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Synthesis of and Tautomerism in 3-Acyltetramic Acids

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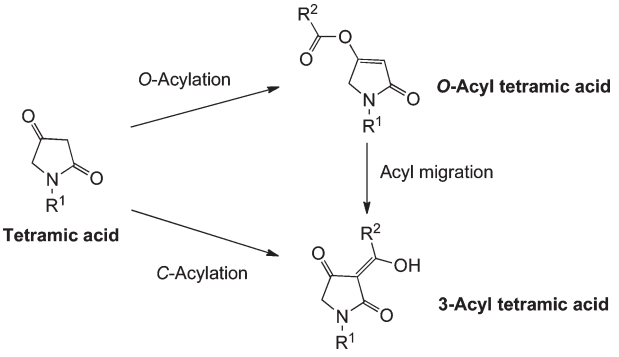

The synthesis of 3-acyltetramic acids, the substructure of bioactive natural products, via *O*-acylation of tetramic acids with carboxylic acids followed by acyl migration, has been investigated. This acylation sequence is mediated by *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) and is very sensitive to the nature of the nitrogen substituent (R^1), the nature of the carboxylic acid (R^2CO_2H), and the amount of DMAP. Acylation of *N*-acyl tetramic acids with an alkyl carboxylic acid using 1.3 equiv of DMAP (with 1.1 equiv of DCC) unexpectedly gave the 3-acyltetramic acid directly as a result of acyl migration induced by excess amounts of DMAP. On the other hand, *N*-unsubstituted, *N*-alkyl, and *N*-acyl tetramic acids with alkyl and aromatic carboxylic acids gave the *O*-acyl tetramic acids by using only 0.1 equiv of DMAP (with 1.1 equiv of DCC); these could be further rearranged to the acyl product by treatment with excess DMAP. The tautomeric equilibrium of these 3-acyltetramic acids in solution was found to strongly depend on the nitrogen substituent group (R^1) rather than the 3-acyl group.

Introduction

The identification of novel lead compounds inspired by bioactive natural products and optimized by diverted total synthesis has been demonstrated to be an effective strategy for drug development.[1] In this regard, naturally occurring 3-acyltetramic acids[2,3] are core structural skeletons that have been found in various biological active products such as magnesidin A (antibiotic activity),[3a] reutericyclin (antibiotic activity),[3b] tenuazonic acid (antiviral and antitumor activity),[3c] Sch 213766 (anti-HIV activity),[3d] integramycin (anti-HIV activity),[3e] the melophlins (antitumor activity),[3f] and the macrocidins (herbicidal activity)[3g] (Figure 1). Their antibiotic activity in particular has been of interest recently since the discovery of the key role of the 3-acyltetramic acids formed from *N*-acylhomoserine lactones, a class of common autoinducers responsible for quorum sensing of Gram-negative bacteria.[3h−j]

Given the biological importance of this motif, various synthetic methodologies for 3-acyltetramic acids[2,5−14] as well as tetramic acids themselves[4] have been developed, and there are two main routes for their synthesis (Figure 2). One is to incorporate the acyl group (R^2) before the construction of the tetramic acid core,[6−10] and the most common approach is by Dieckmann-type cyclization of *β*-keto amide **A** under basic conditions ($KOBu^t$ or NaH).[6−9] However, even though such cyclizations, including solid phase

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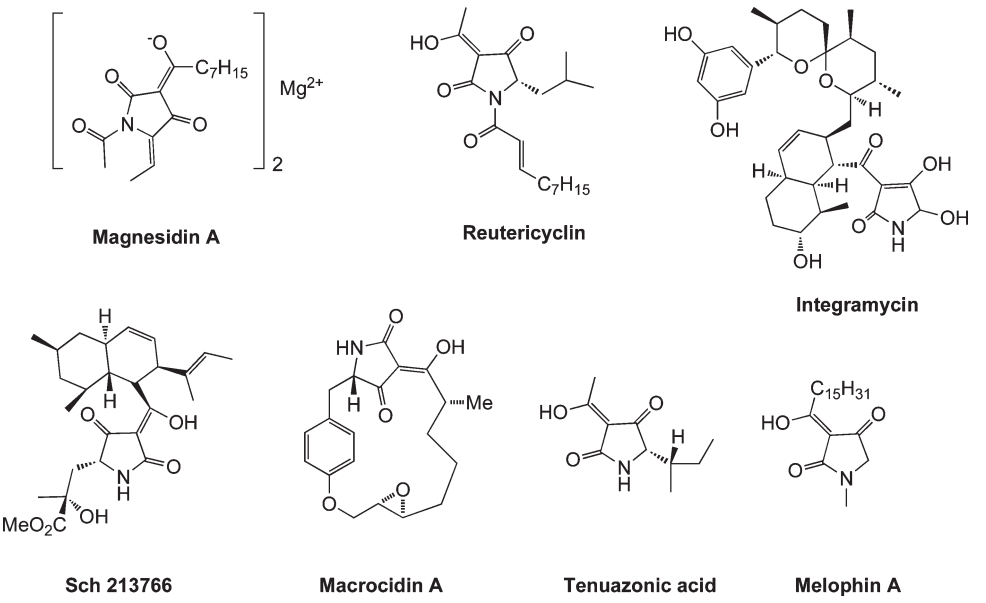

FIGURE 1. Examples of naturally occurring 3-acyltetramic acids.

protocols,[9] have been widely applied for the synthesis of natural[6,7] and unnatural[8] analogues, only *N*-unsubstituted and *N*-alkyl 3-acyltetramic acids (R^1 = H, alkyl) have been prepared in this way, but critically not the *N*-acyl system found in magnesidin A and reutericyclin (R^1 = acyl). This is likely to be due to the difficulty of accessing the required *N*-diacyl precursor **A** (R^1 = acyl). Importantly, the Markopoulou group has elegantly circumvented this difficulty to some extent by *in situ* C-acylation of β-keto esters and malonates with activated ester **B** to give precursors **C** followed by intramolecular condensation under basic conditions (NaH),

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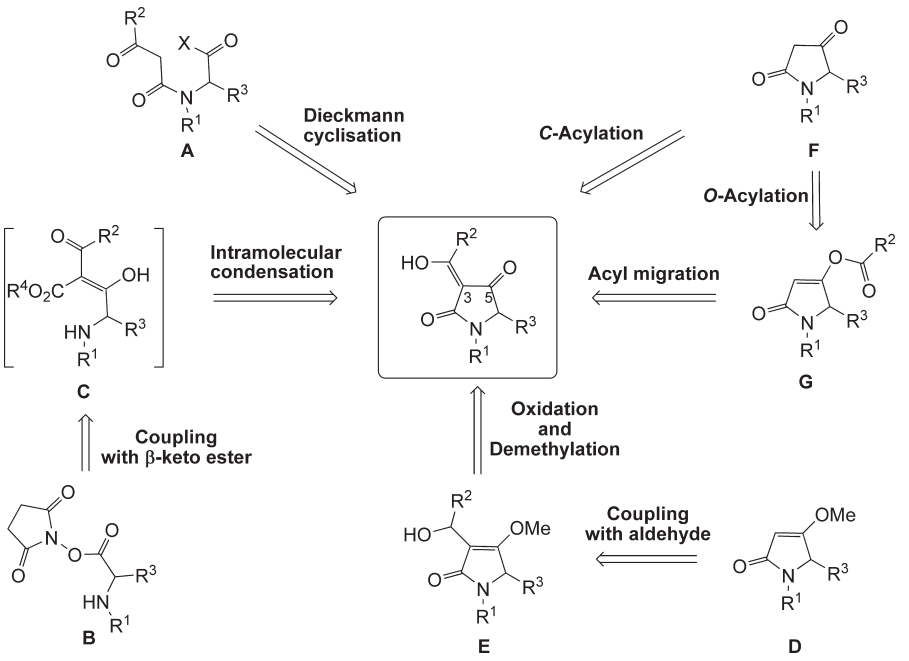

FIGURE 2. Synthetic approaches to 3-acyltetramic acids.

which established access not only to *N*-unsubstituted and *N*-methyl but also some *N*-acyl and *N*-alkoxycarbonyl 3-acyltetramic acids.[10]

The second alternative route is to incorporate the acyl group (R^2) after the construction of the tetramic acid main core.[11−13] In this manner, Jones' group has developed methodology involving base-mediated (*n*-BuLi) condensation of 4-*O*-methyl tetramic acid **D** with aldehydes (R^2CHO) to give hydroxy adducts **E**, and oxidation followed by demethylation under basic conditions gave the desired 3-acyltetramic acids.[11] This method was particularly efficient for 1,5,5-trisubstituted tetramates **D** but with less substituted tetramates suffered from side reactions caused by lithiation at both N(1) and C(5).[11b] More conveniently, direct acylation at the 3-position of tetramic acid **F** could be achieved with acid chlorides ($R^2C(O)Cl$) activated by Lewis acid catalysts such as $BF_3 \cdot OEt_2$ and $TiCl_4$,[12] although with 5-unsubstituted tetramic acids, self-condensation under these conditions has been reported.[12d] Finally, their synthesis via base-induced acyl migration of *O*-acyl tetramic acids **G**, themselves readily prepared from tetramic acids **F** using Keck coupling conditions in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) with a catalytic amount of 4-dimethylaminopyridine (DMAP),[13a] has been reported; for example, the *in situ* or stepwise acyl-migration of *O*-acyl tetramic acids **G** induced by triethylamine,[13b,c] triethylamine with hydroxybenzotriazole,[13d] or acetone cyanohydrin[13e] is possible.

Analysis of existing natural products suggested that, as a result of the high level of substituent variance and complexity at the R^2 position relative to the R^1 and R^3 groups, the latter acyl-migration method might be expected to be more general than the others, because it permits a high level of variability at the R^2 position at a late stage as well as avoiding harsh reaction conditions, such as strong Lewis acid (e.g., $BF_3 \cdot OEt_2$ or $TiCl_4$) and strong base (e.g., NaH, *n*-BuLi, or $KOBu^t$). Of interest is that although this Fries-type rearrangement approach has been widely used in tetronic acid synthesis,[16] it has been much less widely applied in tetramates,[13] and in particular its suitability for *N*-acyl tetramic acids has not yet been studied. Moreover, Hori[13b] indicates that although reaction in a stepwise manner in one-pot by formation of the kinetic *O*-acylate followed by acyl migration after the addition of triethylamine gives very high yields of 3-alkanoylation for *N*-unsubstituted and *N*-alkyl systems, it is less efficient for unsubstituted acids, and no examples were given for aromatic carboxylates. In fact, the effect of the R^1 and R^2 substituents on this reaction sequence has not been studied in detail, although a recent report describing the synthesis of penicillenol A1 using a related method has been reported.[13e] We therefore decided to develop this methodology further, with two points of diversity at the R^1 and R^2 groups; significantly, we found improved reaction conditions suitable for the acylation of *N*-acyl tetramic acids, providing wider access to this important class of compound, and this has enabled detailed study of the effect of functional groups R^1 and R^2 on the tautomeric behavior of the 3-acyltetramic acids, likely to be of importance in the manifestation of their biological activity.

Results and Discussion

Synthesis of 3-Acyltetramic Acids. Tetramic acids **1**, **2**, **3**, **4**, and **6** were prepared by literature methodology,[5] whereas **5**, which possessed a 2-methylbenzoyl group on N(1), was prepared by cyclization of the corresponding *N*-acyl glycine using standard methodology.[10] Using these as starting points, we examined stepwise *O*-acylation followed by the acyl migration using the known method (Scheme 1

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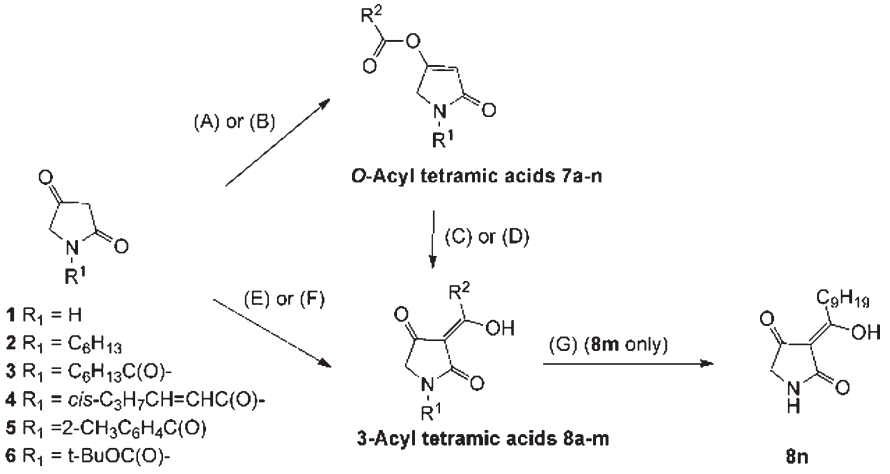
SCHEME 1. Synthesis of 3-Acyltetramic Acids



Reaction conditions; (A) R^2CO_2H (1.1 eq), DCC (1.1 eq), DMAP (0.1 eq), CH_2Cl_2, r.t.; (B) R^2COCl (1.1 eq), Et_3N (1.2 eq), CH_2Cl_2, r.t.; (C) $(CH_3)_2C(OH)CN$ (0.5 eq), Et_3N (2.0 eq), CH_3CN, r.t.; (D) DMAP (1.3 eq), CH_2Cl_2, r.t.; (E) R^2CO_2H (1.1 eq), DCC (1.1 eq), DMAP (1.3 eq), CH_2Cl_2, r.t.; (F) $C_9H_{19}CO_2H$ (1.1 eq), DCC (1.1 eq), DMAP (0.5 eq), CH_2Cl_2, r.t.; (G) CF_3CO_2H, CH_2Cl_2, r.t..

TABLE 1. Preparation of *O*-Acyltetramates 7 and 3-Acyltetramates 8 from Tetramic Acids 1−6 (see Scheme 1)

					compound/yield (%)[b]	
entry	tetramic acid	R^1	R^2	method[a]	*O*-acyl	3-acyl
1	**1**	H	phenyl	A then C	**7a** (77)	**8a** (80)
2	**1**	H	1-naphthyl	A then C	**7b** (52)	**8b** (80)
3	**1**	H	cyclohexyl	A then C	**7c** (55)	**8c** (60)
4	**1**	H	hexyl	A then C	**7d** (25)	**8d** (70)
5	**2**	hexyl	cyclohexyl	A then C	**7e** (26)[c]	**8e** (80)
6	**2**	hexyl	hexyl	A then C	**7f** (25)[c]	**8f** (70)
7	**3**	$C_6H_{13}C(O)$	phenyl	A then C	**7g** (43)	**8g** (59)
8	**3**	$C_6H_{13}C(O)$	$-CH{=}CHC_5H_{11}$	A then C	**7h** (40)	decomp[d]
9	**3**	$C_6H_{13}C(O)$	$-CH{=}C(CH_3)_2$	B then C	**7i** (69)	decomp[d]
10	**3**	$C_6H_{13}C(O)$	$-CH_2CH(CH_3)CH_2C(CH_3)_3$	B then C	**7j** (71)	**8h** (63)
11	**3**	$C_6H_{13}C(O)$	adamantyl	B then C	**7k** (95)	decomp[d]
12	**3**	$C_6H_{13}C(O)$	*p*-CH_3-S-Ph	B then C	**7l** (85)	**8i** (73)
13	**4**	$C_3H_7CH{=}CHC(O)$	phenyl	A then D	**7m** (52)	decomp[d]
14	**4**	$C_3H_7CH{=}CHC(O)$	decanoyl	A then D	**7n** (15)	**8j** (91)
15	**4**	$C_3H_7CH{=}CHC(O)$		E		**8j** (85)
16	**4**	$C_3H_7CH{=}CHC(O)$		F		**8j** (60)
17	**1**	H	hexyl	E	decomp[d]	
18	**2**	hexyl	hexyl	E	decomp[d]	
19	**3**	$C_6H_{13}C(O)$	hexyl	E		**8k** (94)
20	**5**	2-$CH_3CC_6H_4(O)$	octyl	E		**8l** (92)
21	**6**	*t*-BuOC(O)	decanoyl	E		**8m** (76)
22	**8m**	*t*-BuOC(O)	H	G		**8n** (63)

[a]Reaction conditions in Scheme 1. [b]Isolated yield(%). [c]About 10−20% of unidentified side product(s) was observed in the ^1H NMR spectrum after column chromatography, and the impure *O*-acyl tetramic acids were used without further purification for the next step. [d]After the reaction, complicated TLC spots without starting tetramic acid were observed.

and Table 1).[13c,e] *O*-Acylation of **1**, **2**, **3**, and **4** was achieved with the appropriate carboxylic acids in the presence of DCC with a catalytic amount (0.1 equiv) of DMAP (Method A)[13c] or the appropriate acid chloride in the presence of triethylamine (Method B).[13e] The yields from Method A strongly depended on the identity of the carboxylic acid (R^2 group) but not the nature of the R^1 substituent at N(1). Thus, the reactions of **1**, **3**, and **4** with aromatic and α-olefinic carboxylic acids were better (entries 1, 2, 7, 8, and 13, about 75−40%) than those of **1**, **2**, and **4** with linear alkyl carboxylic acids (entries 4, 6, and 14, about 25−15%). In the case of the reaction with cyclohexyl carboxylic acid, the yields were between 25% and 55% (entries 3 and 5). On the other hand, *O*-acylation of **3** using the acid chloride and triethylamine (Method B) gave uniformly high yields with various R^2 groups, including aromatic, α-olefinic, linear alkyl, and bulky alkyl (entries 9−12, 70−95%). For the practical synthesis of *O*-acyl tetramic acids, however, Method B using the acid chloride is better than Method A on the basis of better yields as well as the simplicity of purification by column chromatography or crystallization without the complicating urea as a byproduct.

With the *O*-acyl derivatives in hand, Fries-type migration of the *O*-acyl tetramic acids using a catalytic amount (0.5 equiv) of acetone cyanohydrin in the presence of triethylamine (2.0 equiv) in acetonitrile, according to the previous

TABLE 2. Preparation of 3-Acyltetramic Acids from Tetramic Acids 3 and 5 with Various Carboxylic Acids[a]

Tetramic acids 3 and 5 **3-Acyl tetramic acids 9a-j**

Method E: R^2CO_2H (1.1 equiv), DCC (1.1 equiv), DMAP (1.3 equiv), CH_2Cl_2, r.t.

entry	tetramic acid	R^2	3-acyltetramic acid/yield (%)[b]
1	**3** (R^1 = C_6H_{13})	cyclohexyl	decomp[c]
2	**3** (R^1 = C_6H_{13})	*tert*-butyl	decomp[c]
3	**3** (R^1 = C_6H_{13})	cyclohexaneacetyl	**9a** (74)
4	**3** (R^1 = C_6H_{13})	2-norbornaneacetyl	**9b** (77)
5	**3** (R^1 = C_6H_{13})	1-adamantaneacetyl	**9c** (57)
6	**3** (R^1 = C_6H_{13})	-CH_2CO_2Et	**9d** (33)
7	**3** (R^1 = C_6H_{13})	-CH_2NHBoc	**9e** (63)
8	**3** (R^1 = C_6H_{13})	-$CH_2(OC_2H_4)_2OCH_3$	**9f** (38)
9	**3** (R^1 = C_6H_{13})	3-indoleacetyl	**9g** (57)
10	**3** (R^1 = C_6H_{13})	phenyl	decomp[c]
11	**3** (R^1 = C_6H_{13})	1-naphthyl	decomp[c]
12	**3** (R^1 = C_6H_{13})	benzyl	decomp[c]
13	**3** (R^1 = C_6H_{13})	-$(CH_2)_4Ph$	**9h** (76)
14	**5** (R^1 = 2-$CH_3C_6H_4$)	-CH=CH-C_5H_{11}	decomp[c]
15	**5** (R^1 = 2-$CH_3C_6H_4$)	-CH_2CH=CHC_2H_5	**9i** (67)
16	**5** (R^1 = 2-$CH_3C_6H_4$)	-$(CH_2)_4CH$=CH_2	**9k** (77)

[a]See Scheme 1 for reaction conditions. [b]Isolated yield. [c]After the reaction, complex TLC spots without starting tetramic acid were observed.

report,[13e] was then tried (Method C); only one example (R^2 = phenyl) using this approach had previously been described. The yields of Method C (Table 1) were found to depend on the nature of the acyl group (R^2) rather than the substituent at N(1) (R^1). The phenyl, linear, and cyclic alkyl R^2 groups of **1**, **2**, and **3** derivatives gave uniformly high yields (entries 1−7, 10, and 12, 60−80%), and purification could be easily achieved using acid−base extraction for the **1** series, washing with basic and acidic water for the **2** series, and column chromatography for the **3** series. On the other hand, α-olefinic and adamantyl derivatives, sterically hindered at the α-position, failed (entries 8, 9, and 11). Although in the case of **7i**, a 10% yield of the corresponding 3-acyl tetramic acid was obtained as about a 1:1 mixture along with an unidentified and inseparable side product, for **7k** only starting tetramic acid **3** was recovered.

Noteworthy is that we were able to significantly optimize these reaction conditions with linear alkyl carboxylic acids. Thus, the acylation reactions of *N*-acyl tetramic acids **3**, **4**, **5**, and **6** with linear alkyl carboxylic acids using 1.3 equiv of DMAP with DCC (1.1 equiv) in dichloromethane gave not the expected *O*-acyl tetramic acids but the corresponding 3-acyltetramic acids directly and generally with high yields (about 76−94%) (Method E, entries 15 and 19−21), whereas the acylation reactions of **1**, **2**, and **4** with linear alkyl carboxylic acids by Method A (with a catalytic amount of DMAP) gave the corresponding *O*-acyl tetramic acids in low yields as described above (entries 4, 6, and 14). This change in reactivity was traced to the use of different amounts of DMAP (ranging from 0.1 to 1.3 equiv). In a comparison of the yields for the synthesis of the *N*-unsubstituted 3-acyltetramic acids, Method E then G for **8n** (48% yield in two steps from **6**, entries 21 and 22) is more efficient than Method A then C for **8d** (18% yield in two steps from **1**, entry 4). Disappointingly, when these new conditions (Method E) were applied to the reaction of *N*-unsubstituted tetramic acids **1** and *N*-hexyl-substituted tetramic acids **2** with alkyl carboxylic acids (entries 17 and 18), neither the *O*-acyl nor the 3-acyltetramic acids were obtained, indicating that the yields of Method E were strongly dependent upon the R^1 substituent group at N(1). Of interest is that *N*-unsubstituted 3-alkyl tetramic acid **8n** could be obtained via the acid-mediated deprotection of the corresponding *N*-Boc 3-acyltetramic acid **8m** (entry 22).

After demonstrating that these conditions are applicable for the acylation of variously substituted tetramic acids, most importantly *N*-acyl ones, we examined the range of suitable carboxylic acids with *N*-acyl tetramic acids **3** and **5** and found that the yields of Method E were strongly dependent on the identity of the carboxylic acid (R^2 group) (Table 2). Although the reaction with alkyl carboxylic acids that are sterically hindered at the α-position such as cyclohexyl carboxylic acid and pivalic acid did not give the desired product(s) (entries 1 and 2), those that were sterically hindered at the β-position such as cyclohexaneacetic acid, 2-norbornaneacetic acid, and 1-adamantaneacetic acid did give the desired 3-acyltetramic acids with reasonable yields (entries 3−5). In the case of unsaturated acids, the α-unsaturated carboxylic acid did not give the desired product (entry 14), whereas the β-unsaturated as well as the terminal olefinic carboxylic acids did and in good yields (entries 15 and 16). Moreover, the reaction with carboxylic acids possessing various functional groups at the β-position, such as ester, *N*-Boc, ether, and 3-indole functionality, successfully produced 3-acyltetramic acids (entries 6−9). Lastly, in the case of the aromatic acid derivatives, the reaction with 5-phenylvaleric acid gave the desired product (entries 13), whereas the reaction with benzoic acid, 1-naphthoic acid, and phenylacetic acid (entries 10−12) did not.

In order to further develop these new reaction conditions (Method E), the acylation of *N*-acyl tetramic acid **4** with decanoic acid in the presence of 0.5 equiv of DMAP (rather than 0.1 or 1.3 equiv, Method F) was carried out and gave not the *O*-acyl tetramic acid **7n** but instead 3-acyltetramic acid **8j** directly in 60% yield (Table1, entry 16), consistent with DMAP playing a role as a catalyst for the acyl migration. Interestingly, the treatment of *O*-acyl tetramic acid **7n** with only 1.3 equiv of DMAP (Method D) gave the acyl compound **8j** in high yield (Table 1, entry 14), whereas the same reaction of *O*-acyl tetramic acid **7m** did not give acyl migration but led only to decomposition (Table 1, entry 13). These results were consistent with the corresponding reactions of *N*-acyl tetramic acids with alkyl (good yield, Table 1, entries 15, 19, 20, and 21) and aromatic (decomposition, Table 2, entries 10 and 11) carboxylic acids. Even though the byproduct(s) in the case of the reactions giving low yields and decomposition for Methods A, C, and E could not be identified, a few possible side-reactions may be competitive with the desired process; thus, the dimerization of tetramic acids,[5,15a] as well as side reactions of *O*-acyl tetramic acids, such as internal Michael reaction of α-olefin[13b] and double-bond migration to the C(5) position[15b] under basic conditions, have all been reported. In the case of Method E with the *N*-acyl tetramic acids and alkyl carboxylic acids, the use of excess amounts of DMAP appears not only to induce the acyl migration but also prevents such side reactions and permits efficient overall conversion. These results clearly extend the synthetic scope of the original Hori report[13b] by the use of excess amounts of DMAP and DCC although the efficiency of the method is strongly sensitive to the identity of both the carboxylic acid and the nitrogen substituent; this is likely to be of importance in the synthesis of both natural and unnatural 3-acyl tetramic acids.

In the course of this work, we found that the ^{1}H NMR spectra of the product *N*-acyl 3-acyltetramic acids after silica gel column chromatography were extremely broad in $CDCl_3$, and the ^{13}C NMR signals, especially for carbonyl groups, were very weak, whereas those of the 3-acyltetramic acids prepared from **1** and **2** prepared without silica gel column chromatography were sharp. Optimization of the NMR conditions with different solvents (acetone-d_6, methanol-d_4, CH_3CN, and DMSO), temperature (218, 253, 300, and 363 K), and concentration (1, 5, and 10 mg/mL) failed to improve the spectra (see S-Figure 1 in Supporting Information). We initially attributed this phenomenon to well-documented dynamic internal tautomerization and rotameric effects,[3a,5,13d,17] but recent papers describing the isolation of 3-acyltetronic acids as the calcium-chelated and 3-acyltetramates as metal-chelated forms after silica gel chromatography and their conversion to the free form by treatment with 0.5 N aqueous hydrochloric acid caused us to re-examine our own work.[18] In fact, the high affinity of 3-acyl tetramic acids for metal cations, including the existence of metal-chelated natural products,[3a,m] has been reported.[3j] With those clues, we suspected that our 3-acyl tetramic acids might become metal-chelated during chromatographic purification, and washing of 3-acyltetramic acids after silica gel chromatography with aqueous hydrochloric acid ($3 < pH < 5$) and comparison of before and after NMR spectra clearly showed much improved signal resolution and sharpness and improved intensity of carbonyl signals; this simple procedure therefore provides direct access to the tetramates as the nonchelated form. Furthermore, melting point and solubility were also changed; for example, in the case of **8k**, melting point after silica gel chromatography was higher with a broad range (170−210 °C) compared with that after acidic washing (47−50 °C), and solubility in acetone was also improved after acidic washing. This method therefore provides rapid access to functionalized tetramates with two points of diversity, on the nitrogen and at C(3). The approach is applicable for a wide range of alkyl, aryl, and acyl groups at these points, and although the isolation of metal chelate salts at the end of the sequence was frequently observed, the free tetramate may be readily accessed by washing with acid.

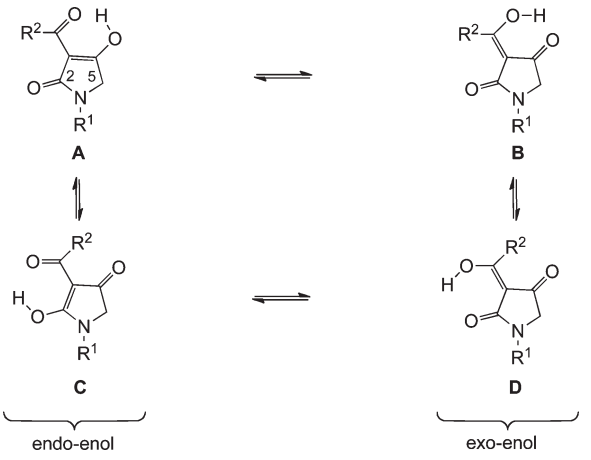


FIGURE 3. Tautomerisation in 3-acyltetramic acids.

Tautomerism. 3-Acyltetramic acids can exist as four types of tautomeric enol, forms A−D, in solution (Figure 3).[3a,10a,19−21] The predominance of the exo-enol tautomeric forms B and D, stabilized by an intramolecular hydrogen bond that contributes as much as 8.8 kcal/mol, has been demonstrated by Gromak for *N*-H and *N*-Me systems,[21] as estimated by

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TABLE 3. Selected ^{13}C NMR Data of Representative 3-Acyltetramic Acids, Grouped by External Pairs AB and CD

		C(2)		C(4)		3-acyl			
entry	compound	AB	CD	AB	CD	AB	CD	solvent	ratio AB:CD[a,b]
1	**8a**		177.1		193.1		182.6	CD_3OD	1:99 (D)
2	**8c**	170.5	176.8	199.3	192.6	196.2	192.6	$CDCl_3$	25:75 (B, D)
3	**8d**	170.3	176.4	198.8	192.8	192.9	189.1	$CDCl_3$	20:80 (B, D)
4	**8e**		173.9		191.5		191.3	$CDCl_3$	10:90 (D)
5	**8f**		173.4		191.6		187.9	$CDCl_3$	10:90 (D)
6	**8g**	164.7	175.4	196.9	187.4	189.2	183.3	$CDCl_3$	55:45 (AB, D)
7	**8k**	165.4	173.4	194.1	189.2	198.1	192.5	$CDCl_3$	55:45 (AB, D)
8	**8j**	165.6	173.6	194.2	189.3	198.2	192.7	$CDCl_3$	55:45 (AB, D)
9	**8l**	164.2	172.6	194.4	188.9	198.3	193.1	$CDCl_3$	55:45 (AB, D)
10	**8m**	164.3	173.3	193.9	189.1	197.5	192.2	$CDCl_3$	40:60 (AB, D)
11	**9d**	165.1	172.6	190.7	189.2	191.0	181.1	$CDCl_3$	70:30 (AB, D)
12	**9e**	165.0	173.2	187.9	189.2	196.3	195.2	$CDCl_3$	75:25 (AB, D)
13	**9f**	165.2		188.3		196.9		$CDCl_3$	99:1 (AB)

[a]Determined by the intensity of C(5) protons in ^1H NMR spectra. [b]Parentheses indicate the major contributing tautomers in each external tautomer.

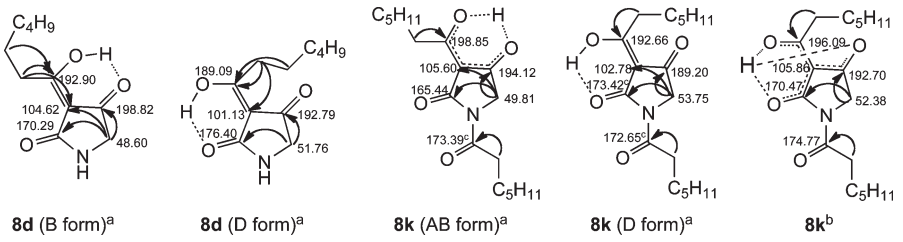

FIGURE 4. HMBC correlation of **8d** and **8k**: ([a]) $CDCl_3$ and ([b]) CD_3OD. [([c]) Chemical shifts are tentatively assigned].

AM1 calculations. Moreover, these authors showed that the order of stability for the different tautomeric possibilities is D > B > C > A, with the difference in energies between D and B estimated to lie in the range 0.5−2.1 kcal/mol; on the other hand, tautomers C and A are so high in energy (4−7.8 kcal/mol) that they are unlikely to be present at equilibrium at greater than 0.2%. The authors assigned the carbonyl region of the IR spectra of *N*-H and *N*-Me 3-acetyltetramates as 1718 (C=O), 1659 (lactam C=O), and 1631 (exo-enol C=C) cm^{-1} to the main exo-enol tautomeric form D with a stabilizing hydrogen bond to the lactam carbonyl, although they note that a second form, presumed to be the alternative exo-enol B, is detectable as a result of the presence of shoulders and additional weak peaks; by the nature of the IR experiment, quantification of the relative contributions of each tautomer to confirm the molecular mechanics calculations was not possible. Even though previous reports have recognized the existence of this phenomenon, the effects of R^1 and R^2 groups on the position of the tautomeric equilibrium have not been studied in detail, and since the synthetic protocol reported herein provided access to an unprecedented range of compounds, a detailed investigation was warranted. We expected that NMR spectroscopic analysis might be more useful than IR, especially for quantitative examination of the tautomeric ratio, despite the fact that it has been noted[21] that literature NMR assignments have been inconsistent and ambiguous.[3a,10a,19,20] For this reason, and in particular the fact that no *N*-acyl systems had been previously examined, we conducted a detailed NMR and molecular mechanics analysis to elucidate the substituent effect on tautomerism.

Each tautomeric pair (AB and CD) can be usually easily distinguished by NMR spectroscopy, since each pair differs from the other both by conformational and tautomeric interchange, whereas each set of internal tautomers (A ↔ B and C ↔ D), which differ only by proton transfer, are generally observed as an averaged hybrid structure because of their rapid interconversion on the NMR time scale. The ratio of contributors in the hybrid structure can be calculated when the chemical shifts of each internal tautomer are known accurately, but this is not usually the case.[19a,b] Therefore, in this study, the ratio of the internal tautomers was determined from their estimated chemical shifts. Two sets of signals for the external tautomers, especially the protons on C(5) in the ^1H NMR and the signals of the carbonyl region in the ^{13}C NMR spectra are usually distinguishable, and their ratio can be determined from the intensity of each of the C(5)-protons. This tautomeric assignment was made by comparison with previously reported NMR data of 3-acyltetramic acids[10a,19] as well as by consideration of inductive effects. The hydrogen-bonded carbonyl on C(4) in form B and C(2) in form D should resonate more downfield than the corresponding free carbonyl on C(4) in forms C and D and C(2) in forms A and B, while the enolic carbonyl on C(4) in form A should occur at higher field than the corresponding free carbonyl in forms C and D. For the same reason, the hydrogen-bonded carbonyl of the 3-acyl group in forms A and C should occur more downfield than the corresponding enolic carbonyl in forms B and D.[10a,19] Furthermore, the chemical shift of C(2) in tautomeric pair AB and of C(4) in pair CD are only weakly affected by changes in the hybridization or remote atoms, and therefore they show the normal chemical shift of the free carbonyl. Using this analysis, it has been possible to determine the favored tautomers of 3-acyltetramic acids and show that the ratio depends on both the different substituent groups on N(1) and the 3-acyl group.

In the ^{13}C NMR study, two sets of the signals for each external tautomer or one set resulting from the presence of

TABLE 4. Calculated Energy and Dipole Moments of the Ground State of Some 3-Acyltetramic Acids

		calcd relative energy (kcal/mol)[a,b] (dipole moment (Debye)[b]			
entry	compound	form A	form B	form C	form D
1	**8d**	+3.80[b] (2.75)	+1.43[b] (1.41)	+4.03[b] (3.78)	0[b] (1.54)
2	**8f**	+3.64[b] (2.89)	+1.37[b] (1.50)	+3.88[b] (4.54)	0[b] (1.88)
3	**8k**	+1.44[b] (1.10)	−0.01[b] (2.76)	+5.28[b] (2.00)	0[b] (2.47)
4	**8m**	+1.65[b] (0.82)	+0.81[b] (1.86)	+4.29[b] (3.33)	0[b] (1.62)

[a]The energy difference between the each tautomer related to tautomer D. [b]Calculated by using DFT B3LYP (6-31G*) in Spartan 02.

only one external tautomer or a low concentration of the minor one were observed. Table 3 shows the ^{13}C chemical shifts of the C(2), C(4), and 3-acyl carbonyl carbons for representative compounds, and these proved to be very valuable for the structure elucidation. In order to assign relevant chemical shifts, HMBC NMR spectra of representative compounds were acquired, and their correlation to the main heterocyclic ring was determined as shown in Figure 4 (see also S-Figure 2 in Supporting Information); this allowed confident assignment for the main molecular skeleton. All of the *N*-unsubstituted and *N*-hexyl 3-acyltetramic acids were found to prefer form D with only a minor contribution from form B (Table 3, entries 1−5). In the chemical shifts of **8d** (entry 3 and Figure 4), for example, the free carbonyl on C(4) (about 192 ppm), the hydrogen-bonded amide on C(2) (about 176 ppm) in form D, the hydrogen-bonded carbonyl on C(4) (about 199 ppm), and the free amide on C(2) (about 170 ppm) in form B and the enolic carbonyl on 3-acyl group (about 190 ppm) in both forms were readily assigned, and importantly, this assignment coincided well with previous reports.[19a−d] In the same manner, *N*-acyl 3-acyltetramic acids derivatives with *n*-alkyl and phenyl groups on the 3-acyl position were found to exist as both external tautomers in a ratio of about 50:50 (entries 6−10). In this case, two sets of signals were apparent, and each set could be assigned to the appropriate external tautomer. For example, two sets of signals in **8k** were assigned to tautomeric forms AB and D (entry 7 and Figure 4); in the AB external tautomer, the chemical shift on C(2) (165.44 ppm) arose more upfield than that of the hydrogen-bonded carbonyl on C(2) in tautomer D (173.42 ppm). In addition, the signal of C(4) (194.12 ppm) arose between the chemical shift of form A (about 185 ppm)[3a] and form B (about 200 ppm), and the signal of the 3-acylcarbonyl (198.85 ppm) arose between the chemical shift in form A (about 205 ppm) and in form B (about 190 ppm). In the D external tautomer, the chemical shift on C(4) (189.20 ppm) corresponded to the expected chemical shift for the free carbonyl on C(4) (about 190 ppm), and the signal on C(2) (173.42 ppm) arose in the expected range for the hydrogen-bonded carbonyl on C(2) (about 175 ppm; higher field than the free carbonyl on C(2)). In addition, the ratio of two external tautomers changed with variation of the 3-acyl group. The ratio of **9a**, **9b**, **9c**, and **9g** was similar to that of **8k** (that is, approximately equal amounts of each external tautomer), whereas for **9d**,**e**, in which a heteroatom is introduced on the β-position, tautomer AB was significantly preferred or, in the case of **9f**, almost exclusively preferred (entries 11−13).

However, the NMR spectroscopic behavior was found to be solvent-dependent; for example, in the case of **8a**, the NMR spectrum in CD_3OD exhibits sharp signals, consistent with the presence of the most stable tautomer D (Table 3, entry 1), but for **8k** in CD_3OD solvent, although the ^1H NMR spectrum appears as one tautomer with sharp signals, in the ^{13}C NMR spectrum, the signals for C(2)−C(5) and the 3-acyl carbon were very weak and broad, and the C(3) carbon appeared as a triplet. This phenomenon may result from solvent-assisted proton transfer reactions and/or deuterium exchange.

In order to further support this NMR interpretation, especially the effect of the R^1 group, the energy of the ground state of each tautomer was calculated (Table 4). For **8d** and **8f** (entries 1 and 2), the most stable tautomer was clearly exo-enol form D, the next most stable one was form B and the pair of endo-enol tautomers C and A were least stable, with a large energy difference compared to D (2.27−4.03 kcal/mol). This result supported the above NMR interpretation for the favored tautomeric pair of BD over AB, as well as the favored internal tautomers (D over B) and fitted well with previously reported calculation results.[20] According to a previous report,[19b] the preference for tautomer D in *N*-unsubstituted and *N*-hexyl 3-acyltetramic acids can be understood by the formation of a strong intramolecular hydrogen bond of the lactam carbonyl on C(2) in form D rather than the carbonyl group on C(4) in form B. In the calculation results for *N*-acyl and *N*-Boc 3-acyltetramic acids, **8k** and **8m** (entries 3 and 4), the tautomers A and B are more stabilized compared to **8d** and **8f**; therefore the energy of tautomer B becomes similar to that of tautomer D, and the energy difference between internal tautomers A and B becomes smaller (1.45 kcal/mol for **8k** and 0.84 kcal/mol for **8m**) than that for **8d** and **8f** (2.37 and 2.27 kcal/mol respectively). This calculation result supported the similar ratio between the two external tautomers and the favored internal tautomers in each external tautomer (tautomer AB and D) in the NMR spectra of **8k** and **8m**. This phenomenon may be explained by the different electronic effects in these compounds; the ability to form a hydrogen bond with the carbonyl on C(4) is increased by the electron-withdrawing acetyl group on N(1), leading to stabilization of form B relative to D.[10c,19e] This outcome extends the results reported by Gromak who examined only *N*-H and *N*-Me substituents[21] and indicates that the presence of more highly functionalized substituents leads to smaller differences in energies between the exo-enol and endo-enol forms, presumably as a result of modified electronic and steric effects. Of interest is that the least stable tautomers were invariably the most polar as shown by calculation of the dipole moment (with the exception of **8k** (Table 4, entry 3)), but the most stable tautomers were not always the least polar (Table 4, entries 1, 2, 4).

Therefore, it may be concluded that all *N*-H and *N*-alkyl forms favor exo-enol form D, but that *N*-acyl 3-acyltetramates favor forms AB and D approximately equally, although for those with β-heteroatom functionality on the 3-acyl unit, pair AB becomes more preferred, and in one case is exclusively formed.

These results are of importance, given the recent reports of the inhibitory role of β-dicarbonyl containing compounds for several molecular targets, including RNA polymerase,[22a] UPPS,[22b] acetyl-CoA carboxylase[22c] and LuxR.[22d,e]

Experimental Section

Synthesis of 1-(2-Methylbenzoyl)pyrrolidine-2,4-dione (5). This compound was prepared by cyclization of the corresponding *N*-acyl glycine using standard methodology.[10] Yield 65%, mp 183 °C. ^{1}H NMR (400 MHz, CD_3OD, only enol form): 7.33−7.19 (m, 4H, C9−12), 4.94 (brs, 2H, C3 and OH), 4.45 (s, 2H, C5), 2.27 (s, 3H, C13). ^{13}C NMR (100 MHz, CD_3OD): 178.6 (C═O), 172.4 (C═O), 170.8 (C═O), 138.1 (C8), 135.8 (C7), 131.1 (ArCH), 130.6 (ArCH), 127.6 (ArCH), 126.5 (ArCH), 95.0 (C3), 50.0 (C5), 19.3 (C13). MS (ES^-): 216.08 (M − H). HRMS (M − H): calcd for $C_{12}H_{10}N_1O_3$; 216.0666, found 216.0664.

Synthesis of *O*-Acyl Tetramic Acids by Using Carboxylic Acid and DCC (Method A). 4-Benzoyl-pyrrolidine-2-one (7a). To a mixture of pyrrolidine-2,4-dione **1**, (0.96 g, 9.69 mmol) and benzoic acid (1.3 g, 10.7 mmol) in dichloromethane (200 mL) was added DCC (2.2 g, 10.7 mmol) and DMAP (0.13 g, 1.07 mmol). The mixture was stirred 24 h at room temperature. The crude reaction mixture was filtered with dichloromethane. Concentration *in vacuo* followed by flash column chromatography gave **7a** (1.5 g, 7.38 mmol, 25% yield) as a solid. Mp 155 °C (decomposes). ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (d, 2H, J = 7.2 Hz, ArH), 7.66 (t, 1H, J = 7.2 Hz, ArH), 7.62 (s, 1H, NH), 7.51 (t, 2H, J = 7.2 Hz, ArH), 6.17 (s, 1H, C3), 4.30 (s, 2H, C5). ^{13}C NMR (100 MHz, $CDCl_3$): 174.6 (ArC), 164.4 (ArC), 162.3 (ArC), 134.5 (ArCH), 130.3 (ArCH), 128.9 (ArCH), 127.9 (quart ArC), 108.0 (C3), 47.6 (C5). MS (ES^-): 202.1 (M − H). MS (ES^+): 204.1 (M + H). HRMS (M + Na): calcd for $C_{11}H_9N_1Na_1O_3$ 226.0483, found 226.0475.

The following were prepared using this general method:

5-Oxo-2,5-dihydro-1*H*-pyrrol-3-yl 1-Naphthoate (7b). Yield 52%, mp 158 °C. ^{1}H NMR (400 MHz, mixture of CD_3OD and $CDCl_3$): 8.93 (d, 1H, J = 8.8 Hz, ArH), 8.35 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz, ArH), 8.15 (d, 1H, J = 8.4 Hz, ArH), 7.94 (d, 1H, J = 8.0 Hz, ArH), 7.68−7.64 (m, 1H, ArH), 7.60−7.54 (m, 2H, ArH), 6.18 (s, 1H, C3), 4.34 (s, 2H, C5). ^{13}C NMR (100 MHz, mixture of CD_3OD and $CDCl_3$): 175.5 (ArC), 165.6 (ArC), 162.7 (ArC), 135.9 (ArCH), 134.4 (ArC), 132.2 (ArCH), 132.0 (ArC), 129.3 (ArCH), 128.9 (ArCH), 127.0 (ArCH), 125.4 (ArCH), 124.8 (ArCH), 124.0 (ArC), 107.3 (C3), 48.00 (C5). MS (ES^-): 252.3 (M − H); MS (ES^+): 254.3 (M + H). HRMS (M + Na): calcd for $C_{15}H_{11}N_1Na_1O_3$ 276.0631, found 276.0631.

5-Oxo-2,5-dihydro-1*H*-pyrrol-3-yl Cyclohexanecarboxylate (7c). Yield 55%, mp 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (s, 1H, NH), 5.97 (s, 1H, C3), 4.11 (s, 2H, C5), 2.51−2.44 (m, 1H, C7), 1.99−1.95 (m, 2H, CH_2), 1.81−1.77 (m, 2H, CH_2), 1.68−1.64 (m, 1H, CH_2), 1.54−1.44 (m, 2H, CH_2), 1.36−1.22 (m, 3H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 174.7 (ArC), 171.6 (ArC), 164.4 (C4), 107.3 (C3), 47.4 (C5), 43.2 (C7), 28.6 (C8 and C12), 25.5 (C9 and C11), 25.2 (C10). MS (ES^-): 208.1 (M − H). MS (ES^+): 210.1 (M + H). HRMS (M + Na): calcd for $C_{11}H_{15}N_1Na_1O_3$ 232.0942, found 232.0944.

5-Oxo-2,5-dihydro-1*H*-pyrrol-3-yl Heptanoate (7d). Yield 25%, mp 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (s, 1H, NH), 5.91 (s, 1H, C3), 4.11 (s, 2H, C5), 2.49 (t, 2H, J = 7.2 Hz, C7), 1.71−1.63 (m, 2H, C8), 1.36−1.24 (m, 6H, C9−11), 0.87 (t, 3H, J = 6.8 Hz, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 174.6 (ArC), 169.3 (ArC), 164.2 (C4), 107.4 (C3), 47.4 (C5), 34.2 (C7), 31.3 (C8), 28.6 (C9), 24.4 (C10), 22.4 (C11), 14.0 (C12). MS (ES^+): 212.1 (M + H). HRMS (M + Na): calcd for $C_{11}H_{17}N_1Na_1O_3$ 234.1100, found 234.1101.

1-Hexyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Cyclohexanecarboxylate (7e). Yield 26% (with about 10% of inseparable impurity). ^{1}H NMR (400 MHz, $CDCl_3$): 5.91 (s, 1H, C3), 4.05 (s, 2H, C5), 3.38 (t, 2H, J = 7.2 Hz, C6), 2.48−2.41 (m, 1H, C13), 1.96−1.89 (m, 2H, C7), 1.79−1.71 (m, 2H, C16), 1.53−1.41 (m, 4H, C14 and C18), 1.31−1.18 (m, 10H, C8−10, C15 and C17), 0.85 (t, 3H, J = 6.8 Hz, C11). ^{13}C NMR (100 MHz, $CDCl_3$): 171.7 (ArC), 170.8 (ArC), 161.8 (C4), 107.7 (C3), 51.0 (C5), 43.2 (C13), 41.5 (C6), 31.5 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 14.0 (C11).

1-Hexyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Heptanoate (7f). Yield 25% (with about 20% of inseparable impurity). ^{1}H NMR (400 MHz, $CDCl_3$): 5.92 (s, 1H, C3), 4.04 (s, 2H, C5), 3.38 (t, 2H, J = 7.2 Hz, C6), 2.46 (t, 2H, J = 7.6 Hz, C13), 1.69−1.48 (m, 4H, C7, C14), 1.34−1.20 (m, 12H, C8−10 and C15−17), 0.87−0.81 (m, 6H, C11 and C18). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8 (ArC), 169.4 (ArC), 161.6 (C4), 107.7 (C3), 51.0 (C5), 41.5 (C6), 34.2 (C13), 31.5 (CH_2), 31.3 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 24.4 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 14.0 (C11 and C18).

1-Heptanoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Benzoate (7g). Yield 43%, mp 106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.11 (d, 2H, J = 8.0 Hz, C15 and C19), 7.69 (t, 1H, J = 7.2 Hz, C17), 7.53 (t, 2H, J = 7.6 Hz, C16 and C18), 6.23 (s, 1H, C3), 4.55 (s, 2H, C5), 2.96 (t, 2H, J = 7.6 Hz, C7), 1.71−1.64 (m, 2H, C8), 1.41−1.31 (m, 6H, C9−11), 0.88 (t, 3H, J = 6.4 Hz, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 173.0 (ArC), 169.0 (ArC), 164.5 (ArC), 161.9 (ArC), 134.8 (C17), 130.4 (C15 and C19), 128.9 (C16 and C18), 127.4 (C14), 107.7 (C3), 48.9 (C5), 36.8 (C7), 31.5 (C10), 28.8 (C9), 24.1 (C8), 22.5 (C11), 14.0 (C12). MS (ES^+): 316.16 (M + H). HRMS (M + Na): calcd for $C_{18}H_{21}N_1Na_1O_4$ 338.1363, found 338.1363.

(*E*)-1-Heptanoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Oct-2-enoate (7h). Yield 40%, mp 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.32−7.23 (m, 1H, C15), 6.14 (s, 1H, C3), 5.96 (d, 1H, J = 15.6 Hz, C14), 4.46 (s, 2H, C5), 2.97 (t, 2H, J = 7.2 Hz, C7), 2.33 (q, 2H, J = 7.6 Hz, C16), 1.74−1.66 (m, 2H, C8), 1.58−1.51 (m, 2H, C17), 1.42−1.34 (m, 10H, C9−11, C18 and C19), 0.95−0.90 (m, 6H, C12 and C20). ^{13}C NMR (100 MHz, $CDCl_3$): 172.9 (ArC), 169.2 (ArC), 164.5 (ArC), 161.5 (ArC), 155.6 (C15), 118.7 (C14), 107.1 (C3), 48.8 (C5), 36.8 (C7), 32.6 (C16), 31.5 (CH_2), 31.2 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 14.0 (CH_3), 13.9 (CH_3). MS (ES^+): 336.25 (M + H), 358.22 (M + Na). HRMS (M + Na): calcd for $C_{19}H_{29}N_1Na_1O_4$ 358.1989, found 358.1989.

(*E*)-1-(Hex-2-enoyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Benzoate (7m). Yield 52%, mp 121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (d, 2H, J = 7.6 Hz, C14 and C18), 7.70 (t, 1H, J = 7.6 Hz, C16), 7.54 (t, 2H, J = 7.6 Hz, C15 and C17), 7.36 (d, 1H, J = 15.6 Hz, C7), 7.25−7.17 (m, 1H, C8), 6.27 (s, 1H, C3), 4.62 (s, 2H, C5), 2.29 (q, 2H, J = 7.2 Hz, C9), 1.59−1.50 (m, 2H, C10), 0.97 (t, 3H, J = 7.2 Hz, C11). ^{13}C NMR (100 MHz, $CDCl_3$): 169.4 (ArC), 164.9 (ArC), 164.7 (ArC), 161.9 (ArC), 151.2 (C8), 134.9 (C14 and C18), 130.5 (C16), 129.0 (C15 and C17), 127.5 (C13), 122.4 (C7), 107.9 (C3), 49.2 (C5), 34.7 (C9), 21.5 (C10), 13.8 (C11). MS (ES^+): 300.1 (M + H). HRMS (M + Na): calcd for $C_{17}H_{17}N_1Na_1O_4$ 322.1050, found 322.1037.

(*E*)-1-Hex-2-enoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Decanoate (7n). was obtained as a solid (0.05 g, 0.15 mmol, 15%) from (*E*)-1-hex-2-enoylpyrrolidine-2,4-dione **4** (0.20 g, 1.0 mmol). Mp 68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 (d, 1H, J = 15.2 Hz, COCH═CH), 7.21−7.14 (m, 1H, COCH═CH), 6.09 (s, 1H, C3), 4.45 (s, 2H, C5), 2.55 (t, 2H, J = 7.2 Hz, $COCH_2$), 2.27 (q, 2H, J = 7.2 Hz, CH═CHCH_2), 1.74−1.66 (m, 2H, $COCH_2CH_2$), 1.58−1.48 (m, 2H, CH═$CHCH_2CH_2CH_3$), 1.38−1.24 (m, 12H, $CO(CH_2)_2(CH_2)_6CH_3$), 0.95 (t, 3H, J = 8.0 Hz, $CH(CH_2)_2CH_3$), 0.88 (t, 3H, J = 6.8 Hz, $CO(CH_2)_8CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 169.4 (ArC), 169.1 (ArC), 164.9 (ArC), 164.5 (ArC), 151.1 (COCH═CH), 122.4 (COCH═CH),

107.4 (C3), 49.0 (C5), 34.7 (CH_2), 34.3 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 24.4 (CH_2), 22.7 (CH_2), 21.5 (CH_2), 14.1 (CH_3), 13.7 (CH_3). MS (ES^+): 350.2 (M + H). HRMS (M + Na): calcd for $C_{20}H_{31}N_1Na_1O_4$ 372.2145, found 372.2139.

Synthesis of *O*-Acyl Tetramic Acids by Using Acid Chloride (Method B). 1-Heptanoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3-Methylbut-2-enoate (7i). To a mixture of 1-heptanoylpyrrolidine-2,4-dione **3** (250 mg, 1.18 mmol) and triethylamine (130 mg, 1.30 mmol) in dichloromethane (50 mL) was slowly added 3,3-dimethylacryloyl chloride (155 mg, 1.30 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature. The crude reaction mixture was extracted with acidic water (1 N HCl). The organic layer concentrated *in vacuo* followed by flash column chromatography gave **7i** (240 mg, 0.818 mmol, 69% yield) as a solid. Mp 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 6.08 (s, 1H, C3), 5.80 (s, 1H, HC=C(CH_3)$_2$), 4.39 (s, 2H, C5), 2.93 (t, 2H, J = 6.8 Hz, CO-$CH_2C_5H_{11}$) 2.24 (s, 3H, HC=C(CH_3)$_2$), 2.01 (s, 3H, HC=C(CH_3)$_2$), 1.70−1.62 (m, 2H, CO−$CH_2CH_2C_4H_9$), 1.40−1.30 (m, 6H, CO-$C_2H_4C_3H_6CH_3$), 0.88 (t, 3H, J = 6.8 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 173.0 (C=O), 169.5 (C=O), 164.9 (ArC), 164.8 (ArC), 160.9 (HC=C(CH_3)$_2$), 113.4 (HC=C(CH_3)$_2$), 106.5 (C3), 48.9 (C5), 36.8 (CO-$CH_2C_5H_{11}$), 31.5 (CH_2), 28.9 (CH_2), 27.9 (HC=C(CH_3)$_2$), 24.2 (CH_2), 22.5 (CH_2), 20.9 (HC=C(CH_3)$_2$), 14.0 (CH_3). MS (ES^+): 294.17 (M + H), 316.14 (M + Na). HRMS (M + Na): calcd for $C_{16}H_{23}N_1Na_1O_4$ 316.1519, found 316.1520.

The following were prepared using Method B:

1-Heptanoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,5,5-Trimethylhexanoate (7j). Yield 71% (oil). ^{1}H NMR (400 MHz, CD_3Cl): 6.07 (s, 1H, C3), 4.39 (s, 2H, C5), 2.93 (t, 2H, J = 7.2 Hz, C7), 2.54 (dd, 1H, J_1 = 15.6 Hz, J_2 = 6.0 Hz, C14), 2.37 (dd, 1H, J_1 = 15.6 Hz, J_2 = 7.6 Hz, C14), 2.14−2.06 (m, 1H, C15), 1.70−1.63 (m, 2H, C8), 1.38−1.30 (m, 6H, C9−11), 1.25−1.16 (m, 2H, C17), 1.04 (d, 3H, J = 6.8 Hz, C16), 0.92−0.86 (m, 12H, C12 and C19−21). ^{13}C NMR (100 MHz, CD_3Cl): 173.0 (ArC), 169.2 (ArC), 168.2 (ArC), 164.3 (ArC), 107.3 (C3), 50.3 (C17), 48.8 (C5), 43.7 (C14), 36.8 (C7), 31.6 (CH_2), 31.0 (C18), 29.8 (C19−21), 28.9 (CH_2), 26.8 (C15), 24.2 (CH_2), 22.6 (C16), 22.5 (CH_2), 14.0 (C12). MS (ES^+): 352.26 (M + H), 374.21 (M + Na). HRMS (M + Na): calcd for $C_{20}H_{33}N_1Na_1O_4$ 374.2302, found 374.2297.

1-Heptanoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Adamantane-1-carboxylate (7k). Yield 95%, mp 103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 6.05 (s, 1H, C3), 4.40 (s, 2H, C5), 2.93 (t, 2H, J = 7.6 Hz, C7), 2.08 (br s, 3H, C16, C18 and C20), 1.96 (d, 6H, J = 2.4 Hz, C15, C21 and C22), 1.79−1.70 (m, 6H, C17, C19 and C23), 1.68−1.63 (m, 2H, C8), 1.40−1.28 (m, 6H, C9−11), 0.88 (t, 3H, J = 7.2 Hz, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 173.0 (ArC), 172.7 (ArC), 169.3 (ArC), 164.8 (ArC), 107.2 (C3), 48.8 (C5), 41.6 (C14), 38.3 (C15, C21 and C22), 36.8 (C7), 36.1 (C17, C19 and C23), 31.6 (C10), 28.9 (C9), 27.5 (C16, C18 and C20), 24.2 (C8), 22.5 (C11), 14.0 (C12). MS (ES^+): 396.21 (M + Na). HRMS (M + Na): calcd for $C_{22}H_{31}N_1Na_1O_4$ 396.2145, found 396.2141.

1-Heptanoyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 4-(Methylthio) benzoate (7l). Yield 85%, mp 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.99 (d, 2H, J = 8.8 Hz, C15 and C16), 7.31 (d, 2H, J = 8.8 Hz, C17 and C18), 6.22 (s, 1H, C3), 4.55 (s, 2H, C5), 2.97 (t, 2H, J = 7.6 Hz, C7), 2.55 (s, 3H, C20), 1.73−1.65 (m, 2H, C8), 1.42−1.30 (m, 6H, C9−11), 0.89 (t, 3H, J = 6.8 Hz, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 173.1 (ArC), 169.2 (ArC), 164.6 (ArC), 161.7 (ArC), 148.7 (C19), 130.6 (C15 and C16), 125.0 (C17 and C18), 123.0 (C14), 107.6 (C3), 48.9 (C5), 36.9 (C7), 31.6 (C10), 28.9 (C9), 24.2 (C8), 22.5 (C11), 14.6 (C20), 14.0 (C12). MS (ES^+): 384.16 (M + Na). HRMS (M + Na): calcd for $C_{19}H_{23}N_1Na_1O_4S_1$ 384.1240, found 384.1238.

Synthesis of 3-Acyltetramic Acids via Acyl Migration with Acetone Cyanohydrin and Triethylamine (Method C). 3-(α-Hydroxybenzylidene)pyrrolidine-2,4-dione (8a). To a mixture of **7a** (500 mg, 2.46 mmol) and triethylamine (500 mg, 4.92 mmol) in CH_3CN (50.0 mL) was added acetone cyanohydrin (100 mg, 1.23 mmol), and the reaction mixture was stirred for 12 h at room temperature. The crude reaction mixture was concentrated *in vacuo* and extracted with ether and 1 N NaOH. The aqueous layer was acidified with conc HCl to about pH 3−1 and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated to afford **8a** (400 mg, 1.97 mmol, 80% yield) as a solid. Form AB:CD = 1: 99 (major; D). Mp 137 °C (decomposes). ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (d, 2H, J = 7.2 Hz, ArH), 7.63 (t, 1H, J = 7.2 Hz, ArH), 7.52 (t, 2H, J = 7.2 Hz, ArH), 6.18 (brs, 1H, NH), 3.89 (s, 2H, C5). ^{1}H NMR (400 MHz, MeOH): 8.15 (d, 2H, J = 7.2 Hz, ArH), 7.62 (t, 1H, J = 7.6 Hz, ArH), 7.50 (t, 2H, J = 7.6 Hz, ArH), 3.87 (s, 2H, C5). ^{13}C NMR (100 MHz, MeOH): 193.1 (C4), 182.6 (3-acyl), 177.1 (C2), 133.5 (ArC), 133.0 (quart ArC), 129.6 (ArCH), 128.1 (ArCH), 100.6 (C3), 50.9 (C5). MS (ES^-): 202.3 (M − H). HRMS (M − H): calcd for $C_{11}H_8N_1O_3$ 202.0509, found 202.0510.

The following were prepared using Method C:

3-(Hydroxy(naphthalen-1-yl)methylene)pyrrolidine-2,4-dione (8b). Yield 80%, mp 118 °C; Form AB:CD = 20:80 (major; B, D). ^{1}H NMR (400 MHz, $CDCl_3$): 12.81 (brs, 1H, OH), 9.08−7.52 (m, 7H of ArH), 4.05 (s, 2H, C5 AB), 3.75 (s, 2H, C5 CD). ^{13}C NMR (100 MHz, $CDCl_3$): 200.2 (C4 AB), 190.6 (C4 CD), 186.6 (C6 AB), 181.7 (C6 CD), 177.2 (C2 CD), 171.7 (C2 AB), 134.1 (ArC), 133.9 (C7 AB), 133.6 (C7 CD), 132.9 (ArC), 131.6 (C13), 131.4 (ArC), 130.0 (C8), 129.2 (ArC), 128.7 (ArC), 128.0 (ArC), 127.5 (ArC), 126.5 (ArC), 126.3 (ArC), 125.9 (ArC), 125.0 (ArC), 124.6 (ArC), 105.4 (C3 AB), 101.8 (C3 CD), 51.6 (C5 CD), 48.4 (C5 AB). MS (ES^-): 252.1 (M − H). HRMS (M + Na): calcd for $C_{15}H_{11}N_1Na_1O_3$ 276.0635, found 276.0631.

3-(Cyclohexyl(hydroxy)methylene)pyrrolidine-2,4-dione (8c). Yield 59%, mp 115 °C; Form AB:CD = 25: 75 (major; B, D). ^{1}H NMR (400 MHz, $CDCl_3$): 12.84 (brs, 1H, OH), 7.49 (s, 1H, NH CD), 7.36 (s, 1H, NH AB), 3.88 (s, 2H, C5 AB), 3.74 (s, 2H, C5 CD), 3.37−3.29 (m, 1H, C7), 1.75−1.63 (m, 4H, C8 and C12), 1.50−1.11 (m, 6H, C9−11). ^{13}C NMR (100 MHz, $CDCl_3$): 199.3 (C4 AB), 196.2 (C6 AB), 192.6 (C4 CD), 192.6 (C6 CD), 176.8 (C2 CD), 170.5 (C2 AB), 103.3 (C3 AB), 99.6 (C3 CD), 51.7 (C5 CD), 48.4 (C5 AB), 41.2 (C7 AB), 40.7 (C7 CD), 28.4 (C8 AB and C12 AB), 28.4 (C8 CD and C12 CD), 25.5 (C9 AB, C11 AB), 25.4 (C9 CD and C11 CD), 25.2 (C10 CD), 25.2 (C10 AB). MS (ES^-): 208.1 (M − H). MS (ES^+): 210.1 (M + H). HRMS (M + Na): calcd for $C_{11}H_{15}N_1Na_1O_3$ 232.0946, found 232.0944.

3-(1-Hydroxyheptylidene)pyrrolidine-2,4-dione (8d). Yield 70%, mp 118 °C. Form AB:CD = 20:80 (major; B, D). ^{1}H NMR (400 MHz, $CDCl_3$): 12.76 (brs, 1H, OH), 7.35 (s, 1H, NH CD), 7.19 (s, 1H, NH AB), 3.89 (s, 2H, C5 AB), 3.75 (s, 2H, C5 CD), 2.83 (t, 2H, J = 7.2 Hz, C7 AB), 2.77 (t, 2H, J = 7.6 Hz, C7 CD), 1.63−1.55 (m, 2H, C8), 1.35−1.28 (m, 2H, C9), 1.24−1.19 (m, 4H, C10−11), 0.81 (t, 3H, J = 7.2 Hz, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 198.8 (C4 AB), 192.9 (C6 AB), 192.8 (C4 CD), 189.1 (C6 CD), 176.4 (C2 CD), 170.3 (C2 AB), 104.6 (C3 AB), 101.1 (C3 CD), 51.8 (C5 CD), 48.6 (C5 AB), 33.6 (C7 AB), 32.8 (C7 CD), 31.4 (C8 AB), 31.4 (C8 CD), 28.9 (C9), 25.9 (C10 CD), 25.5 (C10 AB), 22.4 (C11), 14.0 (C12). MS (ES^-): 210.1 (M − H). HRMS (M + Na): calcd for $C_{11}H_{17}N_1Na_1O_3$ 234.1102, found 234.1101.

3-(Cyclohexyl(hydroxy)methylene)-1-hexylpyrrolidine-2,4-dione (8e). Yield 80%, mp 53 °C; Form AB:CD = 10:90 (major; D). ^{1}H NMR (400 MHz, $CDCl_3$): 3.76 (s, 2H, C5 AB), 3.62 (s, 2H, C5 CD), 3.35 (t, 2H, J = 7.6 Hz, C6), 1.76−1.13 (m, 19H, C7−10 and C13−18), 0.82 (t, 3H, J = 7.2 Hz, C11). ^{13}C NMR (100 MHz, $CDCl_3$, only CD form): 191.5 (C4), 191.3 (C12),

173.9 (C2), 100.2 (C3), 55.4 (C5), 41.5 (C6), 40.9 (C13), 31.4 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 14.0 (C11). (ES^-): 292.2 (M − H). MS (ES^+): 294.2 (M + H). HRMS (M + H): calcd for $C_{17}H_{28}N_1O_3$; 294.2064, found 294.2069.

1-Hexyl-3-(1-hydroxyheptylidene)pyrrolidine-2,4-dione (8f). Yield 70% (oil); Form AB:CD = 10:90 (major; D). ^1H NMR (400 MHz, $CDCl_3$): 3.76 (s, 2H, C5 AB), 3.64 (s, 2H, C5 CD), 3.36 (t, 2H, J = 7.2 Hz, C6), 2.85 (t, 2H, J = 7.2 Hz, C13 AB), 2.75 (t, 2H, J = 7.6 Hz, C13 CD), 1.60−1.50 (m, 4H, C7 and C14), 1.32−1.24 (m, 12H, C8−10 and C15−17), 0.87−0.89 (m, 6H, C11 and C18). ^{13}C NMR (100 MHz, $CDCl_3$, only CD form): 191.6 (C4), 187.9 (C12), 173.4 (C2), 101.7 (C3), 55.3 (C5), 41.4 (C6), 32.7 (C13), 31.4 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 26.4 (CH_2), 25.88 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 14.0 (C11 and C18). MS (ES^-): 294.5 (M − H). MS (ES^+): 296.4 (M + H), 318.3 (M + Na). HRMS (M + Na): calcd for $C_{17}H_{29}N_1Na_1O_3$ 318.2038, found 318.2040.

1-Heptanoyl-3-(hydroxy(phenyl)methylene)pyrrolidine-2,4-dione (8g). Yield 59%, mp 58 °C; Form AB:CD = 55:45. ^1H NMR (500 MHz, $CDCl_3$): 8.20−8.11 (m, 2H, C15 and C19), 7.68−7.64 (m, 1H, C17), 7.55−7.51 (m, 2H, C16 and C18), 4.40 (s, 2H, C5 AB), 4.16 (s, 2H, C5 CD), 3.04 (t, 2H, J = 7.5 Hz, C7 CD), 3.00 (t, 2H, J = 7.5 Hz, C7 AB), 1.76−1.66 (m, 2H, C8), 1.44−1.26 (m, 6H, C9−11), 0.93−0.87 (m, 3H, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 196.9 (C4 AB), 189.2 (C13 AB), 187.4 (C4 CD), 183.3 (C13 CD), 175.4 (C2 CD), 173.6 (C6 AB), 172.5 (C6 CD), 164.7 (C2 AB), 134.6 (ArCH), 134.3 (ArCH), 132.1 (C14 AB), 130.9 (C4 CD), 130.2 (ArCH), 130.0 (ArCH), 128.2 (ArCH), 128.2 (ArCH), 104.8 (C3 AB), 101.6 (C3 CD), 53.3 (C5 CD), 49.9 (C5 AB), 37.8 (CH_2), 37.3 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 28.8 (CH_2), 24.2 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 14.0 (C12). MS (ES^-): 314.12 (M − H). HRMS (M − H): calcd for $C_{18}H_{20}N_1O_4$ 314.1398, found 314.1393.

1-Heptanoyl-3-(1-hydroxy-3,5,5-trimethylhexylidene)pyrrolidine-2,4-dione (8h). Yield 63% (oil); Form AB:CD = 50:50. ^1H NMR (400 MHz, $CDCl_3$): 4.28 (s, 2H, C5 AB), 4.10 (s, 2H, C5 CD), 3.00−2.96 (m, 2H, C7), 2.92−2.80 (m, 2H, C14), 2.23−2.11 (m, 1H, C15), 1.72−1.64 (m, 2H, C8), 1.41−1.17 (m, 8H, C9−11 and C17), 1.02 (d, 2H, J = 4.0 Hz, C16 AB or CD), 1.00 (d, 2H, J = 4.0 Hz, C16 AB or CD), 0.91−0.86 (m, 12H, C12 and C19−21). ^{13}C NMR (100 MHz, $CDCl_3$): 197.0 (C13 AB), 194.8 (C4 AB), 191.8 (C13 CD), 189.2 (C4 CD), 173.4 (C2 CD), 173.4 (C6 AB), 172.6 (C6 CD), 165.4 (C2 AB), 106.2 (C3 AB), 103.6 (C3 CD), 53.7 (C5 CD), 50.7 (C17), 50.7 (C17), 50.0 (C5 AB), 43.8 (C14), 42.0 (C14), 37.7 (C7), 37.3 (C7), 31.5 (CH_2), 31.5 (CH_2), 31.1 (C18), 29.9 (CH_2), 29.8 (C19−21), 28.8 (C19−21), 28.8 (CH_2), 28.4 (C15), 27.4 (C15), 24.2 (CH_2), 24.1 (CH_2), 22.6 (C16), 22.5 (CH_2), 22.5 (CH_2), 22.4 (C16), 14.0 (C12). MS (ES^-): 350.21 (M − H). HRMS (M − H): calcd for $C_{20}H_{32}N_1O_4$ 350.2337, found 350.2333.

1-Heptanoyl-3-(hydroxy(4-(methylthio)phenyl)methylene)pyrrolidine-2,4-dione (8i). Yield 73%, mp 92 °C; Form AB:CD = 50:50; ^1H NMR (400 MHz, $CDCl_3$): 8.25−8.13 (m, 2H, ArH), 7.33−7.29 (m, 2H, ArH), 4.37 (s, 2H, C5 AB), 4.14 (s, 2H, C5 CD), 3.04−2.98 (m, 2H, C7), 2.54 (s, 3H, C20), 1.76−1.65 (m, 2H, C8), 1.42−1.29 (m, 6H, C9−C11), 0.92−0.87 (m, 3H, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 197.3 (C4 AB), 187.4 (C13 AB), 187.3 (C4 CD), 182.2 (C13 CD), 175.7 (C2 CD), 173.6 (C6 AB), 172.4 (C6 CD), 165.0 (C2 AB), 149.1 (C19), 148.7 (C19), 130.8 (C15 and C16), 130.5 (C15 and C16), 127.5 (C14), 126.8 (C14), 124.3 (C17 and C18), 104.3 (C3 AB), 101.02 (C3 CD), 53.1 (C5 CD), 50.1 (C5 AB), 37.8 (C7), 37.4 (C7), 31.5 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 24.2 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 14.5 (C20), 14.0 (C12). MS (ES^-): 360.10 (M − H). HRMS (M − H): calcd for $C_{19}H_{22}N_1O_4S_1$ 360.1275, found 360.1272.

Acyl Migration with DMAP (Method D). 1-((*E*)-Hex-2-enoyl)-3-(1-hydroxydecylidene)pyrrolidine-2,4-dione (8j). To a solution of **7n** (35 mg, 0.179 mmol) in dichloromethane (10 mL) was added DMAP (28 mg, 0.233 mmol), and the mixture was stirred overnight at room temperature. Concentration *in vacuo* followed by flash column chromatography gave metal-chelated **8j** as a solid. The solid was dissolved in dichloromethane (20 mL) and washed with aqueous HCl (3 < pH < 5, 50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give **8j** (32 mg, 0.163 mmol, 91% yield). Form AB:CD = 55:45. Mp 86 °C. ^1H NMR (500 MHz, $CDCl_3$): 7.36−7.15 (m, 2H, COCH=CH-CH_2), 4.35 (s, 2H, C5 AB), 4.16 (s, 2H, C5 CD), 2.95−2.92 (m, 2H, $CH_2C_8H_{17}$), 2.31−2.25 (m, 2H, CH=CHCH_2), 1.73−1.65 (m, 2H, $CH_2CH_2C_7H_{15}$), 1.58−1.50 (m, 2H, CH=CH$CH_2CH_2CH_3$), 1.42−1.26 (m, 12H, $C_2H_4(CH_2)_6CH_3$), 0.98−0.94 (m, 3H, CH=$CHC_2H_4CH_3$), 0.88 (t, 3H, J = 7.0 Hz, $(CH_2)_8CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): 198.2 (3-acyl AB), 194.2 (C4 AB), 192.7 (3-acyl CD), 189.3 (C4 CD), 173.6 (C2 CD), 165.6 (C2 AB), 165.3 (*N*-acyl AB), 164.5 (*N*-acyl CD), 152.0 (CH=$CHCH_2$ AB), 151.1 (CH=$CHCH_2$ CD), 122.5 (CH=$CHCH_2$ AB), 122.5 (CH=$CHCH_2$ CD), 105.7 (C3 AB), 102.9 (C3 CD), 53.9 (C5 CD), 50.0 (C5 AB), 35.4 (CH_2), 34.7 (CH_2), 34.7 (CH_2), 33.2 (CH_2), 31.8 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 21.4 (CH_2), 21.3 (CH_2), 14.1 (CH_2), 13.7 (CH_3), 13.67 (CH_3). MS (ES^-): 348.2 (M − H). HRMS (M + Na): calcd for $C_{20}H_{31}N_1Na_1O_4$ 372.2145, found 372.2147.

Direct Synthesis of 3-Acyltetramic Acids from Tetramic Acids (Method E). *tert*-Butyl 3-(1-Hydroxydecylidene)-2,4-dioxopyrrolidine-1-carboxylate (8m). To a solution of decanoic acid (475 mg, 2.76 mmol) in dichloromethane (50 mL) were added DCC (570 mg, 2.76 mmol), *tert*-butyl 2,4-dioxopyrrolidine-1-carboxylate **6** (500 mg, 2.51 mmol) and DMAP (400 mg, 3.26 mmol), and the mixture was stirred overnight at room temperature. The crude reaction mixture was washed with dichloromethane. Concentration *in vacuo* followed by flash column chromatography gave metal-chelated **8m** as a solid. The solid was dissolved in dichloromethane (50 mL) and washed with aqueous HCl (3 < pH < 5, 50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give **8m** as an oil (670 mg, 1.90 mmol, 76% yield). Form AB:CD = 40:60. ^1H NMR (500 MHz, $CDCl_3$): 4.22 (s, 2H, C5 AB), 4.03 (s, 2H, C5 CD), 2.92 (t, 2H, J = 7.5 Hz, $CH_2C_8H_{17}$ AB), 2.88 (t, 2H, J = 7.5 Hz, $CH_2C_8H_{17}$ CD), 1.69−1.62 (m, 2H, $CH_2CH_2C_7H_{15}$), 1.54 (s, 9H, Boc-CH_3), 1.38−1.24 (m, 12H, $C_2H_4C_6H_{12}CH_3$), 0.85 (t, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 197.5 (3-acyl AB), 194.0 (C4 AB), 192.2 (3-acyl CD), 189.1 (C4 CD), 173.3 (C2 CD), 164.33 (C2 AB), 149.6 (Boc-CO AB), 148.6 (Boc-CO CD), 105.4 (C3 AB), 102.4 (C3 CD), 84.0 ($C(CH_3)_3$ CD), 83.3 ($C(CH_3)_3$ AB), 54.6 (C5 CD), 50.7 (C5 AB), 34.9 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 28.0 (Boc-CH_3), 27.9 (Boc-CH_3), 25.8 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3). MS (ES^-): 352.2 (M − H). HRMS (M + Na): calcd for $C_{19}H_{31}N_1Na_1O_5$ 376.2094, found 376.2094.

Deprotection of 8m (Method G). 3-(1-Hydroxydecylidene)-pyrrolidine-2,4-dione (8n). Compound **8m** (540 mg, 1.528 mmol) was dissolved in a mixture of dichloromethane (20 mL) and trifluoroacetic acid (5 mL). The mixture was stirred for 2 h at 0 °C. After completion of the reaction as shown by TLC, the solution was washed with water and dried with $MgSO_4$. The organic layer was evaporated to give **8n** (300 mg, 0.821 mmol, 54% yield) as a solid. Form AB:CD = 20:80 (major; B, D). Mp 119 °C. ^1H NMR (400 MHz, $CDCl_3$): 12.87 (brs, 1H, OH), 7.15 (s, 1H, NH CD), 7.00 (s, 1H, NH AB), 3.94 (s, 2H, C5 AB), 3.80 (s, 2H, C5 CD), 2.89 (t, 2H, J = 7.2 Hz, $CH_2C_8H_{17}$ AB), 2.83 (t, 2H, J = 7.2 Hz, $CH_2C_8H_{17}$ CD), 1.69−1.61 (m, 2H, $CH_2CH_2C_7H_{15}$), 1.36−1.24 (m, 12H, $C_2H_4(CH_2)_6CH_3$), 0.86 (t, 3H, J = 6.8 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 198.9

(C4 AB), 192.9 (3-acyl AB), 192.7 (C4 CD), 189.2 (3-acyl CD), 176.5 (C2 CD), 170.2 (C2 AB), 104.6 (C3 AB), 101.2 (C3 CD), 51.8 (C5 CD), 48.5 (C5 AB), 33.9 (CH_2), 33.56 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.97 (CH_2), 25.59 (CH_2), 24.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3). MS (ES^-): 252.2 (M − H). HRMS (M + H): calcd for $C_{14}H_{24}N_1O_3$ 254.1751, found 254.1751.

Synthesis of 3-Acyl Tetramic Acids from Tetramic Acids (Method E). 1-Heptanoyl-3-(1-hydroxyheptylidene)pyrrolidine-2,4-dione (8k). Yield 94%, mp 50 °C; Form AB:CD = 55:45. ^{1}H NMR (500 MHz, $CDCl_3$): 4.29 (s, 2H, C5 AB), 4.10 (s, 2H, C5 CD), 2.99−2.91 (m, 4H, C7 and C14), 1.72−1.65 (m, 4H, C8 and C15), 1.42−1.25 (m, 12H, C9−11 and C16−18), 0.90−0.87 (m, 6H, C12 and C19). ^{1}H NMR (500 MHz, CD_3OD): 4.19 (s, 2H, C5), 2.99−2.79 (m, 4H, C7 and C14), 1.69−1.63 (m, 4H, C8 and C15), 1.42−1.29 (m, 12H, C9−11 and C16−18), 0.93−0.90 (m, 6H, C12 and C19). ^{13}C NMR (125 MHz, $CDCl_3$): 198.1 (C13 AB), 194.1 (C4 AB), 192.5 (C13 CD), 189.2 (C4 CD), 173.4 (C2 CD), 173.4 (C6 AB), 172.7 (C6 CD), 165.4 (C2 AB), 105.6 (C3 AB), 102.8 (C3 CD), 53.75 (C5 CD), 49.8 (C5 AB), 37.6 (CH_2), 37.2 (CH_2), 35.3 (CH_2), 33.2 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 24.2 (CH_2), 24.2 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.4 (CH_2), 13.99 (CH_3), 13.96 (CH_3). ^{13}C NMR (125 MHz, CD_3OD): 196.1 (C13), 192.7 (C4, triplet), 174.8 (C6), 170.6 (C2), 105.9 (C3), 52.4 (C5), 38.4 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 30.2 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 14.55 (CH_3), 14.52 (CH_3). MS (ES^-): 322.2 (M − H). HRMS (M + Na): calcd for $C_{18}H_{29}N_1Na_1O_4$ 346.1989, found 346.1983.

3-(1-Hydroxynonylidene)-1-(2-methylbenzoyl)pyrrolidine-2,4-dione (8l). Yield 92% (oil); Form AB:CD = 55:45. ^{1}H NMR (500 MHz, $CDCl_3$): 7.43−7.37 (m, 1H, C9), 7.32−7.26 (m, 3H, C10−12), 4.52 (s, 2H, C5 AB), 4.33 (s, 2H, C5 CD), 2.93 (t, 2H, J = 7.5 Hz, C15 CD), 2.85 (t, 2H, J = 7.5 Hz, C15 AB), 2.36 (s, 3H, C13 CD), 2.34 (s, 3H, C13 AB), 1.70−1.60 (m, 2H, C16), 1.42−1.24 (m, 10H, C17−21), 0.90−0.86 (m, 3H, C22). ^{13}C NMR (125 MHz, $CDCl_3$): 198.3 (C14 AB), 194.4 (C4 AB), 193.1 (C14 CD), 188.9 (C4 CD), 172.6 (C2 CD), 169.3 (C6 AB), 168.5 (C6 CD), 164.2 (C2 AB), 135.9 (ArC), 135.6 (ArC), 134.9 (ArC), 134.6 (ArC), 130.4 (ArCH), 130.4 (ArCH), 130.2 (ArCH), 130.0 (ArCH), 126.6 (ArCH), 126.4 (ArCH), 125.5 (ArCH), 105.1 (C3 AB), 102.3 (C3 CD), 53.7 (C5 CD), 49.9 (C5 AB), 35.2 (C15 AB), 33.3 (C15 CD), 31.7 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 25.9 (CH_2), 24.7 (CH_2), 22.6 (CH_2), 19.3 (C13), 19.3 (C13), 14.0 (C22). MS (ES^-): 356.18 (M − H). HRMS (M − H): calcd for $C_{21}H_{26}N_1O_4$ 356.1867, found 356.1870.

3-(2-Cyclohexyl-1-hydroxyethylidene)-1-heptanoylpyrrolidine-2,4-dione (9a). Yield 74% (oil); Form AB:CD = 55:45. ^{1}H NMR (400 MHz, $CDCl_3$): 4.28 (s, 2H, C5 AB), 4.10 (s, 2H, C5 CD), 3.01−2.96 (m, 2H, C7), 2.83 (d, 2H, J = 6.8 Hz, C14), 1.96−1.82 (m, 1H, C15), 1.76−1.05 (m, 18H, C8−11 and C16−20), 0.91−0.88 (m, 3H, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 196.9 (C13 AB), 195.0 (C4 AB), 191.8 (C13 CD), 189.3 (C4 CD), 173.5 (C2 CD), 173.4 (C6 AB), 172.7 (C6 CD), 165.5 (C2 AB), 106.1 (C3 AB), 103.5 (C3 CD), 53.8 (C5 CD), 50.1 (C5 AB), 42.0 (C14), 40.5 (C14), 37.7 (C7), 37.3 (C7), 36.7 (C15), 35.8 (C15), 33.1 (CH_2), 33.0 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 26.02 (CH_2), 26.00 (CH_2), 25.95 (CH_2), 24.2 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 14.0 (C12). MS (ES^-): 334.2 (M − H). HRMS (M − H): calcd for $C_{19}H_{28}N_1O_4$ 334.2024, found 334.2023.

3-(2-((1*S*,2*R*,4*R*)-Bicyclo[2.2.1]heptan-2-yl)-1-hydroxyethylidene)-1-heptanoylpyrrolidine-2,4-dione (9b). Yield 77% (oil); Form AB:CD = 55: 45.^{1}H NMR (500 MHz, $CDCl_3$): 4.28 (s, 2H, C5 AB), 4.10 (s, 2H, C5 CD), 2.99−2.96 (m, 2H, C7), 2.93−2.87 (m, 1H, C14), 2.81−2.76 (m, 1H, C14), 2.24 (s, 1H, C17), 2.02 (s, 1H, C20), 1.99−1.93 (m, 1H, C15), 1.72−1.64 (m, 2H, C8), 1.55−1.11 (m, 14H, C9−11, C16, C18, C19 and C21), 0.90−0.87 (m, 3H, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 196.9 (C13 AB), 194.6 (C4 AB), 191.6 (C13 CD), 189.3 (C4 CD), 173.4 (C2 CD), 172.6 (C6 AB, CD), 165.5 (C2 AB), 105.9 (C3 AB), 103.3 (C3 CD), 53.7 (C5 CD), 49.9 (C5 AB), 41.5 (CH_2), 41.1 (C17 AB*), 41.0 (C17 CD*), 39.6 (C15 AB*), 39.4 (CH_2), 38.6 (C15 CD*), 37.7 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 37.2 (CH_2), 36.7 (C20), 35.3 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 29.70 (CH_2), 29.6 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 14.0 (C12). MS (ES^-): 346.2 (M − H). HRMS (M − H): calcd for $C_{20}H_{28}N_1O_4$ 346.2024, found 346.2016.

3-(2-(Adamantan-1-yl)-1-hydroxyethylidene)-1-heptanoylpyrrolidine-2,4-dione (9c). Yield 48%, mp 82 °C; Form AB:CD = 50:50; ^{1}H NMR (500 MHz, $CDCl_3$): 4.27 (s, 2H, C5 AB), 4.10 (s, 2H, C5 CD), 3.01−2.97 (m, 2H, C7), 2.75 (s, 2H, C14),1.98 (br s, 3H, C17, C19 and C21), 1.72−1.63 (s, 14H, C8, C16, C18, C20 and C22−24), 1.39−1.30 (m, 6H, C9−11), 0.92−0.88 (m, 3H, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 196.1 (C4 AB), 195.2 (C13 AB), 190.7 (C13 CD), 189.3 (C4 CD), 173.5 (C2 CD), 173.4 (C6 AB[a]), 172.7 (C6 CD[a]), 165.6 (C2 AB), 106.9 (C3 AB), 104.5 (C3 CD), 53.8 (C5 CD), 50.4 (C5 AB), 46.9 (CH_2), 46.3 (CH_2), 42.7 (CH_2), 42.6 (CH_2), 37.7 (CH_2), 37.4 (CH_2), 36.7 (C15), 36.6 (CH_2), 36.3 (C15), 31.6 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 28.8 (CH), 28.8 (CH), 24.16 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 14.0 (C12). MS (ES^-): 386.3 (M − H). HRMS (M − H): calcd for $C_{23}H_{32}N_1O_4$ 386.2337, found 386.2343.

Ethyl 3-(1-Heptanoyl-2,4-dioxopyrrolidin-3-ylidene)-3-hydroxypropanoate (9d). Yield 33%, mp 33 °C; Form AB:CD = 70:30. ^{1}H NMR (500 MHz, $CDCl_3$): 4.38 (s, 2H, C5 AB), 4.23 (q, 2H, J = 7.0 Hz, C16), 4.15 (s, 2H, C5 CD), 3.98 (s, 2H, C14 CD), 3.95 (s, 2H, C14 AB), 3.00−2.94 (m, 2H, C7), 1.69−1.64 (m, 2H, C8), 1.38−1.26 (m, 9H, C9−11 and C17), 0.91−0.88 (m, 3H, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 191.0 (C13 AB), 190.7 (C4 AB), 189.2 (C4 CD), 181.1 (C13 CD), 173.2 (C6 AB), 172.6 (C6 CD), 172.6 (C2 CD), 166.5 (C15 AB), 166.0 (C15 CD), 165.1 (C2 AB), 106.97 (C3 AB), 104.7 (C3 CD), 62.0 (C16 CD), 61.8 (C16 AB), 54.0 (C5 CD), 48.7 (C5 AB), 43.4 (CH_2), 38.9 (CH_2), 37.7 (CH_2), 37.1 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 14.1 (C17), 14.00 (C12). MS (ES^-): 324.2 (M − H). HRMS (M − H): calcd for $C_{16}H_{22}N_1O_6$ 324.1453, found 324.1454.

***tert*-Butyl (2-(1-Heptanoyl-2,4-dioxopyrrolidin-3-ylidene)-2-hydroxyethyl)carbamate (9e).** Yield 63%, mp 129 °C; Form AB:CD = 75:25. ^{1}H NMR (500 MHz, $CDCl_3$): 5.23 (brs, 1H, NH), 4.49 (s, 2H, C14), 4.41 (s, 2H, C5 AB), 4.11 (s, 2H, C5 CD), 2.94 (t, 2H, J = 7.5 Hz, C7), 1.69−1.63 (m, 2H, C8), 1.45 (s, 9H, C17−19), 1.38−1.24 (m, 6H, C9−11), 0.88 (t, 3H, J = 6.5 Hz, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 196.3 (C13 AB), 195.2 (C13 CD), 189.2 (C4 CD), 187.9 (C4 AB), 173.2 (C2 CD), 173.1 (C6 AB), 168.7 (C6 CD), 165.0 (C2 AB), 157.0 (C15 CD), 155.7 (C15 AB), 106.01 (C3 AB), 103.3 (C3 CD), 83.6 (C16 CD), 80.1 (C16 AB), 53.4 (C5 CD), 51.6 (C14 CD), 48.1 (C5 AB), 47.4 (C14 AB), 37.0 (C7 CD), 36.9 (C7 AB), 31.6 (CH_2 CD), 31.5 (CH_2 AB), 28.9 (CH_2 CD), 28.8 (CH_2 AB), 28.2 (C17−19 AB), 27.9 (C17−19 CD), 24.2 (CH_2 CD), 24.1 (CH_2 AB), 22.5 (CH_2 CD), 22.5 (CH_2 AB), 14.1 (C12 CD), 14.0 (C12 AB). MS (ES^-): 367.2 (M − H). HRMS (M − H): calcd for $C_{18}H_{27}N_2O_6$ 367.1875, found 367.1869.

1-Heptanoyl-3-(1-hydroxy-2-(2-(2-methoxyethoxy)ethoxy)-ethylidene)pyrrolidine-2,4-dione (9f). Yield 38%, mp 37 °C; Form AB:CD = 99:1. ^{1}H NMR (500 MHz, $CDCl_3$): 4.79 (s, 2H, C14), 4.42 (s, 2H, C5), 3.79−3.55 (m, 8H, C15−18), 3.38 (s, 3H, C19), 2.93 (t, 2H, J = 7.0 Hz, C7), 1.70−1.64 (m, 2H, C8), 1.39−1.29 (m, 6H, C9−11), 0.88 (t, 3H, J = 7.0 Hz, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 196.9 (C13), 188.3 (C4), 173.0 (C6), 165.2 (C2), 105.8 (C3), 73.0 (C14), 71.8 (CH_2O), 71.1 (CH_2O), 70.50 (CH_2O), 70.47 (CH_2O), 59.0 (C19), 48.4 (C5), 36.9 (C7), 31.5 (CH_2), 28.8 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 14.0 (C12). MS (ES^-): 370.2 (M − H). MS (ES^+): 372.2 (M + H), 394.2 (M + Na). HRMS (M + Na): calcd for $C_{18}H_{29}N_1Na_1O_7$; 394.1836, found 394.1830.

1-Heptanoyl-3-(1-hydroxy-2-(1*H*-indol-3-yl)ethylidene)pyrrolidine-2,4-dione (9g). Yield 57% (oil); Form AB:CD = 55:45. ^{1}H NMR (500 MHz, $CDCl_3$): 8.21 (brs, 1H, NH), 7.75 (d, 1H, J = 8.0 Hz, C21 CD), 7.73 (d, 1H, J = 8.0 Hz, C21 AB), 7.37−7.15 (m, 4H, C16 and C18−20), 4.39 (s, 2H, C14 AB), 4.36 (s, 2H, C14 CD), 4.28 (s, 2H, C5 AB), 4.12 (s, 2H, C5 CD), 3.04 (t, 2H, J = 7.5 Hz, C7 AB), 2.94 (t, 2H, J = 7.5 Hz, C7 CD), 1.76−1.64 (m, 2H, C8), 1.44−1.28 (m, 6H, C9−11), 0.94−0.88 (m, 3H, C12). ^{13}C NMR (125 MHz, $CDCl_3$): 195.2 (C14 AB), 193.5 (C4 AB), 189.3 (C14 CD), 189.2 (C4 CD), 173.4 (C2 CD), 173.4 (C7 AB), 172.7 (C7 CD), 165.4 (C2 AB), 136.0 (C17 AB), 135.9 (C17 CD), 127.2 (C22 CD), 127.0 (C22 AB), 124.1 (ArCH), 124.1 (ArCH), 122.4 (ArCH), 122.4 (ArCH), 112.0 (ArCH), 119.9 (ArCH), 119.1 (ArCH), 119.1 (ArCH), 111.2 (ArCH), 107.7 (C15 CD), 107.2 (C15 AB), 105.4 (C3 AB), 102.3 (C3 CD), 53.8 (C5 CD), 49.5 (C5 AB), 37.6 (C7 AB), 37.2 (C7 CD), 32.0 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 22.51 (CH_2), 22.4 (CH_2), 14.03 (C12 AB), 13.98 (C12 CD). MS (ES^-): 367.2 (M − H). HRMS (M − H): calcd for $C_{21}H_{23}N_2O_4$ 367.1663, found 367.1661.

1-Heptanoyl-3-(1-hydroxy-5-phenylpentylidene)pyrrolidine-2,4-dione (9h). Yield 76%, mp 53 °C; Form AB:CD = 55:45. ^{1}H NMR (400 MHz, $CDCl_3$): 7.30−7.27 (m, 2H, C20 and C22), 7.20−7.17 (m, 3H, C19, C21 and C23), 4.30 (s, 2H, C5 AB), 4.10 (s, 2H, C5 CD), 3.01−2.96 (m, 4H, C7 and C14), 2.68−2.64 (m, 2H, C17), 1.77−1.68 (m, 6H, C8, C15 and C160), 1.41−1.31 (m, 6H, C9−11), 0.92−0.89 (m, 3H, C12). ^{13}C NMR (100 MHz, $CDCl_3$): 197.8 (C13 AB), 193.9 (C4 AB), 192.0 (C13 CD), 189.2 (C4 CD), 173.4 (C2 CD), 173.3 (C6 AB), 172.6 (C6 CD), 165.4 (C2 AB), 141.8 (C18 AB0, 141.7 (C18 CD), 128.35 (ArCH), 128.3 (ArCH), 125.8 (ArCH), 125.8 (ArCH), 105.7 (C3 AB), 102.9 (C3 CD), 53.8 (C5 CD), 49.7 (C5 AB), 37.6 (CH_2), 37.2 (CH_2), 35.5 (CH_2), 35.4 (CH_2), 35.2 (CH_2), 32.8 (CH_2), 31.53 (CH_2), 31.5 (CH_2), 30.8 (CH_2), 30.8 (CH_2), 28.8 (CH_2), 28.8 (CH_2), 25.5 (CH_2), 24.4 (CH_2), 24.2 (CH_2), 24.1 (CH_2), 22.48 (CH_2), 22.46 (CH_2), 14.0 (C12). MS (ES^-): 370.2 (M − H). HRMS (M − H): calcd for $C_{22}H_{28}N_1O_4$ 370.2024, found 370.2024.

3-((*E*)-1-Hydroxyhex-3-en-1-ylidene)-1-(2-methylbenzoyl)pyrrolidine-2,4-dione (9i). Yield 67% (oil); Form AB:CD = 55:45. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43−7.36 (m, 1H, C9), 7.31−7.26 (m, 3H, C10−12), 5.83−5.63 (m, 1H, C17), 5.51−5.42 (m, 1H, C16), 4.54 (s, 2H, C5 AB), 4.34 (s, 2H, C5 CD), 3.63 (dd, 2H, J_1 = 7.2 Hz, J_2 = 0.8 Hz, C15 CD), 3.56 (dd, 2H, J_1 = 7.2 Hz, J_2 = 0.8 Hz, C15 CD), 2.36 (s, 3H, C13 CD), 2.34 (s, 3H, C13 AB), 2.09−1.99 (m, 2H, C18), 1.01−0.95 (m, 3H, C19). ^{13}C NMR (100 MHz, $CDCl_3$): 196.5 (C14 AB), 193.5 (C4 AB), 190.2 (C14 CD), 188.8 (C4 CD), 172.5 (C2 CD), 169.3 (C6 AB), 168.5 (C6 CD), 164.1 (C2 AB), 138.5 (C16), 138.1 (C16), 135.8 (ArC), 135.5 (ArC), 134.9 (ArC), 134.6 (ArC), 130.4 (ArCH), 130.3 (ArCH), 130.2 (ArCH), 130.0 (ArCH), 126.6 (ArCH), 126.4 (ArCH), 125.4 (ArCH), 118.9 (C17), 118.8 (C17), 104.9 (C3 AB), 102.0 (C3 CD), 53.7 (C5 CD), 49.5 (C5 AB), 39.1 (C15 AB), 36.5 (C15 CD), 25.5 (C18), 25.5 (C18), 19.3 (C13), 19.2 (C13), 13.24 (C19), 13.19 (C19). MS (ES^-): 312.10 (M − H). HRMS (M − H): calcd for $C_{18}H_{18}N_1O_4$ 312.1241, found 312.1235.

3-(1-Hydroxyhept-6-en-1-ylidene)-1-(2-methylbenzoyl)pyrrolidine-2,4-dione (9j). Yield 77% (oil); Form AB:CD = 55:45. ^{1}H NMR (400 MHz, $CDCl_3$): 7.44−7.36 (m, 1H, C9), 7.30−7.26 (m, 3H, C10−12), 5.84−5.70 (m, 1H, C19), 5.05−4.93 (m, 2H, C20), 4.53 (s, 2H, C5 AB), 4.33 (s, 2H, C5 CD), 2.95 (t, 2H, J = 7.6 Hz, C15 CD), 2.87 (t, 2H, J = 7.6 Hz, C15 AB), 2.36 (s, 3H, C13 CD), 2.34 (s, 3H, C13 AB), 2.12−2.01 (m, 2H, C18), 1.74−1.61 (m, 2H, C16), 1.54−1.37 (m, 2H, C17). ^{13}C NMR (100 MHz, $CDCl_3$): 198.1 (C14 AB), 194.1 (C4 AB), 192.7 (C14 CD), 188.89 (C4 CD), 172.5 (C2 CD), 169.3 (C6 AB), 168.5 (C6 CD), 164.2 (C2 AB), 138.05 (C19), 137.99 (C19), 135.86 (ArC), 135.5 (ArC), 134.9 (ArC), 134.6 (ArC), 130.4 (ArCH), 130.3 (ArCH), 130.2 (ArCH), 130.0 (ArCH), 126.6 (ArCH), 126.4 (ArCH), 125.5 (ArCH), 115.0 (C20), 114.8 (C20), 105.2 (C3 AB), 102.4 (C3 CD), 53.7 (C5 CD), 49.8 (C5 AB), 35.1 (CH_2), 33.3 (CH_2), 33.2 (CH_2), 33.0 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 25.3 (CH_2), 24.0 (CH_2), 19.26 (C13), 19.25 (C13). MS (ES^-): 326.16 (M − H). HRMS (M − H): calcd for $C_{19}H_{20}N_1O_4$ 326.1398, found 326.1401.

Conclusion

We have investigated the synthesis of 3-acyltetramic acids via *O*-acylation followed by acyl migration from tetramic acid core templates and identified the effects of the substituent group on N(1), the identity of the carboxylic acid and the amount of DMAP in this process. The acylation reaction of tetramic acids activated by DCC and DMAP proved to be very sensitive to these effects, whereas the *O*-acylation with acid chloride and the acyl migration activated by acetone cyanohydrin with triethylamine was not affected and gave high yields with the exception only of the migration of α-olefinic and adamantyl *O*-acyl tetramic acids. The acylation reaction of *N*-acyl tetramic acid with alkyl carboxylic acids using 1.3 equiv of DMAP with DCC (1.1 equiv) gave 3-acyltetramic acids directly, whereas those of *N*-unsubstituted, *N*-hexyl, and *N*-acyl tetramic acids with alkyl and aromatic carboxylic acids by using 0.1 equiv of DMAP with DCC (1.1 equiv) gave the *O*-acyl tetramic acids.

In addition, the tautomeric nature of these 3-acyltetramic acids in solution was examined by NMR spectroscopy and energy calculations. It was found that the favored tautomer strongly depended on the substituent group on N(1) rather than on the 3-acyl group, and the ratio between two external tautomers depended on the substituent group on N(1) and the 3-acyl group. However, whereas *N*-unsubstituted and *N*-hexyl 3-acyltetramic acids favored the exo-enol tautomer D, in *N*-acyl 3-acyltetramic acids the ratio between the endo-enol tautomeric pair AB and the exo-enol tautomer D depended on the substituent group on 3-acyl group; the former is favored by β-heteroatom functionality on the 3-acyl unit. The position of this equilibrium and the ease of interconversion of tautomers, as dictated by the ring substituents, are likely to play a role in the biological activity of tetramic acids. This study of a substantial library of variously functionalized tetramates provides a detailed understanding of the effect of the nature of ring substituents on tautomeric behavior and is likely to be of importance for detailed mechanistic studies of the biological roles of tetramates and their application in drug discovery.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all compounds and Spartan calculation data. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. There were errors in Scheme 1 and Table 2 in the version published on 1/20/2011. These were fixed in the version published on 2/1/2011.