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Synthesis and Supramolecular Self-Assembly of a Bicyclic Dilactam

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Abstract: The design and synthesis of a novel bicyclic dilactam is described. It crystallizes from solution as a highly ordered self-assembly directed by intermolecular hydrogen bonding and hydrophobic interactions.

INTRODUCTION

There is much activity in the field of supramolecular chemistry where compounds are designed to associate spontaneously into ordered and often predetermined self-assemblies either in solution or in the solid state.[1] The application of molecular recognition principles, coupled to modern crystallographic notions has contributed to the emergence of "crystal engineering",[2] an important concept for the development of new materials.[2,3] The packing of molecular crystals can be viewed as a cooperative interplay of intermolecular forces. Among these, hydrogen bonding (H-bonding) has proven to be a powerful vector for ordering self-assemblies by virtue of its strength and directional character.[4] For example, the H-bonding motif found in the 2-pyridone dimer can be harnessed for directing supramolecular self-assemblies in solution and in the solid state.[4c,5]

As a study of controlled self-assembly, the complex bicyclic dilactam **1** (Figure 1) was designed to aggregate *via* a complement of H-bonding and hydrophobic interactions.[6] The bicyclic core provides a relatively polar domain to which is attached a non-polar hexyl chain. In addition, the rigid core maintains two lactams[7] in a fixed relative disposition, producing a self-complementary head group *via* H-bonding interactions. With dilactam **1**, one can envisage a variety of self-assembly motifs, including cyclic and ribbon patterns.[3,4j,8] Although cyclic aggregation *via* H-bonding can be thermodynamically favored,[4c,5d] the kinetic nature of the crystallization process can certainly lead to alternative lactam directed self-assembly motifs. Moreover, self-assembly of crystals from solution will be biased toward structures that optimize close-packing, in general agreement with the Kitaigorodskii model.[9] For this initial study, dilactam **1** was prepared in racemic form, offering an even wider range of self-assembly permutations.

RESULTS AND DISCUSSION

The synthesis of racemic dilactam **1** is shown in Schemes 1 and 2. Baylis-Hillman reaction[10] of heptanal **2** with methyl acrylate, followed by conjugate addition of veratrylamine[11] to the 2-substituted propenoate **3**, provided the 3,4-dimethoxybenzyl (DMB) protected aminoalcohol **4** in 96% overall yield. Protection of the secondary amine in **4** with di-t-butyl dicarbonate afforded hydroxyester **5** which was then dehydrated *via* the corresponding mesylate to generate α,β-unsaturated esters **6** in 78% yield overall from **4**. Michael addition of dimethyl sodiomalonate[12] to **6** and subsequent decarbomethoxylation of one of the methyl esters in **7** in Krapcho fashion[13] produced diester **8**, as a mixture of stereoisomers. This mixture would be epimerized to a

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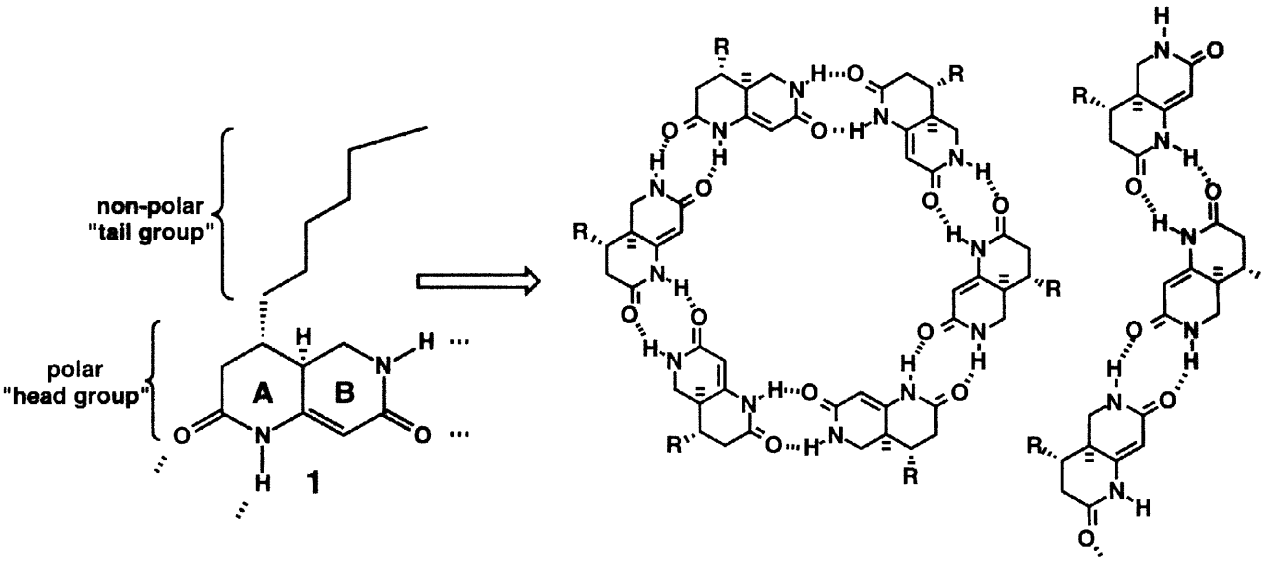
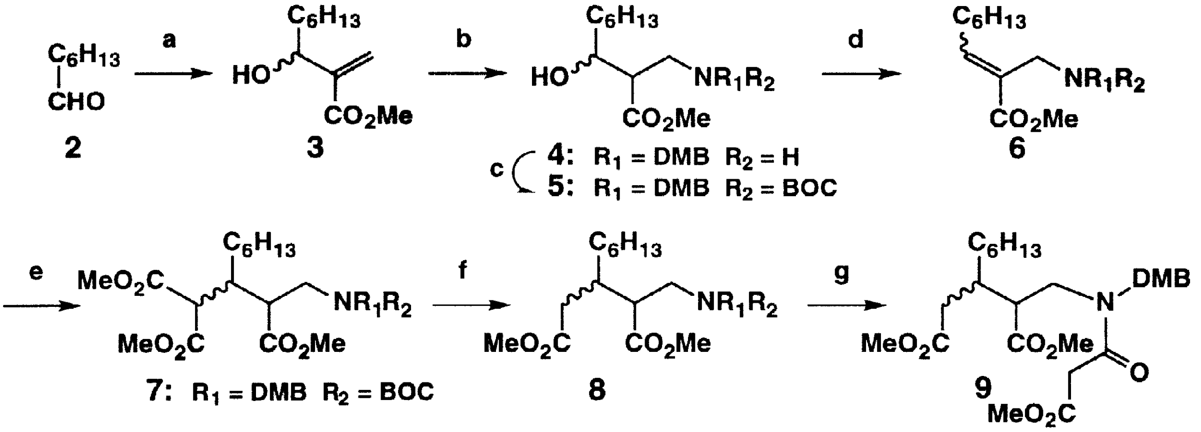


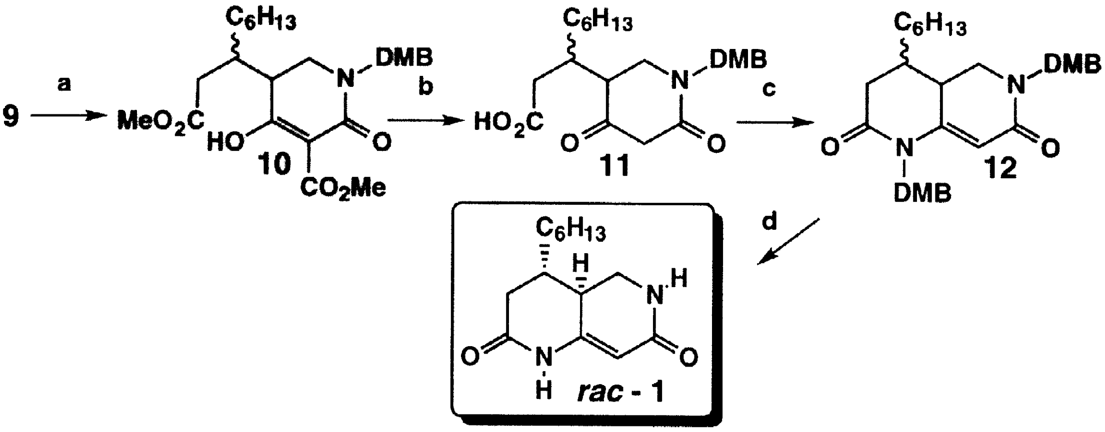
Figure 1. Some possible self-assembly motifs of dilactam 1.

single diastereoisomer at the end of the synthetic sequence. The BOC protecting group in **8** was removed with dilute TFA at 0° and the resulting secondary amine was acylated *in situ* with methylmalonyl chloride and pyridine to afford **9** in 99% yield.[14] Addition of the ring A nitrogen and closure of the two rings would complete the dilactam synthesis. The B ring was closed first by a Dieckmann condensation of **9** with t-BuOK in THF to afford the cyclic adduct **10** in 85% yield (Scheme 2). The ^{1}H-NMR spectrum **10** showed a concentration-independent singlet at 14.09 ppm typical of the H-bonded enol proton. Although the A ring nitrogen could, in



Scheme 1. a) Methyl acrylate, cat. DABCO, 96%; b) veratrylamine, MeOH quantitative; c) di-t-butyl dicarbonate, Et_3N, MeOH, 98%; d) MsCl, DBU, CH_2Cl_2, -30°, 80%; e) dimethyl sodiomalonate, MeOH, 79%; f) NaCl, DMSO, 140°, 89%; g) TFA, CH_2Cl_2, 0°, then methylmalonyl chloride, pyridine, 99%.

principle, be introduced directly into compound **10** by addition/elimination of the enol hydroxyl with an amine nucleophile,[15] we were unable to substitute the enol hydroxyl of **10** with any amine.[16] However, treatment of **10** with LiOH in methanol promoted hydrolysis/decarboxylation of the ring B ester to afford β-ketolactam **11** in 55% yield. The NMR spectrum of **11** in $CDCl_3$ showed only keto tautomer. Refluxing β-ketolactam **11** with veratrylamine in benzene produced the protected dilactam **12** directly in 60% yield as an inseparable mixture of diastereomers (7:1 ratio), presumably *via* enamine formation and subsequent cyclyzation with the carboxylic acid. Final deprotection of the nitrogen functionalities in **12** proved to be non-trivial since standard methods (CAN, DDQ, etc...) failed to accomplish the desired oxidative cleavage. Nevertheless, oxidative cleavage using the buffered potassium persulfate method of Huffman[17] afforded racemic dilactam **1** as a single diastereoisomer, in 38% yield. The ring junction epimer could not be isolated from the reaction, and was presumed to epimerize to **1** during the final deprotection step.



Scheme 2. a) t-BuOK, THF, 0°, 85%; b) aq LiOH, MeOH, 55%; c) veratrylamine, benzene, reflux, 60%; d) $KHSO_5$, Na_2HPO_4, aq CH_3CN, reflux, 38%.

The relative configuration of dilactam **1** was probed initially by ^{1}H-NMR nOe experiments, the results of which were consistent with the hexyl chain being pseudoequatorial and *cis* to the ring junction methine.[18] Slow evaporation of a methanol solution of **1** produced crystallographically suitable material from which the structure was readily solved, confirming the previous NMR structural assignment (Figure 2).

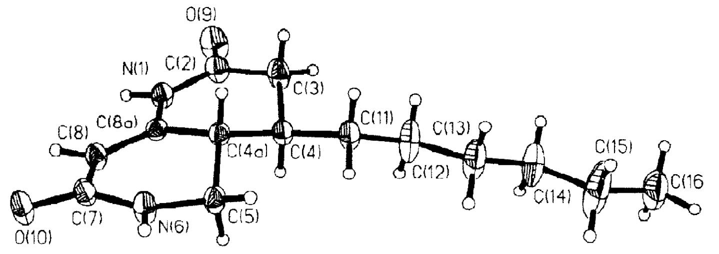


Figure 2. Thermal ellipsoid diagram and atom numbering scheme of dilactam **1**.

The propensity for self-assembly of **1** in solution was assessed by simple NMR experiments. Cooling a 7.2 mM solution of **1** in $CDCl_3$ from 50°C to -40°C resulted in a substantial downfield drift of the N_1-H (7.80 → 10.0 ppm) and N_6-H (5.61 → 6.86 ppm) protons, indicating an increase in population of intermolecularly H-bonded species. Dilution experiments of a $CDCl_3$ solution of **1** at 298K, however, painted a more complex picture. Diluting **1** from 3.5 mM to ≈2 mM resulted in predictable upfield drifts of both N_1-H (7.77 → <7.4 ppm) and N_6-H (5.67 → 5.18 ppm) protons. However, dilution down to ≈0.5 mM, caused the N_6-H proton to drift downfield to 6.02 ppm. Evidently, the dilution data would not shed light on the aggregation geometry of **1**. The dilution results were also unsuitable for a Saunders-Hyne analysis of the aggregation order.[19,5d]

In contrast to the solution studies, X-ray crystallography of **1** provided an unambiguous picture of the sold-state self-assembly. The same crystalline structure was obtained from slow evaporation of either methanol or methanol/hexane solutions of **1**. The supramolecular stucture is multi-lamellar, directed by intra- and inter-lamellar H-bonding interactions, and interdigitation of the hexyl chains (Figure 3). The polar head groups of **1** are considerably wider than the non-polar tails which can favor the interdigitation of the tail sections and maximize packing during the crystallization process. This produces extended sheets made up from single enantiomers. Within one sheet, the tadpole-like structures repeat every 9Å and, as a result, produce an inter-chain distance of ≈ 4.5Å. Laterally, the polar heads span ≈9.7Å while the non-polar domain spans ≈9.8Å.

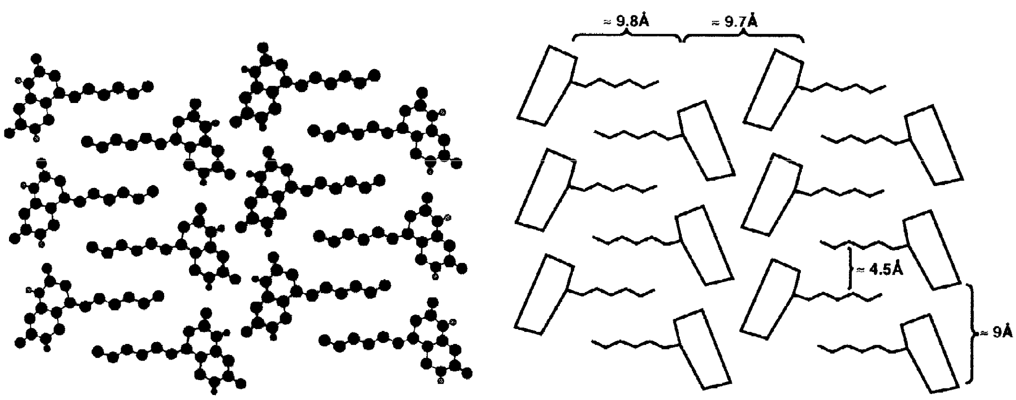


Figure 3. Ball & stick and "tadpole" cartoons of a single sheet of crystalline dilactam **1**.

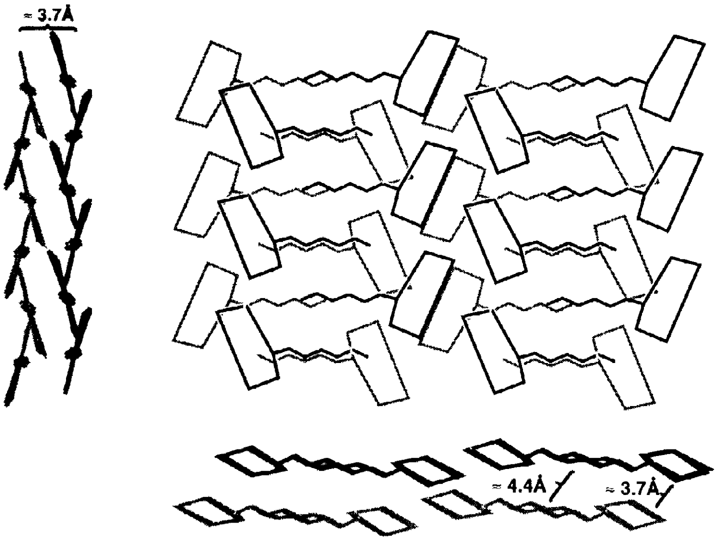


Figure 4. "Tadpole" cartoons of two sheets of crystalline dilactam **1**. Centre: Top view of two sheets, one is black, the other (enantiomer) is lighter. Left: side view. Below: bottom view.

The individual sheets stack on top of each other (Figure 4) and the absolute stereochemistry of the monomers alternates between adjacent sheets, a direct consequence of the $P2_1/c$ space group in which **1** crystallizes. Antiparallel stacking of the sheets maintains good van der Waals contact between the bicyclic heads (≈3.7Å). The side view reveals a criss-cross pattern where head groups of adjacent sheets come into close contact in a pairwise fashion.

Analysis of the H-bonding interactions proved to be most interesting. The X-ray data for **1** were of very high quality, allowing all the ring bound hydrogens (including both NH groups) to be located in the Fourier difference map. At first glance, the dilactam groups within one sheet appear to associate as cyclic trimers involving three H-bonds: N_1-H···O=C_7, N_1-H···O=C_7, and N_6-H···O=C_2 (Figure 5). However, close inspection of the structure reveals only two optimal H-bonds between any two intra-lamellar monomers *via* N_1-H···O=C_7 interactions.[20] The N_6-H and O=C_2 groups are too far for H-bonding to occur[21] (H···O = 2.99Å, N–H···O = 105°). In fact, the O=C_2 group does not participate in any H-bonding interactions (including C-H···O contacts[22]), in apparent violation of Etter's rules.[4h] Thus, the lamellar dimension is devoid of two-point interactions typical of the 2-pyridone dimer; only single point contacts involving the most acidic donor (N_1-H) and the most basic acceptor (O=C_7) are present. The 2-pyridone dimer motif does appear, however, in the inter-lamellar contacts that were seen in the criss-cross pattern of the side view (Figure 4). As illustrated in Figure 5, such dimers are formed between one dilactam of one sheet and the enantiomer of a neighboring sheet in head-to-head fashion. These inter-layer interactions must surely stabilize the supramolecular structure and prevent shearing of adjacent sheets. It is worth noting that both sp^2 lone pairs of the more basic O=C_7 carbonyl are involved in intra- and inter-layer H-bonding.

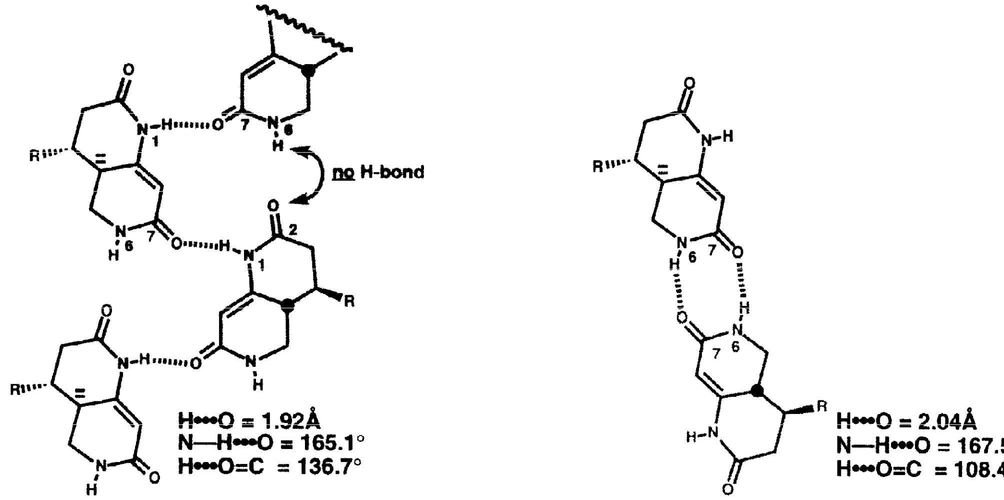


Figure 5. Hydrogen bonding in crystalline dilactam **1**. Left: intra-lamellar. Right: inter-lamellar.

The solid state structure of **1** is considerably different from the simpler self-assemblies one might conceive from pyridone-like dimerizations (cf. Figure 1). In hindsight, the observed motif is perhaps not so surprising if one considers the following: The H-bonded dimers formed between two dilactam enantiomers (Figure 5b) appear to be key components of the self-assembly. This dimerization motif should be more stable than any single-point H-bonded interaction. It is also highly symmetric (center of symmetry, *i*) and is sterically preferred over the other lactam-lactam pairing permutations. Self-assembly could not propagate further along the dimer plane *via* two-point contacts involving the N_1-H and O=C_2 sites since it would preclude close packing of the hexyl chains. In the dimers, however, the most acidic protons (N_1-H) and an sp^2 lone pair on the most basic carbonyls (O=C_7) can, on their own, direct further assembly. Inter-dimer aggregation involving single H-bonds between these points will allow close packing of the hexyl chains with concomittant formation of the multi-lamellar network. Thus, it appears that close-packing principles dictate the self-assembly into a centrosymmetric arrangement while maximizing the H-bonding opportunities.

Predicting the structure of crystalline solids remains a most difficult challenge. Perhaps, the study of preorganized compounds such as **1** can broaden our understanding of self-assembly. A functional handle on the dilactam 'tail' would allow for rapid modification of its length, steric bulk and stereoelectronic demands, and permit a more systematic study of the self-assembly. The resolution and crystallization of enantiopure dilactam **1** and its congeners could give rise to non-centrosymmetric crystals with novel physical and chemical attributes. We will report on these developments in due course.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained using a Varian XL-200 or a Varian Unity-400 NMR spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane or to residual solvent peak. Infrared spectra were recorded on a Bruker IFS 25 IR spectrophotometer (KBr tablets) or a Perkin-Elmer 598 IR spectrophotometer ($CHCl_3$ solutions in 0.5mm NaCl cells). High-resolution mass spectra (HRMS) were obtained on a Kratos MS50 TC mass spectrometer in EI mode unless otherwise indicated. Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. THF, ether, and benzene were distilled from Na-benzophenone ketyl; dichloromethane, acetonitrile, and triethylamine were distilled from CaH_2. All reactions were carried out in flame-dried glassware, under argon atmosphere, unless specified otherwise.

*Preparation of 2-substituted propenoate ester **3**.*

1,4-Diazabicyclo[2.2.2]octane (DABCO) (1.16 g, 9.97 mmol) was added to a stirred solution of heptanal **2** (5.75 g, 47.8 mmol) and methyl acrylate (6.44 g, 73.9 mmol) at room temperature. The resulting solution was allowed to stand at room temperature for 18 days. Excess methyl acrylate was evaporated under reduced pressure and the residue was diluted with ether, washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to afford propenoate ester **3** (9.21 g, 96%) as a clear liquid which was used without further purification. ^1H NMR (200 MHz, $CDCl_3$): δ 6.22 (s, 1H), 5.79 (s, 1H), 4.39 (br t, 1H), 3.79 (s, 3H), 2.58 (br s, 1H), 1.66 (m, 2H), 1.29 (m, 8H), 0.88 (t, 3H, J = 6.5 Hz). IR (NaCl, $CHCl_3$): 3608, 2928, 1720, 1630 cm^{-1}.

*Conjugate addition of **3**.*

Veratrylamine (3.5 ml, 22.5 mmol) was added dropwise to a stirred solution of hydroxyester **3** (4.51 g, 22.5 mmol) in MeOH (24 ml) at -78°C. The cooling bath was removed and the mixture was stirred at room temperature for 24 hours. Evaporation of solvents followed by flash chromatography (4% MeOH/$CHCl_3$) afforded secondary amine **4** (8.28 g, 100%) as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 6.78 (s, 3H), 4.02 (m, 1H), 3.84 (s, 3H), 3.836 (s, 3H), 3.67 (s, 3H), 3.63 (dd, 2H, J = 16.2, 10.6 Hz), 3.08 (dd, 1H, J = 12.2, 5.8 Hz), 2.89 (dd, 1H, J = 12.2, 8.3), 2.47 (m, 1H), 1.31 (m, 10H), 0.84 (t, 3H, J = 6.7 Hz). ^{13}C NMR: δ 173.7, 149.0, 148.4, 130.4, 120.6, 111.5, 110.9, 73.4, 55.8, 53.3, 51.8, 48.9, 47.2, 35.8, 31.7, 29.1, 25.5, 22.5, 14.0. IR (NaCl, $CHCl_3$): 3320, 3205, 2929, 1727, 1455, 1220 cm^{-1}. HRMS: calcd. for $C_{20}H_{33}NO_5$ (M+) 367.2358, found *m/z* 367.2359.

*BOC protection of **4**.*

Di-*tert* -butyl dicarbonate (5.73 g, 26.0 mmol) was added to a stirred solution of triethylamine (4.40 ml, 31.6 mmol) and secondary amine **4** (8.28 g, 22.5 mmol) in MeOH (40 ml) at 0°C. The resulting yellow solution was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (30% EtOAc/hexane) to give compound **5** (10.3 g, 98%) as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 6.76 (m, 3H), 4.45-4.15 (m, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.61 (br s, 3H), 2.69 (m, 1H), 1.4 (s, 9H), 1.39 (m, 10H), 0.94 (t, 3H, J = 6.6). ^{13}C NMR: δ 174.5, 156.4, 149.0, 148.3, 130.5, 120.2, 110.9, 110.4, 80.4, 70.0, 55.9, 55.7, 51.9, 51.3, 50.5, 34.7, 31.72, 31.69, 29.1, 29.08, 28.4, 28.0, 25.9, 22.5, 14.0. IR (NaCl, $CHCl_3$): 3410, 2929, 1727, 1680, 1520, 1258 cm^{-1}. HRMS: calcd. for $C_{25}H_{41}NO_7$ (M+) 467.2883, found *m/z* 467.2883.

*Dehydration of **5**.*

1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU, 13.4 ml, 87.8 mmol) was syringed dropwise to a stirred solution of **5** (10.3 g, 21.9 mmol) in anhydrous CH_2Cl_2 (80 ml) at -30°C under argon. The resulting solution was stirred for 15 minutes, methanesulfonyl chloride (3.40 ml, 43.1 mmol) was syringed in and the reaction mixture was stirred at -30°C for 2 hours, the cooling bath was removed and stirring was continued for 8 hours. The reaction was quenched with 1N HCl, the organic layer was separated, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oily residue. The crude product was purified by flash chromatography (20% EtOAc/hexane) to produce α,β-unsaturated esters **6** (7.90 g, 80%) as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 6.76 (m, 4H), 4.30 (m, 2H), 4.15 (m, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 2.14 (br s, 2H), 1.45 (s, 9H), 1.28 (m, 8H), 0.85 (t, 3H, J = 6.6). ^{13}C NMR: δ 168.0, 155.4, 148.9, 148.5, 148, 135.3, 131.1, 124.7, 119.6, 110.8, 110.5, 79.8, 55.9, 55.7, 51.9, 51.7, 51.3, 49.0, 48.6, 41.0, 32.4, 31.6, 31.3, 29.3, 29.2, 29.0, 28.9, 28.7, 28.6, 28.4, 28.4, 28.0, 22.5, 22.4, 14.0. IR (NaCl, $CHCl_3$): 2928, 1710, 1680, 1455, 1262 cm^{-1}. HRMS: calcd. for $C_{25}H_{39}NO_6$ (M+) 449.2777, found *m/z* 449.2777.

*Malonate addition to **6**.*

Small pieces of sodium (439 mg, 19.1mmol) were dissolved in anhydrous MeOH (30 ml) at 0°C under argon and dimethyl malonate (2.35 ml, 19.9 mmol) was syringed in. The cooling bath was removed, and after stirring at room temperature for 30 minutes, the solution was cannulated into a stirred solution of α,β-unsaturated esters **6** (7.14 g, 15.9 mmol) in anhydrous MeOH (30ml). The resulting solution was stirred at room temperature overnight under argon. Most of the solvent was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 and acidified with 1N HCl. The organic layer was separated, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (20% then 40% EtOAc/hexane) gave triesters **7** (7.33 g, 79%) as a thick cloudy oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.77 (m, 3H), 4.6-4.1 (br m, 2H), 3.84 (s, 6H), 3.61 (m, 10H), 3.35 (m, 2H), 3.04 (m, 1H), 2.43 (br s, 1H), 1.46 (s, 9H), 1.24 (m, 10H), 0.83 (t, 3H, J = 6.2). ^{13}C NMR: δ 173.8, 169.3, 169.0, 155.9, 149.0, 148.2, 130.8, 120.2, 119.7, 110.9, 110.6, 80.2, 79.9, 55.9, 55.7, 53.7, 52.4, 52.3, 52.2, 51.7, 51.6, 50.5, 49.7, 46.0, 45.7, 39.2, 38.9, 31.6, 31.5, 30.9, 30.5, 29.5, 29.4, 29.2, 28.4, 28.0, 22.5, 14.0. IR (NaCl, $CHCl_3$): 2952, 1734, 1682, 1462, 1156 cm^{-1}. HRMS: calcd. for $C_{30}H_{47}NO_{10}$ (M+) 581.3199, found *m/z* 581.3200.

Decarboxylation of ***7****.*

A suspension of triester **7** (6.28 g, 10.8 mmol) and sodium chloride (641 mg, 11.0 mmol) in 80% aqueous DMSO (12.6 ml) was heated at 140°C overnight. After cooling to room temperature, water was added and the mixture was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an orange oily residue which was purified by flash chromatography (40% EtOAc/hexane) to provide diesters **8** (5.02 g, 89%) as a thick yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.76 (m, 3H), 4.51 (br m, 1H), 4.09 (br m, 1H), 3.82 (s, 6H), 3.60 (s, 6H), 3.28 (m, 2H), 2.91 (m, 1H), 2.28 (br m, 3H), 1.44 (s, 9H), 1.21 (m, 10H), 0.82 (t, 3H, J = 6.1). ^{13}C NMR: δ 174.3, 173.0, 155.4, 149.0, 148.2, 130.8, 120.0, 119.5, 110.9, 110.4, 80.1, 55.9, 55.7, 55.5, 51.6, 51.5, 51.1, 50.7, 49.9, 47.4, 46.9, 46.5, 45.5, 35.9, 32.0, 31.7, 31.6, 31.4, 30.9, 30.5, 29.2, 29.2, 28.4, 28.0, 27.0, 26.6, 22.5, 22.1, 14.0. IR (NaCl, $CHCl_3$): 2930, 1730, 1680, 1455, 1160 cm^{-1}. HRMS: calcd. for $C_{28}H_{45}NO_8$ (M+) 523.3145, found *m/z* 523.3145.

Preparation of ***9****.*

Trifluoroacetic acid (3.30 ml, 42.4 mmol) was syringed dropwise into a stirred solution of diester **8** (3.74 g, 7.15 mmol) in anhydrous CH_2Cl_2 (80 ml) at 0°C under argon. After stirring for 30 minutes, the reaction mixture was stirred at room temperature for an additional 5 hours. The solution was cooled to 0°C and methylmalonyl chloride (0.81 ml, 7.15 mmol) followed by anhydrous pyridine (7.0 ml, 85.7 mmol) were syringed in. The reaction mixture was warmed to room temperature and stirring was continued for 5 hours. The mixture was washed with 1N HCl, saturated $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated *in vacuo* to produce an oily material. The crude product was purified by flash chromatography (2% MeOH/$CHCl_3$) to give triester amides **9** (3.72 g, 99%) as an orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88-6.68 (m, 3H), 4.90 (d, 1H, J = 14.8), 4.52 (s, 1H), 4.24 (d, 1H, J = 14.8), 3.88 (s, 3H), 3.87 (s, 3H), 3.68 (m, 10H), 3.27 (m, 4H), 2.29 (m, 3H), 1.25 (m, 10H), 0.87 (t, 3H, J = 6.4 Hz). ^{13}C NMR: δ 174.5, 173.6, 173.1, 172.7, 168.5, 167.8, 166.9, 166.8, 149.5, 149.2, 148.6, 148.4, 129.3, 128.5, 120.4, 118.4, 111.4, 111.2, 110.8, 109.4, 55.94, 55.9, 55.85, 52.6, 52.4, 52.3, 52.0, 51.7, 51.67, 51.6, 47.1, 46.4, 46.3, 46.1, 45.7, 41.2, 41.1, 40.7, 36.2, 36.1, 35.9, 35.8, 35.3, 31.7, 31.6, 31.3, 29.2, 29.1, 27.1, 27.0, 22.6, 22.5, 14.0. IR (KBr): 2997, 1726, 1651, 1559 cm^{-1}. HRMS: calcd. for $C_{27}H_{41}NO_9$ (M+) 523.2781, found *m/z* 523.2781.

Cyclization of ***9****.*

Potassium *tert*-butoxide (1.07 g, 9.07 mmol) was added to a stirred solution of triester amide **9** (3.72 g, 7.11 mmol) in anhydrous THF (95 ml) at 0°C under argon and the reaction mixture was stirred overnight at room temperature. 0.3N HCl was added, the organic solution was extracted, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography (2:4:94 MeOH: acetone:$CHCl_3$) afforded diester lactams **10** (2.96 g, 85%) as an orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 14.09 (s, 1H), 6.78 (m, 3H), 4.50 (m, 2H), 3.90 (s, 3H), 3.83 (s, 6H), 3.58 (s, 3H), 3.32 (m, 2H), 2.23 (m, 4H), 1.15 (m, 10H), 0.82 (t, 3H, J = 6.2 Hz); IR (NaCl, $CHCl_3$): 2929, 1729, 1656, 1440, 1220 cm^{-1}; FAB-

MS (in thioglycerol): calcd. for $C_{26}H_{37}NO_8$ (M+H) 492, found 492.

*Hydrolysis and decarboxylation of **10**.*

Lithium hydroxide monohydrate (1.83 g, 42.7 mmol) was added to a stirred solution of diester lactam **10** (2.74 g, 42.7 mmol) in 90% aqueous MeOH (50ml) and the suspension was heated at 70°C overnight. Most of the solvent was removed *in vacuo* , and the residue was acidified with 1N HCl and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily material. Flash chromatography (4% MeOH/$CHCl_3$) afforded β-ketolactams **11** (1.28 g, 55%) as a beige foamy material. ^1H NMR (200 MHz, $CDCl_3$): δ 6.78 (m, 3H), 4.61 (m, 2H), 3.82 (m, 8H), 3.35 (m, 3H), 2.22 (m, 3H), 1.19 (m, 10H), 0.85 (b, 3H). ^{13}C NMR: δ 204.8, 204.6, 176.8, 166.9, 166.8, 149.4, 148.9, 128.5, 128.4, 120.9, 120.8, 119.2, 111.5, 111.4, 111.1, 111.0, 56.0, 55.9, 55.8, 50.7, 50.1, 50.0, 49.9, 49.0, 48.7, 44.5, 44.3, 43.7, 35.6, 35.4, 33.5, 33.3, 31.9, 31.63, 31.58, 31.55, 31.47, 29.2, 29.1, 26.9, 26.8, 22.5, 14.0. IR (NaCl, $CHCl_3$): 2928 , 1728, 1660, 1448, 1220 cm^{-1}. HRMS: calcd. for $C_{23}H_{33}NO_6$ (M+) 419.2308, found *m/z* 419.2308.

*Cyclization of **11**.*

Veratrylamine (0.72 ml, 4.63 mmol) was syringed into a stirred solution of β-ketolactam **11** (919 mg, 2.20 mmol) in anhydrous benzene (35 ml) and the mixture was refluxed under a Dean-Stark trap overnight. The solution was diluted with benzene and washed with 1N HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography (2.5% then 5% MeOH/$CHCl_3$) afforded protected dilactam **12** (730 mg, 60%) as a pale yellow foam in a 7:1 ratio of diastereomers. ^1H NMR (200 MHz, $CDCl_3$): δ 6.72 (m, 6H), 5.50 (s, 1H, minor isomer), 5.46 (s, 1H, major isomer), 5.20 (d, 2H, J = 17 Hz, minor isomer), 5.04, 4.76 (ABq, 2H, J = 15.6 Hz, major isomer), 4.62, 4.40 (ABq, 2H, J = 14.7 Hz, major isomer), 4.20 (d, 2H, J = 17 Hz, minor isomer), 3.83 (m, 12H), 3.37 (dd, 1H, J = 5.5, 11.9 Hz), 3.04 (m, 1H), 2.87 (dd, 1H, J = 3.9, 16.9 Hz), 2.58 (m, 1H), 2.25 (dd, 1H, J = 13.7, 16.9 Hz), 1.71 (br s, 1H), 1.20 (m, 10H), 0.82 (br t, 3H, J = 6.7 Hz). IR (NaCl, $CHCl_3$): 2930, 1636, 1596, 1464 cm^{-1}. FAB-MS (in thioglycerol): calcd. for $C_{32}H_{42}N_2O_6$ 550, found 550.

*Deprotection of **12**.*

A suspension of protected dilactam **12** (427 mg, 0.776 mmol), potassium persulfate (885 mg, 3.26 mmol), and Na_2HPO_4 (462 mg, 3.25 mmol) in 40% aqueous CH_3CN (12 ml) was heated to reflux for 3 hours. Water was added and the solution was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Flash chromatography (5:5:90 MeOH:acetone:$CHCl_3$) afforded the desired racemic dilactam **1** (74.4 mg, 38%) as a beige solid. m.p. (MeOH) 239.8 - 240.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (br s, 1H, N_1-H), 5.67 (br s, 1H, N_6-H), 5.20 (s, 1H, C_8-H), 3.60 (m, 1H, C_5-H eq), 3.19 (t, 1H, J = 12.1 Hz, C_5-H ax), 2.70 (dd, 1H, J = 3.8, 17.1 Hz, C_3-H eq), 2.59 (m, 1H, C_{4a}-H), 2.18 (dd, 1H, J = 17.1, 13.2 Hz, C_3-H ax), 1.80 (br m, 1H, C_4-H), 1.27 (m, 10H), 0.86 (m, 3H). ^{13}C NMR (DMSO-d_6): δ 169.9, 167.1, 151.9, 97.6, 42.3, 36.1, 36.0, 33.7, 31.2, 31.1, 28.8, 24.6, 22.0, 14.0. IR (NaCl, $CHCl_3$): 3429, 3382, 2928, 1660 cm^{-1}. HRMS: calcd. for $C_{14}H_{22}N_2O_2$ (M+) 251.1681, found *m/z* 251.1681.

*X-ray structure determination of **1**.*

Crystals of compound **1** were obtained by slow cooling of a saturated solution of compound **1** in methanol. A colorless crystal (0.45 mm x 0.45 mm x 0.63 mm) was selected and mounted on the end of a thin glass fibre using epoxy cement under dry mineral oil and transferred to the goniometer of a Enraf Nonius CAD4 diffractometer. The unit cell parameters were refined by centering of 25 high angle reflections with $28° < 2\theta < 30°$. Intensities were collected with graphite monochromatised Mo Kα radiation ($\lambda = 0.71069$ Å) using the θ - 2θ scan technique at 20°C. The data set was corrected for Lorentz and polarisation effects. Sample decomposition during data collection was not observed. 5019 reflections were collected to a maximum 2θ of 60°. Of those, 3950 independent reflections were used for structure solution and refinement. Direct methods[23] gave the heavy atom positions and subsequent Fourier difference analysis revealed the hydrogen atom positions except those on the alkyl chain which were included in calculated positions. Full-matrix least-squares refinement on F^2 of 206 parameters gave $R1$ = 0.0611, w$R2$ = 0.117.[24] The final Fourier difference map was featureless. The highest peak had a height 0.260eÅ^{-3}. Details of the data collection and refinement are summarised in Table 1, atomic coordinates and bond lengths are given in Tables 2 and 3, respectively.

Table 1. Crystal Data and Structure Refinement for Dilactam **1**.

Empirical formula	C14H22N2O2
Formula weight	250.34
Crystal system	Monoclinic
Space group	$P2_1/c$
a, Å	14.657(3)
b, Å	9.048(1)
c, Å	10.505(3)
β, deg	100.09(2)
V, Å^3	1371.6(5)
Z	4
d_{calc}, g/cm^3	1.212
μ, cm^{-1}	0.81
Theta range, deg	2.66 to 29.95
Scan type	θ - 2θ
Index ranges	$-20 \le h \le 20$, $-12 \le k \le 1$, $-1 \le l \le 14$
Reflections collected	5019
Independent reflections	3950
R_{int}	0.0364
GoF on F^2	1.212
R1 [I>2σ(I)]	0.0611
wR2	0.1170

Table 2. Atomic Coordinates (× 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 × 10^3) for Dilactam **1** (see Figure 2 for numbering scheme).

Atom	x	y	z	U(eq)
N(1)	8836(1)	-841(2)	-1405(2)	43(1)
C(2)	8317(2)	-1893(2)	-909(2)	50(1)
C(3)	7857(2)	-1426(2)	192(3)	54(1)
C(4A)	8534(1)	1084(2)	147(2)	37(1)
C(4)	7653(1)	223(2)	227(2)	41(1)
C(5)	8367(2)	2738(2)	62(2)	45(1)
N(6)	9171(1)	3531(2)	-205(2)	49(1)
C(7)	9665(1)	3044(2)	-1078(2)	42(1)
C(8A)	8960(1)	608(2)	-993(2)	35(1)
C(8)	9470(1)	1547(2)	-1565(2)	40(1)
C(11)	7225(2)	645(2)	1401(2)	52(1)
C(12)	6299(2)	-43(4)	1455(3)	85(1)
C(13)	5783(2)	619(3)	2403(3)	84(1)
C(14)	4872(2)	-21(4)	2538(3)	86(1)
C(15)	4306(2)	683(4)	3336(4)	137(2)
C(16)	3439(2)	27(4)	3583(3)	91(1)
O(9)	8256(1)	-3129(2)	-1364(2)	74(1)
O(10)	10281(1)	3816(2)	-1419(1)	55(1)

Table 3. Bond Lengths for Dilactam **1** (see Figure 2 for numbering scheme).

Bond	Length (Å)
N(1)-C(2)	1.376(2)
N(1)-C(8A)	1.382(2)
N(1)-H(1)	0.94(2)
C(2)-O(9)	1.213(2)
C(2)-C(3)	1.498(3)
C(3)-C(4)	1.523(3)
C(3)-H(3A)	0.95(2)
C(3)-H(3B)	0.99(2)
C(4A)-C(8A)	1.508(2)
C(4A)-C(5)	1.517(3)
C(4A)-C(4)	1.522(2)
C(4A)-H(4A)	0.99(2)
C(4)-C(11)	1.527(3)
C(4)-H(4)	1.01(2)
C(5)-N(6)	1.448(2)
C(5)-H(5A)	1.05(2)
C(5)-H(5B)	0.94(2)
N(6)-C(7)	1.340(2)
N(6)-H(6)	0.95(2)
C(7)-O(10)	1.243(2)
C(7)-C(8)	1.458(3)
C(8A)-C(8)	1.342(2)
C(8)-H(8)	1.00(2)
C(11)-C(12)	1.503(3)
C(12)-C(13)	1.479(3)
C(13)-C(14)	1.485(3)
C(14)-C(15)	1.428(4)
C(15)-C(16)	1.466(4)

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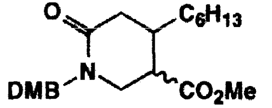

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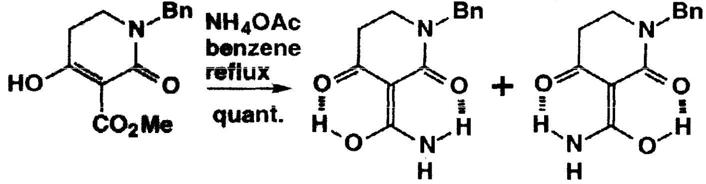
16. For example, refluxing **10** with ammonium acetate in benzene in a Dean-Stark trap resulted in the loss of the B ring ester. This observation is consistent with the following result using a simpler model compound:



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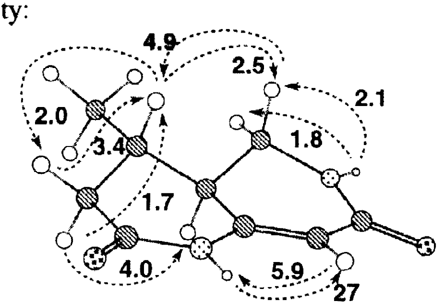
18. Key nOe contacts (%) measured for DMSO-d6 solution of dilactam **1**. The hexyl chain is mutated to a methyl for clarity:



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