* 14.8, 6.6, CH=C*H*Me), 2.97 (3H, s, NCH_3), 2.96 (3H, s, NCH_3), 2.49 (3H, s, $COCH_3$), 1.99 (3H, s, CH_3), 1.84 (3H, d, *J* 6.8, CH_3CH=CH), 1.51 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 170.6, 166.1, 153.2, 145.3, 139.8, 130.5, 121.1, 80.7, 77.8, 26.9, 26.7, 26.2, 19.2, 18.7, 14.7; *m*/*z* (EI) 334.1646 (M^+. $C_{16}H_{22}N_4O_4$ requires 334.1641), 293, 241, 149, 125 (base).

General procedures for condensations of diacylglycolurils 9–18 to give β-ketoacylglycolurils 19–27

A solution of Bu′OLi was prepared by adding dry *tert*-butyl alcohol (1.5 equiv.) then Bu″Li or Bu′Li in hexane (1.1 equiv.) to THF (3 ml per mmol Bu″Li) with stirring at 0 °C. Other alkoxides were prepared similarly from the corresponding alcohol [$EtC(CH_3)_2OLi$], or were used as commercially available solids (Bu′ONa, Bu′OK) dissolved in THF. The solution was stirred at room temperature for 5–10 min and then added to a vigorously stirred solution of the diacylglycoluril (1 equiv.) in THF (80 ml g^{-1}) at 0 °C, and, in some cases, the appropriate crown ether (1.3 equiv.). After the reaction was complete by TLC, work-up ensued. Either a large excess of ammonium hydrogen carbonate powder was added, the mixture was stirred for 5 h, filtered through Celite and the filtrate was concentrated; or sodium hydrogen sulfate (1 M, 7 equiv.) was added, the product was extracted into chloroform (2 × 5 volumes) and the combined organic layers were washed sequentially with water (15 ml) and brine (15 ml) and dried over sodium sulfate prior to filtration and concentration. The resulting solid was purified by flash column chromatography (2% MeOH in $CHCl_3$).

1-(3-Oxobutanoyl)-3,4,7,8-tetramethylglycoluril 19. Compound **9** (0.364 g, 1.29 mmol) was treated with lithium *tert*-butoxide to give **19** (0.339 g, 93%); mp 154–156 °C (Found: C, 50.90; H, 6.35; N, 19.67. $C_{12}H_{18}N_4O_4$ requires C, 51.05; H, 6.43; N, 19.85%); λ_{max}(CH_3OH)/nm 211 (ε/dm^3 mol^{-1} cm^{-1} 7600), 272 (970); ν_{max}(FT, KBr pellet)/cm^{-1} 3224 (NH), 3095, 2931, 1760–1690 (C=O, br), 1500, 1415, 1394, 1385, 1341, 1312, 1264, 1215, 1167, 1108, 1088, 998, 970, 901, 789, 761, 652, 591, 544; δ_H(200 MHz, $CDCl_3$) 13.45 (0.09H, s, enol O*H*), 6.51 (0.09H, s, enol C*H*=C), 5.95 (1H, s, N*H*), 4.31 (0.91H, d, *J* 16.4, COC*H*HCO), 3.59 (0.91H, d, *J* 16.4, COCH*H*CO), 3.01 (0.27H, s, enol NCH_3), 2.98 (2.73H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.25 (2.73H, s, CH_3CO), 2.02 (0.27H, s enol CH_3CO), 1.74 (3H, s, CH_3), 1.56 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$, keto form only) 201.3 (*C*=O ketone), 167.1, 157.1, 152.8, 78.7, 76.6, 52.2, 30.0, 27.1, 26.4, 19.2, 15.7; *m*/*z* (EI) 282.1319 (M^+. $C_{12}H_{18}N_4O_4$ requires 282.1328), 267, 240, 210, 183, 156, 140, 125.

1-(3-Oxo-[1,2-$^{13}C_2$]butanoyl)-3,4,7,8-tetramethylglycoluril and 1-(3-oxo-[3,4-$^{13}C_2$]butanoyl)-3,4,7,8-tetramethylglycoluril 19a, with 1-(3-oxo-[1,2,3,4-$^{13}C_4$]butanoyl)-3,4,7,8-tetramethylglycoluril 19b. This mixture (0.304 g, 87%) was obtained from condensation of **9a** and **9b** (0.35 g); δ_H(200 MHz, $CDCl_3$) 5.96 (1H, s, N*H*), 4.69–3.21 (2H, m, $COCH_2CO$ and ^{13}CO-$^{13}CH_2CO$), 2.98 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.25 (3H, s and dd, *J* 128.0, 6.1, integration ratio of s : dd 1 : 1.27, CH_3CO and $^{13}CH_3{}^{13}CO$), 1.74 (3H, s, CH_3), 1.56 (3H, s, CH_3); *m*/*z* 286 (3.2%, **19b**), 285 (3.2), 284.1385 (9.6, M^+, **19a**. $C_{10}{}^{13}C_2H_{18}N_4O_4$

requires 284.1396), 242 (4), 240 (3.2), 212 (17.6), 140 (24), 125 (100).

1-(3-Oxo-[4-$^2H_3$]butanoyl)-3,4,7,8-tetramethylglycoluril 19d. Compound **9d** (310 mg, 1.09 mmol) was treated with Bu^{t}OLi to give **19d** (247 mg, 80%), which contained **19** (17%); δ_H(500 MHz, $CDCl_3$) 5.97 (1H, s, N*H*), 4.30 (1H, d, *J* 16.4, COC*H*HCO), 3.60 (1H, d, *J* 16.5, COC*H*HCO), 2.98 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.25 (0.52H, s, CH_3CO in **19**), 1.74 (3H, s, CH_3), 1.56 (3H, s, CH_3); δ_D(77 MHz, $CHCl_3$) 2.20 (s, CD_3CO); *m*/*z* 285.1512 (M^+, **19d**. $C_{12}H_{15}D_3N_4O_4$ requires 285.1513), 282 (M^+, **19**), 267, 241, 213, 210, 125 (base).

1-(3-Oxopentanoyl)-3,4,7,8-tetramethylglycoluril 20 and 1-(2-methyl-3-oxobutanoyl)-3,4,7,8-tetramethylglycoluril 21ab from 10. Compound **10** (350 mg, 1.18 mmol) gave a mixture of **20** and **21ab** (284 mg, 81%). For **20**: ν_{max}(FT, KBr pellet)/cm^{-1} 3230 (NH), 2991, 2940, 1743 (C=O), 1717 (C=O), 1689 (C=O), 1457, 1410; δ_H(200 MHz, $CDCl_3$) 5.99 (1H, s, N*H*), 4.33 (1H, d, *J* 16.4, COC*H*HCO), 3.56 (1H, d, *J* 16.4, COC*H*HCO), 2.99 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.54 (2H, q, *J* 7.2, CH_2CH$_3$), 1.75 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.08 (3H, t, *J* 7.2, CH_3CH$_2$); δ_C(50 MHz, $CDCl_3$) 204.4, 167.4, 157.3, 152.8, 78.8, 76.7, 51.2, 35.9, 27.1, 26.4, 19.3, 15.7, 7.4; *m*/*z* (EI) 296.1482 (M^+. $C_{13}H_{20}N_4O_4$ requires 296.1484), 267, 254, 240, 224, 168, 140, 125, 97, 86, 70.

1-(3-Oxohexanoyl)-3,4,7,8-tetramethylglycoluril 22 and 1-(2-ethyl-3-oxobutanoyl)-3,4,7,8-tetramethylglycoluril 23ab from 11. Compound **11** (270 mg, 0.87 mmol) gave a mixture of **22** and **23ab** (237 mg, 88%). For **22**: ν_{max}(FT, KBr pellet)/cm^{-1} 3255 (NH), 2962, 2941, 1745 (C=O), 1725 (C=O), 1692 (C=O), 1466, 1413; δ_H(200 MHz, $CDCl_3$) 6.12 (1H, s, N*H*), 4.32 (1H, d, *J* 16.4, COC*H*HCO), 3.57 (1H, d, *J* 16.4, COC*H*HCO), 2.97 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.61–2.46 (2H, m, CH$_2$CH_2CO), 1.75 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.71–1.60 (2H, m, CH_2CH$_2$CO), 0.93 (3H, t, *J* 7.4, CH_3); δ_C(50 MHz, $CDCl_3$) 203.7, 167.3, 157.1, 152.7, 78.6, 76.5, 51.4, 44.6, 27.0, 26.3, 19.2, 16.7, 15.6, 13.5; *m*/*z* (EI) 310.1637 (M^+. $C_{14}H_{22}N_4O_4$ requires 310.1641), 282, 267, 240, 199, 183, 125.

1-(3-Oxo-4,4-dimethylpentanoyl)-3,4,7,8-tetramethylglycoluril 24. Compound **12** (100 mg, 0.308 mmol) in THF was treated with Bu^{t}OLi at 0 °C using the standard procedure, but the reaction was allowed to proceed for 5 h, producing the condensation product **24** (79 mg, 79%); ν_{max}(FT, KBr pellet)/cm^{-1} 3268 (NH), 3104, 2961, 2924, 1737, 1711, 1692, 1491, 1451, 1410, 1333, 1176, 1112, 1064, 760, 696, 664; δ_H(200 MHz, $CDCl_3$) 13.26 (s, enol O*H*), 6.64 (s, enol C*H*=C), 6.04 (1H, s, N*H*), 4.57 (1H, d, *J* 16.6, COC*H*HCO), 3.68 (1H, d, *J* 16.6, COC*H*HCO), 3.02 (s, enol NCH_3), 2.97 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 1.76 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.20 [9H, s, keto (CH_3)$_3$CO], 1.19 [s, enol (CH_3)$_3$CO]; δ_C(50 MHz, $CDCl_3$) 209.9 (ketone *C*=O), 189.8 (weak, OH*C*=CHCO), 171.6 (weak, OHC=*C*HCO), 168.4, 157.2, 152.6, 86.6, 78.6, 76.6, 46.6, 44.3, 27.4, 27.1, 26.5, 26.4, 19.9 (enol), 19.2, 15.6; *m*/*z* (EI) 325 (M^++1), 267, 143, 125 (base).

1-Methoxycarbonylacetyl-3,4,7,8-tetramethylglycoluril 25. Compound **13** (29.0 mg, 0.097 mmol) and lithium 1,1-dimethylpropoxide (31.0 mg, 0.33 mmol) in THF (2 ml) gave a mixture of **25** and **3** (27.3 mg, 94%, ratio of **25**:**3** 8.5:1), which was separated by chromatography on a Merck LOBAR MPLC column (EtOAc). For **25**: δ_H(200 MHz, $CDCl_3$) 5.99 (1H, s, N*H*), 4.07 (1H, d, *J* 16.4, COC*H*HCO), 3.68 (1H, d, *J* 16.4, COC*H*HCO), 3.70 (3H, s, OCH_3), 2.98 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 1.70 (3H, s, CH_3), 1.54 (3H, s, CH_3).

1-(3-Oxohex-4-enoyl)-3,4,7,8-tetramethylglycoluril 26. Compound **17** (220 mg, 0.71 mmol) gave **26** (132 mg, 60%); mp 147–150 °C (from $CHCl_3$) (Found: C, 53.97; H, 6.63; N, 17.78. $C_{14}H_{20}N_4O_4$ requires C, 54.53; H, 6.54; N, 18.17%); λ_{max}(CH$_3$OH)/nm 304 (ε/dm^3 mol^{-1} cm^{-1} 3500); ν_{max}(FT, KBr pellet)/cm^{-1} 3223, 3094, 2948, 1741, 1717, 1690, 1668; δ_H(500 MHz, $CDCl_3$) (shows 37% enol form) 13.2 (1H, s, enol O*H*), 6.96 (1H, dq, *J* 15.7, 6.7, keto CH_3C*H*=CH), 6.74 (1H, dq, *J* 15.8, 6.6, enol CH_3C*H*=CH), 6.51 (1H, s, enol COC*H*=COH), 6.16–6.12 (2H, m, N*H* and CH=C*H*), 5.90 (1H, d, *J* 15.3, CH=C*H*CO), 4.47 (1H, d, *J* 16.2, COC*H*HCO), 3.75 (1H, d, *J* 16.2, COC*H*HCO), 3.00 (3H, s, enol NCH_3), 2.97 (3H, s, keto NCH_3), 2.86 (3H, s, NCH_3), 1.93 (3H, dd, *J* 6.9, 1.7, keto CH_3CH=CH), 1.88 (3H, dd, *J* 7.0, 1.6, enol CH_3CH=CH), 1.76 (3H, s, CH_3), 1.74 (3H, s, enol CH_3), 1.56 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$, mixture of keto and enol forms) 192.9, 172.6, 171.5, 167.8, 157.2, 152.8, 144.2, 137.3, 131.2, 126.6, 90.8, 78.7, 78.6, 76.8, 76.7, 49.0, 27.1, 26.4, 20.0, 19.3, 18.3, 15.7; *m*/*z* (EI) 308 (M^+), 236, 125 (base).

1-(3-Oxoocta-4,6-dienoyl)-3,4,7,8-tetramethylglycoluril 27. Compound **18** (40 mg, 0.12 mmol) was treated with Bu^{t}OLi to give **27** (24 mg, 60%); λ_{max}(CH$_3$OH)/nm 215 (ε/dm^3 mol^{-1} cm^{-1} 11 500), 280 (11 600), 319 (10 800); ν_{max}(FT, KBr pellet)/cm^{-1} 3426 (NH), 2927, 1719 (C=O); δ_H(500 MHz, $CDCl_3$, contains 46% enol form) 13.18 (0.46H, s, enol O*H*), 7.15–5.83 (4H, m, C*H*=C*H*), 6.56 (0.46H, enol COC*H*=COH), 4.51 (0.54H, d, *J* 16.1, keto COC*H*HCO), 3.74 (0.54H, d, *J* 16.1, keto COC*H*HCO), 3.02 (1.4H, s, enol NCH_3), 2.97 (1.6H, keto NCH_3), 2.86 (3H, s, NCH_3), 1.87 (1.5H, d, *J* 5.0, CH_3CH=CH), 1.85 (1.5H, d, *J* 6.7, CH_3CH=CH), 1.76 (1.5H, s, CH_3), 1.74 (1.5H, s, CH_3), 1.56 (3H, s, CH_3); δ_C(200 MHz, $CDCl_3$) 193.3, 172.9, 167.9, 157.2, 152.6, 144.3, 141.4, 138.5, 137.4, 130.6, 130.1, 126.6, 123.7, 91.9, 78.7, 77.7, 49.3, 27.1, 26.4, 20.0, 19.3, 18.8, 15.7; *m*/*z* (EI) 334.1633 (M^+. $C_{16}H_{22}N_4O_4$ requires 334.1641), 319, 260, 198, 125, 83 (base).

General procedure for reduction of β-ketoacylglycolurils 19, 21ab and 26 with $NaBH_4$

To a solution of the β-ketoacyl compound in MeOH (35 ml g^{-1}) was added sodium borohydride (1.5–1.8 equiv) at 0 °C. This mixture was stirred for 10 min at room temperature and glacial acetic acid (10 ml) was added. The solution was concentrated to give a solid mixture, to which was added dichloromethane (40 ml). The mixture was stirred for 5 min and solid material was removed by filtration. The filtrate was concentrated and purified by flash column chromatography (2% MeOH in $CHCl_3$).

1-(3-Hydroxybutanoyl)-3,4,7,8-tetramethylglycoluril 28. Compound **19** (1.06 g, 3.76 mmol) was treated with $NaBH_4$ (0.21 g, 5.55 mmol) to give **28** (0.985 g, 93%) as a mixture of two diastereomers (Found: C, 50.42; H, 7.10; N, 19.65. $C_{12}H_{20}N_4O_4$ requires C, 50.69; H, 7.09; N, 19.71%); δ_H(200 MHz, $CDCl_3$) 6.19 (1H, s, N*H*), 4.24 (1H, m, C*H*OH), 3.27–2.80 (2H, m, CH_2), 3.01 (3H, s, NCH_3), 2.87 (3H, s, NCH_3) 1.71 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.26 (3H, d, *J* 6.3, CH_3CHOH); δ_C(50 MHz, $CDCl_3$) 173.6, 157.1, 152.9, 78.7, 76.7, 64.1, 44.7, 27.1, 26.4, 22.4, 19.7, 15.5; *m*/*z* (EI) 284.1492 (M^+. $C_{12}H_{20}N_4O_4$ requires 284.1485), 266, 240, 156, 140, 126 (base), 111, 86.

1-(2-Methyl-3-hydroxybutanoyl)-3,4,7,8-tetramethylglycoluril 29. A mixture of the two diastereomeric 1-(2-methyl-3-oxobutanoyl)-3,4,7,8-tetramethylglycolurils **21a** and **21b** (2.1:1 ratio, 351 mg) was treated with $NaBH_4$ (67 mg) to give **29** (210 mg, 60%) as a mixture of four diastereomers; δ_H(500 MHz, $CDCl_3$) 6.28, 6.16, 6.12 and 6.11 (total 1H, 4 × s, N*H*), 4.10–3.65 (2H, m, C*H*OH and CHOHC*H*Me), 2.99 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 1.68, 1.67, 1.66 and 1.65 (total 3H, 4 × s, CH_3), 1.53 (3H, s, CH_3), 1.23–1.08 (6H, 8 × d, CH_3CHOH and CH_3CHCO); δ_C(50 MHz, $CDCl_3$) 177.8, 177.4, 177.2, 157.4, 157.3, 157.2, 153.3, 153.2, 78.5, 77.2, 76.8, 71.0, 70.0, 68.6, 67.4, 45.6, 43.6, 43.5, 27.2, 26.4, 21.5, 20.9, 20.6, 19.7, 19.6, 19.5, 19.1, 15.8, 15.7, 14.8, 14.4, 10.9, 10.3; *m*/*z* (EI) 299.1704 (M^+ + 1. $C_{13}H_{23}N_4O_4$ requires 299.1719), 280 ($M^+ - H_2O$), 254, 125 (base).

1-(3-Hydroxyhex-4-enoyl)-3,4,7,8-tetramethylglycoluril 30. Compound **26** (540 mg, 1.75 mmol) was reduced with $NaBH_4$ (110 mg) to give **30** (240 mg, 44%, with 51% recovered **26**) as a mixture of two diastereomers; ν_{max}(FT, KBr pellet)/cm^{-1} 3390 (OH), 3322 (NH), 1721 (C=O); δ_H(200 MHz, $CDCl_3$) 6.12 and 6.10 (1H, 2 × s, N*H*), 5.76–5.71 (1H, m, *H*C=CH), 5.58–5.53

(1H, m, *H*C=CH), 4.4–4.6 (1H, m, C*H*OH), 3.30–3.00 (2H, m, CH_2CO), 3.02 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 1.71 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.69 (3H, d, *J* 7.2, CH_3CH=CH); δ_C(125 MHz, $CDCl_3$) 173.0, 157.1, 152.1, 132.1, 127.1, 78.7, 76.7, 68.8, 43.5, 27.1, 26.4, 19.7, 19.6, 17.6, 15.7; *m*/*z* 310.1654 (M^+. $C_{14}H_{22}N_4O_4$ requires 310.1641), 292, 240, 199, 125 (base).

1-(But-2-enoyl)-3,4,7,8-tetramethylglycoluril 6 from 28

To 1-(3-hydroxybutanoyl)-3,4,7,8-tetramethylglycoluril **28** (640 mg, 2.25 mmol) dissolved in CH_2Cl_2 (15 ml) was added trifluoroacetic anhydride (3 equiv.) at 23 °C. After stirring for 1 h, a solution of Et_3N (2 equiv.) in CH_2Cl_2 (5 ml) was added dropwise and 10 min later, Et_3N (2 ml) was added. The mixture was heated at reflux for 20 min. The solution was concentrated and the residue was purified by flash column chromatography (1% MeOH in $CHCl_3$) to give **6** (500 mg, 83%) with an *E*:*Z* ratio of 97.4:2.6.

1-(Hexa-2,4-dienoyl)-3,4,7,8-tetramethylglycoluril 7 from 30

Compound **30** (194 mg, 0.626 mmol) was treated with trifluoroacetic anhydride (0.25 ml) and triethylamine (0.1 ml and then 2 ml), as for the preparation of **6** from **28**, to give **7** (157 mg, 86%).

1-Butanoyl-3,4,7,8-tetramethylglycoluril 5 from 6

Compound **6** (220 mg, 0.82 mmol) was dissolved in dry THF (100 ml) under N_2 and cooled in an acetone–dry ice bath. L-Selectride (1 M in THF, 0.82 ml, 0.82 mmol) was added with stirring. The mixture was allowed to reach room temperature over 2 h. Solid NH_4HCO_3 was added, and the mixture was stirred for 4 h. The mixture was filtered through Celite and the filtrate concentrated and purified by flash column chromatography ($CHCl_3$) to give **5** (164 mg, 74%).

1-Butanoyl-6-acetyl-3,4,7,8-tetramethylglycoluril 11 by reduction of 6 and *in situ* acetylation

The above procedure was used for the L-Selectride reduction of **6** (100 mg, 0.385 mmol). Acetyl chloride (0.05 ml) was used to quench the reaction instead of NH_4HCO_3 to give **11** (73 mg, 63%).

Benzyl butanoate and tetramethylglycoluril 1 from 5

A solution of lithium benzalkoxide (C_6H_5-CH_2OLi)[16] was prepared by addition of Bu^{n}Li (1.1 equiv.) to benzyl alcohol (1.5 equiv.) in THF (8 ml $mmol^{-1}$). To a solution of compound **5** (100 mg, 0.37 mmol) in THF (20 ml) was added the prepared lithium benzalkoxide (1 equiv.) at room temperature. The mixture was stirred for 12 h and glacial acetic acid (2 equiv.) was added. The solution was concentrated and $CHCl_3$ was added. The mixture was stirred for a further 0.5 h, and the solid was collected by filtration, washed with $CHCl_3$ and THF and dried to give **1** (68 mg, 92%). The filtrate was concentrated and purified by flash column chromatography (hexane) to give benzyl butanoate (55 mg, 83%); δ_H(200 MHz, $CDCl_3$) 7.37 (5H, m, Ar*H*), 5.11 (2H, s, CH_2Ar), 2.33 (2H, d, *J* 7.4, CH_2CO), 1.67 (2H, sextet, *J* 7.4, CH_2CH$_3$), 0.94 (3H, t, *J* 7.4, CH_3); δ_C(50 MHz, $CDCl_3$) 173.4, 136.1, 128.5 (2C), 128.1 (2C), 66.0, 36.1, 18.4, 13.6; *m*/*z* (EI) 178.1003 (M^+. $C_{11}H_{14}O_2$ requires 178.0994), 108, 91 (base), 71, 43.

Benzyl but-2-enoate and tetramethylglycoluril 1 from 6

Reaction of **6** (165 mg, 0.62 mmol) as for **5** above gave **1** (69 mg, 80%) and benzyl but-2-enoate (43 mg, 55%); ν_{max}(FT, KBr pellet)/cm^{-1} 3034, 2947, 1721, 1658, 1263, 1174, 1103, 1015, 969, 838, 738, 698; δ_H(200 MHz, $CDCl_3$) 7.30 (5H, m, Ar*H*), 7.03 (1H, dq, *J* 15.5, 6.9, MeC*H*=CH), 5.89 (1H, dq, *J* 15.6, 1.5, MeCH=C*H*), 5.17 (2H, s, ArCH_2), 1.88 (3H, dd, *J* 6.9, 1.5, CH_3CH=CH); δ_C(50 MHz, $CDCl_3$) 166.3, 145.1, 136.1, 128.5, 128.1, 122.4, 65.9, 18.0; *m*/*z* (EI) 176 (M^+), 158, 149, 131, 107, 91 (base), 77, 69, 65.

General procedure for L-Selectride-induced reduction–condensation of 14–17

To a stirred solution of the *N*-alk-2-enoyl-*N*′-alkanoylglycoluril in dry THF (150 ml g^{-1}) at −78 °C was added L-Selectride (1 equiv.). The mixture was allowed to reach room temperature over 2 h. Solid NH_4HCO_3 was added, the mixture was stirred for 8 h and filtered through Celite. The filtrate was concentrated and purified by flash column chromatography ($CHCl_3$).

1-(2-Methyl-3-oxobutanoyl)-3,4,7,8-tetramethylglycoluril 21ab from 14. Compound **14** (1.21 g, 4.1 mmol) was treated with L-Selectride to give a mixture of **21ab** (71%, ratio 2.1:1). Flash column chromatography gave: (1) **10** (3%); (2) **21a** (340 mg, 28%); (3) a mixture of **21a** and **21b** (460 mg, 38%) in a 1:1 ratio; and (4) **21b** (56 mg, 5%). The two pure single diastereomers were obtained by recrystallization ($CHCl_3$–Et_2O) of fractions (2) and (4), respectively. For **21a**: ν_{max}(FT, KBr pellet)/cm^{-1} 3346 (NH), 3000, 2940, 1721 (C=O), 1689 (C=O), 1489, 1457, 1411, 1353, 1309, 1245, 1160, 1110; δ_H(200 MHz, $CDCl_3$) 5.94 (1H, s, N*H*), 4.48 (1H, q, *J* 7.3, COC*H*CO), 2.96 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.29 (3H, s, CH_3CO), 1.74 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.34 (3H, d, *J* 7.2, CH_3CHCO); δ_C(50 MHz, $CDCl_3$) 205.9, 170.5, 157.2, 153.0, 78.9, 76.9, 53.8, 28.2, 27.0, 26.4, 19.0, 15.7, 12.0; *m*/*z* (EI) 296.1495 (M^+. $C_{13}H_{20}N_4O_4$ requires 296.1485), 254, 222, 199, 180, 156, 140, 125 (base). For **21b**: ν_{max}(FT, KBr pellet)/cm^{-1} 3319 (NH), 2989, 1720 (C=O), 1698 (C=O), 1490, 1412, 1302, 1112, 1089, 938, 762; δ_H(200 MHz, $CDCl_3$) 6.05 (1H, s, N*H*), 4.60 (1H, q, *J* 7.2, COC*H*CO), 2.99 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.22 (3H, s, CH_3CO), 1.70 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.35 (3H, d, *J* 7.2, CH_3CHCO); δ_C(50 MHz, $CDCl_3$) 204.2, 171.1, 157.0, 153.0, 78.7, 76.6, 53.6, 28.3, 27.1, 26.6, 19.9, 15.8, 12.5; *m*/*z* (EI) 296.1488 (M^+. $C_{13}H_{20}N_4O_4$ requires 296.1485), 254, 125 (base).

1-(2-Ethyl-3-oxobutanoyl)-3,4,7,8-tetramethylglycoluril 23ab from 17. Compound **17** (377 mg, 1.22 mmol) was treated with L-Selectride (1 M, 1.22 ml, 1.22 mmol) to give a mixture of diastereomers **23a** and **23b** (1.6:1 by ^{1}H NMR). Flash column chromatography gave: (1) **11** (71 mg, 19%); (2) **3** (26 mg, 9%); (3) **23a**; (4) a mixture of **23a** and **23b**; and (5) **23b** (total yield 197 mg, 52%). For **23a**: δ_H(200 MHz, $CDCl_3$) 5.97 (1H, s, N*H*), 4.42 (1H, dd, *J* 9.0, 3.9, COC*H*CO), 2.97 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.28 (3H, s, CH_3CO), 1.97–1.90 (2H, m, CH_2CH$_3$), 1.73 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.00 (3H, t, *J* 7.4, CH_3CH$_2$); δ_C(50 MHz, $CDCl_3$) 205.1, 169.8, 157.2, 153.0, 78.7, 76.9, 60.8, 29.0, 27.1, 26.4, 20.6, 19.1, 15.7, 12.7. For **23b**: δ_H(200 MHz, $CDCl_3$) 6.04 (1H, s, N*H*), 4.58 (1H, dd, *J* 8.0, 5.3, COC*H*CO), 2.99 (3H, s, NCH_3), 2.88 (3H, s, NCH_3), 2.21 (3H, s, COCH_3), 1.99–1.81 (2H, m, CH_2CH$_3$), 1.71 (3H, s, CH_3), 1.57 (3H, s, CH_3), 0.97 (3H, t, *J* 7.4, CH_3CH$_2$); δ_C(50 MHz, $CDCl_3$) 203.4, 170.5, 156.9, 153.0, 78.6, 76.6, 60.6, 28.9, 27.1, 26.6, 21.4, 19.9, 15.9, 12.4; *m*/*z* (EI) 311 (M^++1), 310.1627 (M^+. $C_{14}H_{22}N_4O_4$ requires 310.1641), 268, 125 (base).

1-(2,2-Dimethyl-3-oxobutanoyl)-3,4,7,8-tetramethylglycoluril 32. Compound **15** (148 mg, 0.48 mmol) was treated with L-Selectride (1 M, 0.48 ml, 0.48 mmol) to give **32** (101 mg, 68%); (Found: C, 54.05; H, 7.09; N, 17.98. $C_{14}H_{22}N_4O_4$ requires C, 54.18; H, 7.14; N, 18.05%); δ_H(200 MHz, $CDCl_3$) 6.02 (1H, s, N*H*), 2.95 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.21 (3H, s, COCH_3), 1.72 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.37 (3H, s, CH_3); δ_C(50 MHz, $CDCl_3$) 207.5, 173.8, 157.1, 152.3, 78.7, 77.2, 57.7, 27.0, 26.4, 25.0, 23.5, 22.5, 19.1, 15.7; *m*/*z* (EI) 311 (M^++1), 268, 199, 194, 125 (base).

1-(2-Methyl-3-oxohexanoyl)-3,4,7,8-tetramethylglycoluril 33ab. Compound **16** (168 mg, 0.52 mmol) gave 126 mg crude product. Flash column chromatography gave: (1) **5** (15 mg, 9%); (2) a mixture of **33ab** (114 mg, 66%, diastereomer ratio 1:2.1). The two diastereomers were separated in a second column chromatographic separation. For **33a**: δ_H(200 MHz, $CDCl_3$) 5.96 (1H, s, N*H*), 4.46 (1H, q, *J* 7.4, COC*H*CO), 2.95 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 2.68 (1H, dt, *J* 17.8, 7.1, C*H*HCO), 2.54 (1H, dt, *J* 17.8, 7.1, C*H*HCO), 1.74 (3H, s, CH_3), 1.65–1.57

(2H, m, CH_2CH$_3$), 1.33 (3H, d, *J* 7.3, CH_3CHCO), 0.92 (3H, t, *J* 7.4, CH_3CH$_2$); δ_C(50 MHz, $CDCl_3$) 208.2, 170.8, 157.3, 152.9, 78.8, 77.2, 53.4, 42.5, 27.0, 26.4, 19.0, 16.7, 15.7, 13.7, 12.3. For **33b**: mp 134–136 °C (Found: C, 55.79; H, 7.42; N, 17.44. $C_{15}H_{24}N_4O_4$ requires C, 55.54; H, 7.46; N, 17.28%); δ_H(300 MHz, $CDCl_3$) 6.00 (1H, s, N*H*), 4.60 (1H, q, *J* 7.2, COC*H*CO), 2.98 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 2.54 (1H, dt, *J* 17.5, 7.4, C*H*HCO), 2.45 (1H, dt, *J* 17.5, 7.4, C*H*HCO), 1.69 (3H, s, CH_3), 1.65–1.53 (2H, m, CH_2CH$_3$), 1.57 (3H, s, CH_3), 1.34 (3H, d, *J* 7.2, CH_3CHCO), 0.90 (3H, t, *J* 7.4, CH_3CH$_2$); δ_C(75 MHz, $CDCl_3$) 206.1, 171.5, 157.0, 152.9, 78.6, 76.6, 53.1, 42.7, 27.1, 26.5, 19.8, 16.9, 15.9, 13.6, 12.6; *m*/*z* (EI) 324 (M^+), 281, 254, 199, 180, 152, 125 (base).

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