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A useful α, α' - annulation reaction of enamines

Alison J. Frontier,[a] Samuel J. Danishefsky,[a,b*] Gary A. Koppel,[c]
Dongfang Meng[a,b]

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Abstract: The reactions of a series of enamines generated from a range of cyclic ketones with chloromethyl and iodomethyl vinyl ketone have been studied. The principal products are bridged ring diketones. The four carbon bridge, bearing a 2-oxobutyl function, spans the α and α' carbons of the original cyclanone. Presumptive evidence as to the pathway of this novel one step bridging annulation is provided.

Keywords: Addition Reactions; Annulation; Cyclisation

Enamines were introduced by Gilbert Stork and associates[1,2] into organic synthesis owing to their capacity to function as virtual enolates. Through recourse to enamines, many of the complications associated with the generation and use of actual carbanionic agents can be obviated. Scheme I summarizes the logic of the method. The events subsequent to attack of the general electrophile (see E^+) upon **1**, shown here for convenience as the pyrrolidene enamine derived from cyclohexanone, can take several forms. In the simplest situation, the product iminium species **2** survives until hydrolytic workup, whereupon **3** (R is derived from E^+) is obtained. In another variation, a new nucleophilic center is generated *within R* during the alkylation. The nucleophile may then react with the iminium moiety (see formation of **4**, Scheme I). We refer to this process as an *α-ipso annulation*. The adaptability of enamines to the Robinson annulation reaction[2] (see product **7**) is an instance of an *α-ipso annulation*.

Alternatively, **2** may undergo proton transfer to produce a new enamine such as trisubstituted **5**.[2,3] The ensuing sequence of events depends on the character of **5**. It could suffer hydrolysis upon workup to give the previously mentioned **3**, or, it could participate in another enamine-electrophile reaction. Were this second coupling to occur in an intramolecular fashion, the product, following hydrolysis, would be of the type **6** (Scheme I). We categorize the transformation of **1** into **6** *via* **5** as an *α, α'-annulation*. The acrolein bridging annulation reaction of enamines, though mechanistically complicated (see product **8**),[4] is an example of such an annulation.

E-mail: S-Danishefsky@ski.mskcc.org

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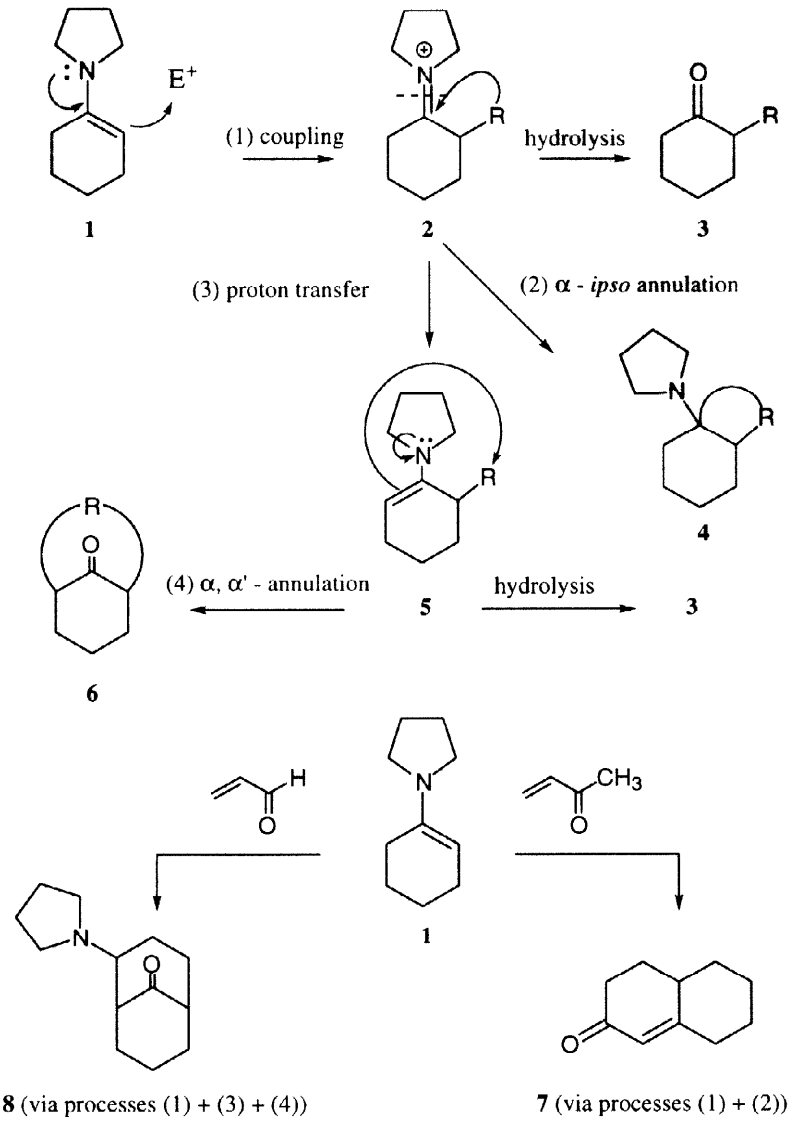
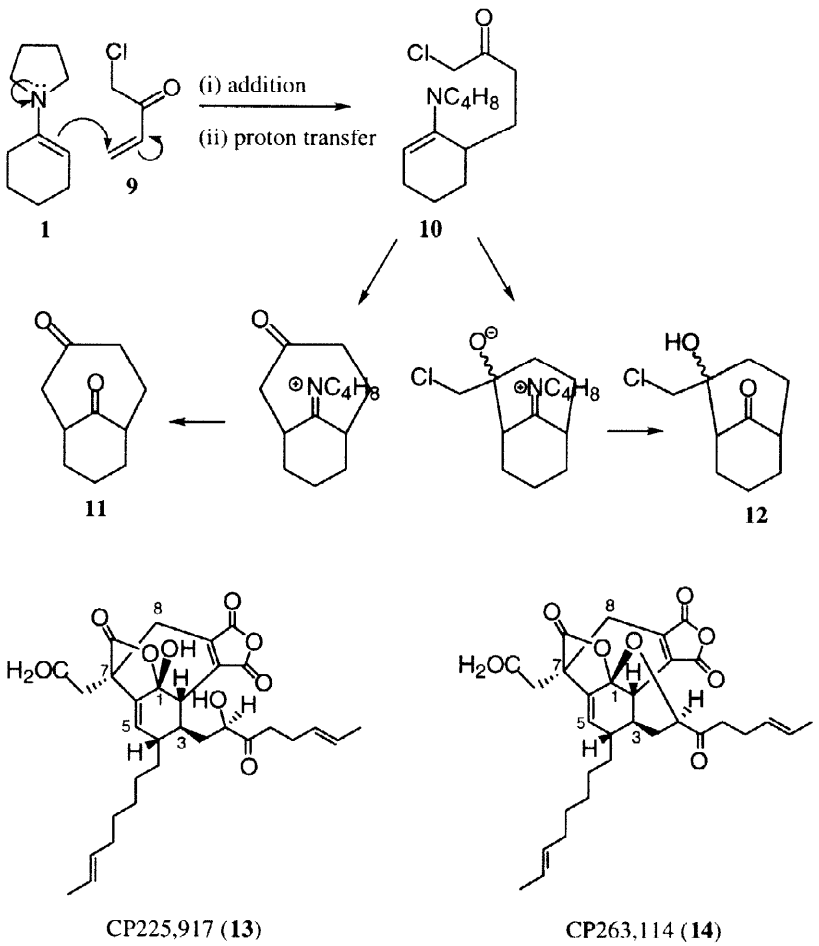
Scheme I



Some years ago,[5] we wondered about the likely course of reaction of simple enamines (cf. **1**) with chloromethyl vinyl ketone **9** (see Scheme II).[6] In practice, the experiment produced virtually a 1:1 mixture of **11** and **12** in a combined yield of 40 - 50%. In terms of transformation type, we classified both of these products as having arisen from an α, α'-annulation sequence (*i. e.* steps 1 + 3 + 4, Scheme I). It seemed that the final outcome was a result of events following the formation of intermediate **10** *via* proton transfer. Nucleophilic attack at the sp^3 carbon, with expulsion of chloride, would ultimately lead to **11**. Alternatively, cyclization in an aldol sense would eventually provide **12**.

Scheme II

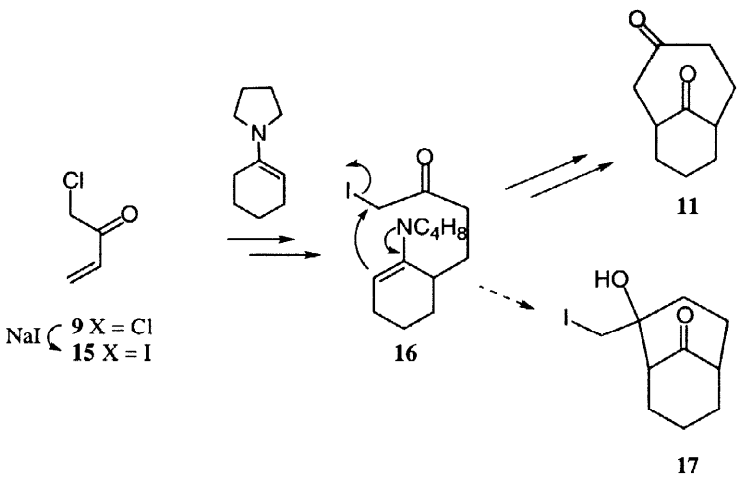


Following the recent publications of Kaneko and co-workers,[7,8] the issues associated with this α, α' annulation process leading to **11** assumed added interest. Thus, the Pfizer workers had isolated two metabolites and demonstrated their structures to be **13** and **14**. Aside from the intrinsic challenges posed to the field of synthesis by these fascinating displays of the inventiveness of biosynthesis, the demonstrated biological activities of the CP compounds as farnesyl transferase and squalene cyclase inhibitors have, not surprisingly, attracted additional notice.[9,10,11] The possibility of gaining viable access to bridged bicyclo [4.3.1]-octane substructures (cf. **11**), prompted a further study of the α, α'-annulation reaction, first reported from our laboratory 30 years ago.[5]

While we had certainly not proven that the divergence point of the reaction pathways leading to **11** and **12** follows formation of **10**, the proposal did not seem unreasonable. Since we were most interested in obtaining the [4.3.1]-bridged ring system (*cf.* **11**, **13** and **14**), the possibility of optimizing its formation relative to the aldol derived product (*cf.* **12**) was investigated. With this in mind, we considered the use of iodomethyl vinyl ketone **15** (see Scheme III) as an alternative. It was hoped that in the terminal phase of the annulation sequence, displacement of iodine would be more competitive with the aldol reaction than the

corresponding replacement of chlorine in **9**. The somewhat unstable iodomethyl compound was readily synthesized from **9** by reaction with sodium iodide in acetone. Treatment of **15** with enamine **1** in benzene at room temperature, followed by a brief period of reflux gave, upon hydrolysis, the bridged ring product **11** in 49% yield. We presume that annulation occurred via intermediate **16**. The hypothetical aldol product **17** was not detected in the crude reaction mixture. We screened a variety of solvents and discovered that when the reaction is conducted in THF with iodomethyl enone **15** as the annulating agent, the yield of **11** rises to 59-63%.

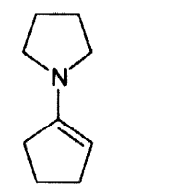
Scheme III

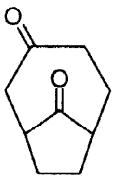


We investigated the generality of the process by surveying its applicability to other cyclic enamines. The data appear in Table I. Inspection of the results reveals that the desired α, α'-annulation can be achieved in workable yields with unsubstituted enamines. The procedure can be conducted on large scale and purification, in most cases, is greatly simplified by filtration of the insoluble iminium salt. Thus, even when the yields are disappointing, the product is practically devoid of side products after hydrolysis and is thus readily purified.

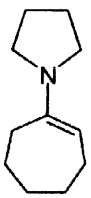
Incorporation of alkyl groups at C_4 is tolerated (see **20** and **21**), though with some loss in yield. However, substitution of C_4 with electron withdrawing groups (see **23** and **24**) results in serious attrition of yields. This diminution may reflect the higher energy associated with the conjugate addition step as a consequence of electron withdrawal in an inductive sense. In contrast, the process does tolerate a 4-methylene group (see **22**). Presumably this *exo* unsaturation can be exploited as an implementation site for further functionalizations.

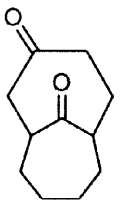
Table I



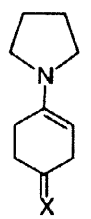


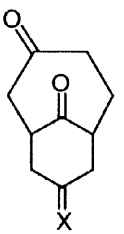
18 (57%)





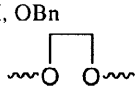
19 (48%)

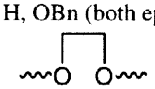


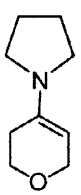


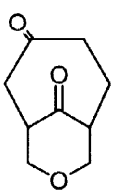
X = H; Et
X = Me; Me
X = CH_2
X = H, OBn

20 X = H; Et (both epimers) 46%
21 X = Me; Me 31%[b]
22 X = CH_2 55%
23 X = H, OBn (both epimers) 21%[b]

X = 

24 X =  < 5%



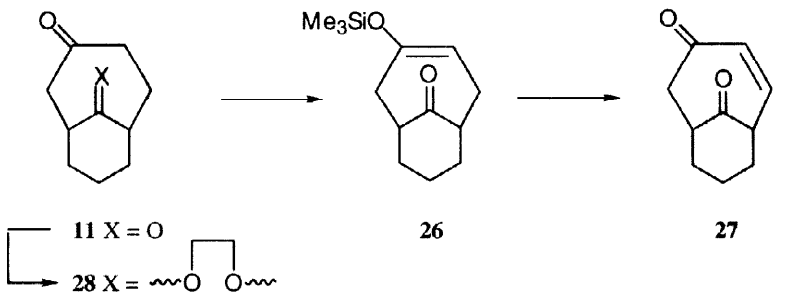


25 (31%)[a]

a) Yield was calculated from tetrahydropyran-4-one; the corresponding enamine was used directly in the annulation
b) Crude enamine was used in the annulation

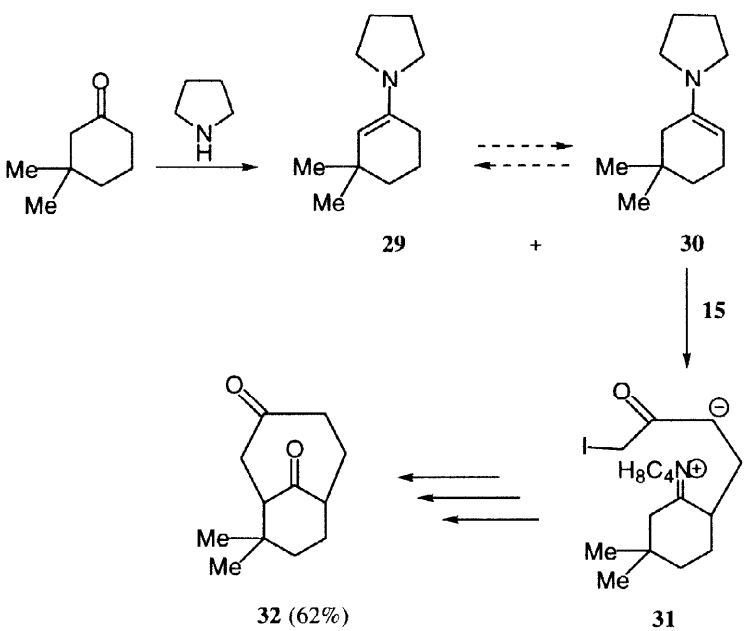
With a view towards an eventual route to the CP compounds **13** and **14**, we carried out some preliminary chemical investigations into the chemistry of diketone **11** (Scheme IV). This compound lent itself to conversion to silyl enol ether **26** and thence, following Saegusa reaction,[12] to enone **27**. Compound **13** also responded to selective ketalization at the C_1 bridged ketone (see compound **28**).

Scheme IV



At this point it seemed prudent to explore the regiochemistry of this kind of α, α'-annulation reaction with an unsymmetrical enamine. We examined the case of 3,3-dimethylcyclohexanone (see Scheme V). The

Scheme V



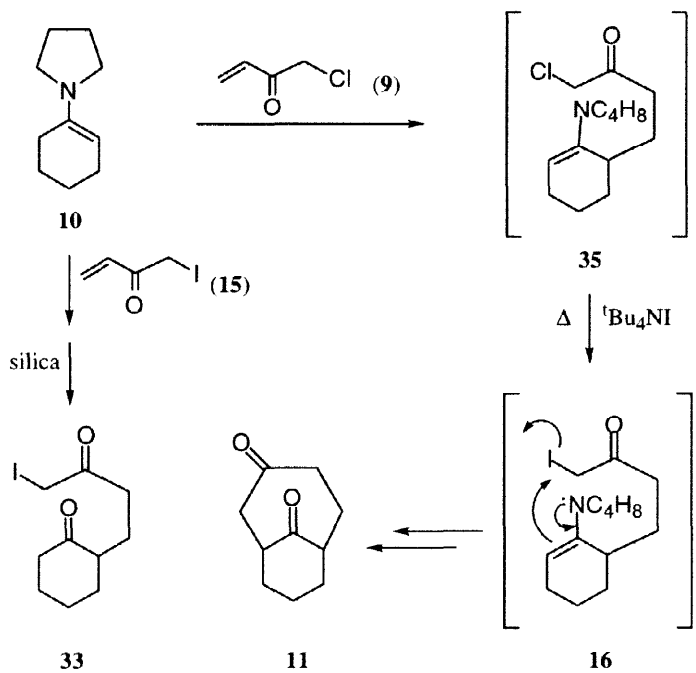
latter was converted to a 1:2 mixture of **29** and **30** under standard enamine forming conditions. Reaction of this material with **15** provided a 62% yield of **32**. We attributed this result to the participation of enamine **30** in an initial conjugate addition. Adduct **31**, produced from the Michael reaction, apparently suffers proton transfer and iodine displacement to lead, after hydrolysis, to **32**. Therefore, it seems that isomer **29** does not react under these conditions. Furthermore, it is possible that equilibration occurs between enamines **29** and **30**

during the reaction. The failure of **29** itself to enter into the annulation sequence is not *per se* surprising, since the initial alkylation step would result in the formation of a secondary neopentyl center.

Further evidence that the initial step in the annulation sequence is conjugate addition was obtained by a detailed study of the reaction of enamine **1** and enone **15**. In the initial phase of the process, the enamine and enone are mixed at room temperature and thin-layer chromatography indicates immediate conversion to a new product *distinct* from **11**. When the mixture is heated, this material disappears and α, α'-annulation product **11** is the only compound isolated from the reaction. It was not possible to isolate the transient material by conventional methods; it seemed to decompose upon workup. However, when the contents of this reaction were subjected directly to silica gel chromatography, we isolated a 1:1 adduct resulting from hydrolysis. The spectral data for this material were consistent with its formulation as **33** (Scheme VI), the hydrolysis product arising from initial conjugate addition.

Given the finding that the Michael addition step can be decoupled from the cyclization phase, we returned to the use of the chloromethyl enone **9**. Once again, reaction with enamine **1** was conducted in tetrahydrofuran at room temperature. Subsequent treatment of the presumed **16** with tetra-*n*-butyl ammonium iodide followed heating at 70 °C produced a 60-75% yield of **11** (Scheme VI). Since no aldol derived products were discerned, we assumed that **16** had indeed undergone Finkelstein type displacement, thereby producing **36** *in situ*. The latter, upon cyclization in the now expected fashion, gave rise to **11**. Hence, we can utilize the more readily accessible chloromethyl compound **9**, and derive the benefits of starting with **15** by generating **36** in situ. Although purification by filtration of the iminium salt becomes difficult under this protocol, avoiding the need to synthesize **15** in a separate step makes this procedure an attractive alternative.

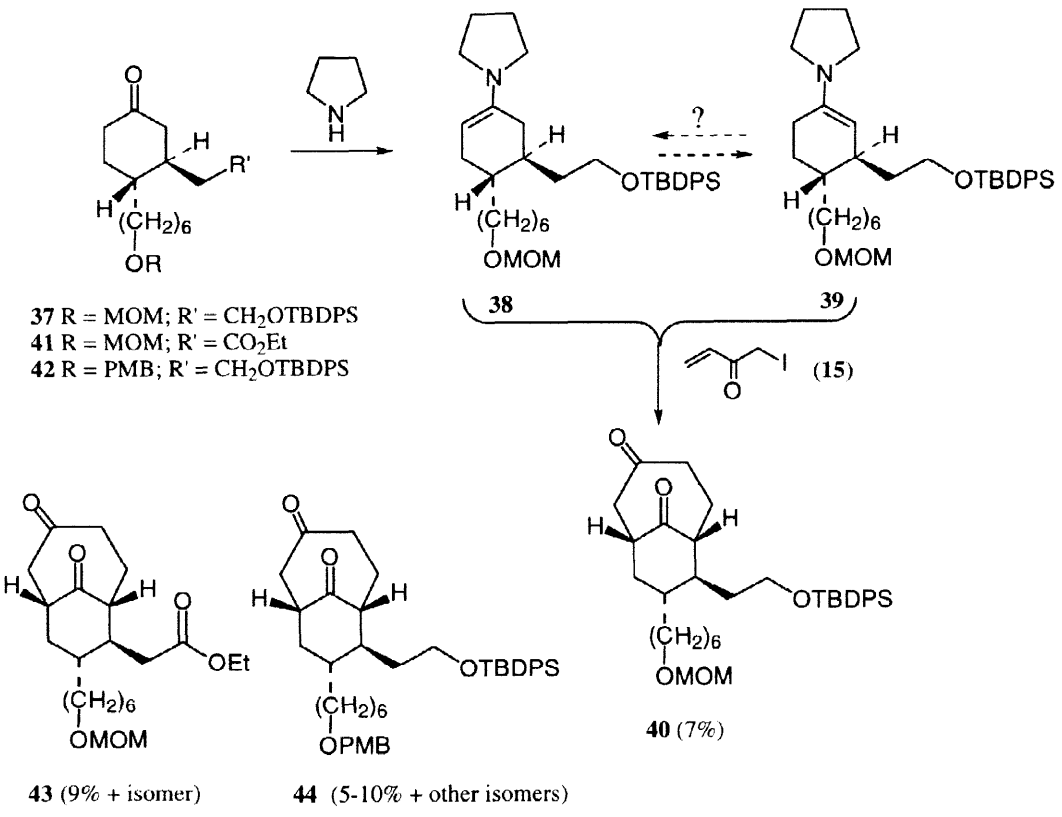
Scheme VI



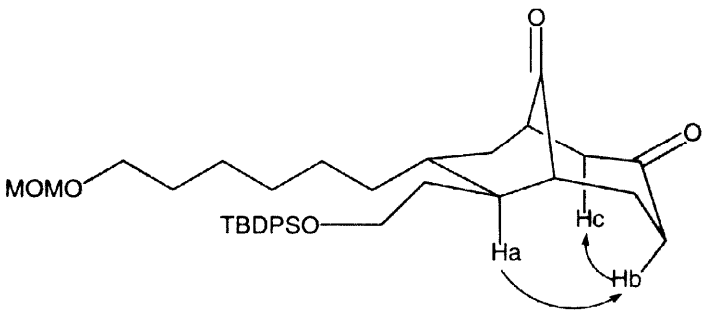
We then examined substrates that might be more realistic for an eventual synthesis of **13** and **14**. Compound **37** (see Scheme VII), available from a parallel but unrelated study,[13] upon reaction with pyrrolidine gave rise to a 1:1 mixture of enamines (**38** and **39**). Treatment with **15** gave a complex mixture. The major component was isolated and identified as **40**, in only 5-10% yield. This assignment was made on the basis of COSY and NOESY experiments. The skeletal structure shown in Scheme VIII was established by proton correlation, and irradiation of H_b (see Scheme VIII) enhanced the signals of H_a and H_c, indicating *trans*-stereochemistry.

We also studied the annulation of ketones **41** and **42** via their enamine mixtures corresponding to the **38, 39** mixture shown for **37**. In each of these instances, an array of closely related products was obtained (ca. 50%). Processing of these materials led to the isolation of **43** (from **41**) and **44**[14] (from **42**), again in only 5 - 10% yields. It will be noted that the annulation sequences on ketones **37**, **41** and **42** correspond in their regiochemistry to having arisen from enamines of the type **39**. However, given the very low yields obtained for the bridged products, and the diversity of products produced, we do not attribute any significance to these results.

Scheme VII



Scheme VIII



In summary, though the route described above is quite interesting for the one step construction of many bridged ring systems from enamines, its application to the synthesis of the CP compounds must await advances in the attainment of synthetically viable control in complex settings.

Experimental

General. Reactions were carried out under an argon atmosphere. THF was distilled from sodium-benzophenone ketyl under an argon atmosphere. Enamines were distilled immediately before use and used directly in the annulations as described in the general procedure below unless otherwise noted. The ketones used in the enamine syntheses were purchased from Aldrich and used without purification. Those ketones that were not commercially available were prepared in one or two steps by literature procedures from starting materials obtained from Aldrich. Chlorotrimethylsilane was distilled. Analytical thin layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed using the indicated solvent on silica gel 60 (40-63 mm). Proton NMR spectra were obtained on a Bruker AMX-400 MHz referenced to $CDCl_3$ (δ 7.26) and the ^{13}C on a Bruker 300 MHz referenced to $CDCl_3$ (δ 77.0). Low- and high resolution mass spectral analyses were obtained on a JEOL JMS-DX-303HF mass spectrometer.

Preparation of 4-methylenecyclohexanone

Methyl triphenylphosphonium bromide (21.4 g, 59.8 mmol) was dissolved in anhydrous benzene (100 mL) at 25° C and potassium *tert*-butoxide was added in a single portion. The resultant solution became bright yellow after stirring at 25° C for 1 h. 1,4-cyclohexanedione *mono*-ethyleneketal (4.15 g, 26.6 mmol) in anhydrous benzene (200 mL) was added *via* cannula. The reaction mixture stirred for 1 h at 25° C and was quenched with sat. NH_4Cl (40 mL). It was then diluted with water (200 mL), the layers were separated and the aqueous layer was extracted with ether (4 x 60 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica (20% ethyl acetate/hexane) gave 4.1 g (100%) of 4-methylenecyclohexanone ethyleneketal.

4-Methylenecyclohexanone ethyleneketal (4.1 g, 26.6 mmol) was taken up in acetone (225 mL) and H_2O (20 mL) was added followed by pyridinium*p*-toluene sulfonate (6.7 g, 26.6 mmol) and the resultant solution was heated to reflux for 6 h. The reaction mixture was cooled to 25° C and concentrated to a small volume (*ca.* 40 mL) *in vacuo*. It was diluted with water (150 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The combined organics were washed successively with sat. aq. $NaHCO_3$ (75 mL), brine (75 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 4-methylenecyclohexanone (2.7 g, 92%) of sufficient purity for conversion to its enamine. Spectral data was in agreement with that previously reported for 4-methylenecyclohexanone.[15]

General preparation of enamines

A 1.0M solution of ketone (1.0 equiv) in benzene was stirred at 25° C in a flask equipped with a Dean-Stark trap and a condenser. Pyrrolidine (1.1 equiv) was added via syringe and the mixture was heated at reflux 12 h, at which point water separation had occurred. The solvent was removed *in vacuo* and the residue was distilled for immediate use in the annulation sequence.

Preparation of 1-iodo-but-3-en-2-one (15).

1-Chloro-but-3-en-2-one[16] **9** (1.35 g, 12.9 mmol) was dissolved in 120 mL acetone at 25° C. Sodium iodide (5.8 g, 39.0 mmol) was added in a single portion. White precipitate appeared immediately and after 5 minutes, the solution was diluted with 300 mL ether and successively washed with water (100 mL), sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was used immediately in the annulation sequence as it rapidly decomposes. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.48 (dd, J=17.5, 10.3, 1H), 6.32 (d, J=17.5, 1H), 5.87 (d, J=10.4, 1H), 3.93 (6s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 132.4, 130.6, 3.6; HRMS (EI) *m/e* calcd for C_4H_5OI 195.9385, found 195.9385 (M^+).

General procedures for the α-α' annulation of enamines

Representative procedure A for annulation with 1-iodo-but-3-en-2-one.

A 0.1-0.2 M solution of freshly distilled enamine (1.0 equiv) in anhydrous THF was stirred at 25° C, and a 1.0 M solution of crude 1-iodo-but-3-en-2-one in THF (prepared from 1.1 equiv 1–chloro-but-3-en-2-one and 1.65 equiv sodium iodide) was added *via* cannula. After consumption of starting material by TLC analysis (typically 0.5-1.0 h at 25° C) the mixture was heated to reflux for 1-2 h, until consumption of intermediate was evident by TLC analysis. The reaction was cooled to 25° C and the insoluble iminium salt was separated by filtration and dried briefly *in vacuo*. (note: some iminium salts were partially soluble in THF- in these cases the filtrate as well as the iminium salt is subjected to the hydrolysis) A 0.2-0.5M solution of iminium salt THF/1N HCl (3:1) was stirred at 25° C for 4 h. The reaction mixture is diluted with 1 N NaOH and extracted repeatedly with CH_2Cl_2 (note: some compounds were extremely resistant to extraction from the aqueous layer). The combined organic layers were washed successively with 10% $Na_2S_2O_4$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Crude products were purified by flash chromatography on SiO_2.

Representative procedure B for annulation of enamines with 1–chloro-but-3-en-2-one and tetrabutylammonium iodide.

Preparation of Bicyclo[4.3.1]decane-3,10-dione (11).

Freshly distilled 1-pyrrolidino-1-cyclohexene **1** (310 mg, 2.0 mmol) was dissolved in 20 mL of anhydrous THF at 25° C. 1–Chloro-but-3-en-2-one (236 mg, 2.3 mmol) in 2 mL anhydrous THF was introduced *via* cannula. Tetrabutylammonium iodide (2.2 g, 6.0 mmol) was then added in one portion. The solution was heated to reflux for 2 h and then cooled to 25° C. 3 N HCl (3.0 mL) was added to the reaction mixture and stirred an additional 5 h. The mixture was diluted with 50 mL 1 N NaOH and extracted with CH_2Cl_2 (6 X 20 mL). The combined organic layers were washed successively with $Na_2S_2O_4$ (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (30% ethyl acetate/ hexane) to give 203 mg (60%) of **11**. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.89 (m, 1H), 2.60-2.79 (m, 3H), 2.52 (ddd, J=16.0, 5.7, 3.9, 1H), 2.40 (ddd, J=16.1, 12.4, 4.1, 1H), 2.13 (m, 1H), 1.80-2.10 (m, 6H), 1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 210.9, 47.7, 44.6, 44.5, 40.7, 32.7, 32.2, 25.5, 15.7; HRMS (EI) *m/e* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1000 (M^+).

Isolation of 2(4-Iodo-3-oxo-butyl)-cyclohexanone (33)

Immediately after the addition of enone **15** to 1-pyrrolidino-1-cyclohexene **1** (as in procedure A), the reaction mixture was passed quickly through a pad of silica and rinsed with 30% EtOAc in hexane. Removal of solvent in vacuo gave iodide **33**. ^1H NMR($CDCl_3$, 400MHz) δ 3.80 (s, 2H), 2.79 (m, 2H), 2.41 - 2.20 (band, 3H), 2.14 - 1.93 (band, 3H), 1.86 (m, 1H), 1.69 - 1.50 (band , 3H), 1.40 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 212.9, 203.1, 49.6, 42.2, 37.0, 34.5, 28.1, 25.1, 22.3, 6.2; LRMS m/e calcd for $C_{10}H_{15}O_2I$ 294.0, found 295.1($M+H^+$)

Preparation of Bicyclo[4.2.1]nonane-3,9-dione (18)

Reaction of 1-pyrrolidino-1-cyclopentene (275 mg, 2.0 mmol) and 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (230 mg, 2.2 mmol) and sodium iodide (495 mg, 3.3 mmol)] via procedure A gave an iminium salt that was partially soluble in THF. Hydrolysis gave a crude product which was purified by flash chromatography on SiO_2 (40% ethyl acetate/hexane) to give 173 mg (57%) of diketone **18**. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.65 (dd, J=14.4, 5.7, 1H), 2.55 (m, 4H), 2.32 (dd, J=14.4, 3.3, 1H), 2.23 (m, 2H), 2.13 (dt, J=20.1, 6.5, 1H), 1.61-1.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.7, 210.3, 45.4, 44.8, 41.0, 40.1, 29.6, 25.83, 25.79; HRMS (EI) *m/e* calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837 (M^+).

Preparation of Bicyclo[4.4.1]undecane-3,11-dione (19)

Reaction of 1-pyrrolidino-1-cycloheptene (330 mg, 2.0 mmol) with 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (230 mg, 2.2 mmol) and sodium iodide (495 mg, 3.3 mmol)] was carried out as described in procedure A. Hydrolysis at 60° C (3.5h) gave a crude product which was purified by flash chromatography on SiO_2 (40% ethyl acetate/hexane) to give 172 mg (48%) of diketone **19**. ^1H NMR ($CDCl_3$,

400 MHz) δ 2.89 (m, 1H), 2.69 (dt, J=16.7, 5.9, 1H), 2.52 (m, 3H), 2.31 (t, J=12.1, 1H), 2.04 (m, 1H), 1.76 (m, 4H), 1.60 (m, 3H), 1.38 (m, 1H), 1.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.1, 209.4, 54.5, 49.1, 46.1, 41.9, 29.9, 28.4, 26.3, 25.4, 23.0; HRMS (EI) *m/e* calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1145 (M^+).

Preparation of 8-ethyl-bicyclo[4.3.1]decane-3,10-dione (20)

Reaction of 1-pyrrolidino-4-ethyl-cyclohexene (900 mg, 5.1 mmol) with 1-iodo-but-3-en-2-one (1.0 g, 5.1 mmol) was carried out as in procedure A. The iminium salt was not isolated before hydrolysis. Purification by flash chromatography on SiO_2 (5% ether/CH_2Cl_2) gave 450 mg (46%) of a diastereomeric mixture of diketone **20**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.82 (m, 1H), 2.65 (m, 3H), 2.48 (m, 1H), 2.37 (m, 1H), 2.13 (m, 1H), 1.65-1.98 (m, 4H), 1.54 (dquintets, J=26.7, 5.0, 2H), 1.25 (m, 2H) 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0, 211.2, 47.2, 45.6, 44.1, 41.0, 39.1, 38.6, 28.7, 28.3, 26.5, 11.6; HRMS (EI) *m/e* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1305 (M^+).

Preparation of 4,4-methyl-bicyclo[4.3.1]decane-3,10-dione (21)

Reaction of *crude* 1-pyrrolidino- 4,4-dimethylcyclohexene[17] (358 mg, 2.0 mmol) with 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (230 mg, 2.2 mmol) and sodium iodide (495 mg, 3.3 mmol)] was carried out as in procedure A. Purification by flash chromatography on SiO_2 (25% ethyl acetate/hexane) gave 136 mg (37%) of diketone **21**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.81 (m, 1H), 2.62-2.75 (m, 3H), 2.37-2.52 (m, 2H), 2.12 (m, 1H), 1.93 (ddd, J=14.1, 9.6, 2.1, 1H), 1.73-1.87 (m, 3H), 1.69 (dd, J=14.1, 3.4, 1H), 1.03 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 210.1, 45.5, 43.1, 41.9, 40.6, 40.1, 32.1, 29.8, 29.5, 26.8; HRMS (EI) *m/e* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1306 (M^+).

Preparation of 4-methylene-bicyclo[4.3.1]decane-3,10-dione (22)

Reaction of 1-pyrrolidino-4-methylene cyclohexene (1.75 g, 10.8 mmol) with 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (1.35 g, 12.9 mmol) and sodium iodide (5.8 g, 39.0 mmol)] was carried out as in procedure A. Purification by flash chromatography on SiO_2 (25% ethyl acetate/hexane) gave 1.05 g (55%) of diketone **22**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.08 (dd, J=6.3, 1.7, 2H), 2.87 (m, 2H), 2.43-2.79 (m, 7H), 2.34 (ddd, J=18.4, 10.6, 4.1, 1H), 2.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 209.9, 138.9, 117.0, 48.0, 44.7, 43.8, 40.1, 39.9, 39.5, 25.1; HRMS (EI) *m/e* calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.1002 (M^+).

Preparation of 8-benzyloxy-bicyclo[4.3.1]decane-3,10-dione (23)

Reaction of *crude* 1-pyrrolidino-4-benzyloxycyclohexene[18] (684 mg, 2.8 mmol) with 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (326 mg, 3.1 mmol) and sodium iodide (693 mg, 1.65 mmol)] was carried out as in procedure A. Purification by flash chromatography on SiO_2 (5% ether/CH_2Cl_2) gave 150 mg (21%) of diketone **23** as a diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 5H), 4.54 (m, 2H), 3.91 (m, 1H), 2.94 (m, 1H), 2.82 (m, 1H), 2.70 (m, 1H), 2.33-2.62 (m, 3H), 2.02-2.25 (m, 5H), 1.81

(m, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 210.6, 128.39, 128.35, 127.6, 127.41, 127. 39, 127,37, 70.4, 69.1, 45.7, 45.3, 41.3, 40.8, 36.4, 35.9, 27.7; HRMS (EI) *m/e* calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1404 (M^+).

Preparation of 8-ethyleneketal-bicyclo[4.3.1]decane-3,10-dione (24)

Reaction of 1-pyrrolidino-4-ethyleneketal cyclohexene (418 mg, 2.0 mmol) and 1-iodo-but-3-en-2-one (196 mg, 2.0 mmol) was carried out as in procedure A. The expected annulation intermediate was detected by TLC analysis but did not convert efficiently to **24**. Hydrolysis was accomplished by addition of H_2O to the reaction mixture and heating to reflux 12 h. Purification by flash chromatography on SiO_2 (25-50% ethyl acetate/hexane) gave 20 mg (<5%) of diketone **24** and two other compounds in minimal yield; these were not characterized. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (t, J=6.3, 2H), 3.83 (t, J=6.3, 2H), 3.55 (dd, J= 10.8, 5.2, 1H), 2.38-2.52 (m, 3H), 2.32 (m, 2H), 2.11-2.21 (m, 5H), 2.02 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.1, 208.8, 106.8, 64.7, 63.6, 47.4, 44.6, 44.44, 44.37, 42.8, 28.4, 25.5; HRMS (EI) *m/e* calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1047 (M^+).

Preparation of 8-oxa-bicyclo[4.3.1]decane-3,10-dione (25)

The crude enamine [prepared as usual from tetrahydro-4*H*-pyran-4-one (220 mg, 2.2 mmol) and pyrrolidine (235 mg, 3.3 mmol)] was dried under high vacuum before being used directly in the annulation. Reaction of this enamine with 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (230 mg, 2.2 mmol) and sodium iodide (495 mg, 3.3 mmol)] was carried out as described in procedure A . Purification by flash chromatography on SiO_2 (50% ethyl acetate/hexane) gave 114 mg (31%, 2 steps from tetrahydro-4*H*-pyran-4-one) of diketone **25**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (dd, J=37.1, 12.0, 2H), 3.82 (dd, J=27.8, 11.9, 2H), 2.95 (ddd, J=18.0, 12.2, 5.5, 1H), 2.67 (m, 4H), 2.52 (dt, 18.1, 4.9, 1H), 2.18 (m, 1H), 2.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 209.7, 71.4, 71.3, 48.8, 48.0, 43.2, 39.1, 25.7; HRMS (EI) *m/e* calcd for $C_9H_{12}O_3$ 168.0786, found 168.0786 (M^+).

Preparation of 9,9-dimethyl-bicyclo[4.3.1]decane-3,10-dione (32)

Reaction of 1-pyrrolidino-3,3-dimethylcyclohexene[19] (523 mg, 2.9 mmol) with 1-iodo-but-3-en-2-one [prepared from 1-chloro-but-3-en-2-one (336 mg, 3.2 mmol) and sodium iodide (723 mg, 4.8 mmol)] was carried out as described in procedure A. Purification by flash chromatography on SiO_2 (40% ethyl acetate/hexane) gave 350 mg (62%) of diketone **32**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.93 (dd, J=21.1, 13.0, 1H), 2.64 (m, 1H), 2.44 (ddd, J=19.1, 6.0, 3.5, 1H), 2.35 (dd, J=13.0, 8.5, 1H), 2.28 (ddd, 19.0, 11.9, 3.8, 1H), 2.17 (t, J=8.3, 1H), 1.88-2.03 (m, 4H), 1.52 (m, 1H), 1.23 (m, 1H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 210.3, 56.2, 46.7, 41.2, 39.3, 38.3, 28.3, 27.0, 26.8, 26.3, 24.2; HRMS (EI) *m/e* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1307 (M^+).

Preparation of Bicyclo[4.3.1]dec-4-ene-3,10-dione (27)

Bicyclo[4.3.1]decane-3,10-dione (**11**) (244 mg, 1.47 mmol) was dissolved in anhydrous THF (12 mL) and cooled to -78° C. Lithium hexamethyldisilazane (1.0M in THF, 1.65 mL) was added via syringe. The resultant mixture stirred at -78° C for 5 minutes, and triethylamine (615 mL, 4.41 mmol) and TMSCl (317µl, 2.25mmol) was added *via* syringe. The reaction mixture warmed to 0° C over *ca.* 0.5 h and was quenched with sat. aq. $NaHCO_3$ (1.0 mL). It was diluted with ethyl acetate (75 mL), washed successively with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($Na_2S_2O_4$), filtered, and concentrated *in vacuo* to give the crude silyl enol ether **26**, which was used in the next reaction without further purification.

Silyl enol ether **26** was azeotroped from benzene (3x10 mL) and dissolved in anhydrous acetonitrile (10 mL) at 25° C. Palladium(II) acetate (363 mg, 1.62 mmol) was added in a single portion and the reaction mixture stirred 12 h at 25° C. The solution was filtered through a pad of celite and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (30% ethyl acetate/hexane) gave 158 mg (66%) of enone **27**. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.31 (dd, J=12.2, 7.6, 1H), 6.19 (d, J=12.3, 1H), 3.47 (m, 1H), 2.84 (m, 1H), 2.63, (m, 2H), 1.84-2.02 (m, 4H), 1.59 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 201.9, 139.2, 133.0, 52.6, 45.8, 44.6, 32.0, 30.7, 15.4 ; HRMS (EI) *m/e* calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0843 (M^+).

Preparation of 10-ethyleneketal-bicyclo [4.3.1] decan-3-one (28)

Bicyclo[4.3.1]decane-3,10-dione (**11**) (62 mg, 0.37 mmol) was dissolved in anhydrous benzene (10 mL) and ethylene glycol (2.1 mL, 37 mmol) was added followed by *p*-toluenesulfonic acid (7 mg, 0.04 mmol). The solution was heated to reflux and monitored by TLC. After 7 days, TLC analysis indicated the consumption of starting material. The reaction mixture was cooled to 25° C and the solvent was removed *in vacuo*. The residue was partitioned between water (15 mL) and CH_2Cl_2 (15 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic fractions were washed successively with sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on SiO_2 (20% ethyl acetate/hexane) gave 54 mg (69%) of ketal **28**. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (dd, J=13.4, 5.5, 4H), 2.85 (dd, J=13.7, 5.8, 1H), 2.50-3.50 (m, 2H), 2.39 (dd, J=13.6, 5.6, 1H), 2.23 (m, 1H), 1.99 (m, 4H), 1.68 (m, 3H), 1.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 111.2, 64.4, 64.1, 44.9, 40.9, 38.5, 37.6, 27.8, 27.6, 24.6, 17.2; HRMS (EI) *m/e* calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1263 (M^+).

Preparation of 7-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-8-(6-methoxy-hexyl)-bicyclo[4.3.1]decane-3,10-dione (40)

Enamines **38** and **39** were prepared from ketone **37** (131 mg, 0.25 mmol) and pyrrolidine (89 mg, 1.25 mmol) in the presence of catalytic *p*-toluenesulfonic acid, isolated as usual and dried under high vacuum. Reaction of the resultant crude mixture of enamines **38** and **39** with 1-iodo-but-3-en-2-one (49 mg, 0.25 mmol) was carried out as described in procedure A. The iminium salt was hydrolyzed without isolation. Proton NMR of the crude mixture after workup showed diketone **40** and a small amount of a diastereomer. Purification by flash chromatography on SiO_2 (5% ether/CH_2Cl_2 and then 25% ethyl acetate/hexane) gave 10

mg (7%, 2 steps from ketone **37**) of diketone **40**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (m, 4H), 7.40 (m, 6H), 4.62 (s, 2H), 3.62-3.73 (m, 2H), 3.51 (t, J=6.6, 2H), 3.36 (s, 3H), 2.70 (dd, J=14.7, 4.9, 1H), 2.53 (m, 1H), 2.46 (m, 3H), 2.35 (dd, J=12.9, 2.2, 1H), 2.06 (m, 1H), 1.98 (ddd, J=14.2, 8.5, 3.3, 1H), 1.68-1.81 (m, 3H), 1.60 (m, 5H), 1.11-1.50 (m, 8H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.8, 210.3, 135.6, 135.5, 133.6, 129.7, 127.7, 96.4, 67.8, 61.0, 55.1, 52.8, 45.9, 44.2, 43.0, 41.9, 39.6, 37.7, 34.7, 32.5, 29.7, 28.9, 26.8, 26.2, 19.2; HRMS (EI) *m/e* calcd for $C_{41}H_{47}O_4Si$ 592.3584, found 631.3244 (M^++K).

Preparation of [8-(6-methoxymethoxy-hexyl)-3,10-dioxo-bicyclo[4.3.1]dec-7-yl]acetic acid ethyl ester (43)

Enamine was prepared from ketone **41** (150 mg, 0.46 mmol) and pyrrolidine (164 mg, 2.30 mmol) in the presence of catalytic *p*-toluenesulfonic acid, isolated as usual and dried under high vacuum. Reaction of the resultant crude mixture of enamines with 1-iodo-but-3-en-2-one (49 mg, 0.25 mmol) was carried out as described in procedure A. The iminium salt was not isolated before hydrolysis. Proton NMR of the crude mixture after workup showed diketone **43** and a small amount of a diastereomer. These diastereomers could not be separated by conventional flash chromatography. Purification by flash chromatography on SiO_2 (5% ether/CH_2Cl_2 and then 35% ethyl acetate/hexane) gave 16 mg of diketone **43** contaminated with an unidentified diastereomer, (9%, 2 steps from ketone **41**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61 (s, 2H), 4.12 (q, J=7.1, 2H), 3.51 (t, J=6.6, 2H), 3.36 (s, 3H), 2.81 (dd, J=13.5, 5.2, 1H), 2.58-2.73 (m, 2H), 2.48 (m, 1H), 2.29-2.41 (m, 2H), 2.11-2.28 (m, 2H), 2.02 (dd, J=16.4, 10.7, 1H), 1.85-1.97 (m, 1H), 1.61 (m, 1H), 1.60 (m, 2H), 1.20-1.43 (m, 8H), 1.26 (t, J=7.1, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 210.6, 172.3, 96.4, 67.7, 60.8, 55.1, 49.4, 47.2, 45.1, 42.4, 40.7, 34.5, 32.5, 32.2, 29.7, 29.5, 29.4, 27.3, 26.8, 26.1, 14.2; HRMS (EI) *m/e* calcd for $C_{22}H_{37}O_6$ 397.2590, found 397.2579 (M^+).

Preparation of 7-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-8-(6-4-methoxy-benzyloxy)-hexyl)-bicyclo[4.3.1]decane-3,10-dione (44)

Enamine was prepared as usual from ketone **42** and pyrrolidine. The crude mixture of enamines (410 mg, 0.62 mmol) was dissolved in 6 mL of anhydrous THF at 25° C. A solution of 1–chloro-but-3-en-2-one (72 mg, 0.69 mmol) in 2 mL anhydrous THF was introduced *via* cannula. Tetrabutylammonium iodide (697 mg, 1.89 mmol) was then added in one portion. The solution was heated to reflux for 2 h and then cooled to 25° C. Aqueous HCl (0.5 N, 3.0 mL) was added to the reaction mixture and stirred an additional 1 h. The mixture was diluted with 20 mL aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 (6 X 20 mL). The combined organic layers were washed successively with $Na_2S_2O_4$ (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (10% ethyl acetate/ hexane) to give 47 mg (11%) of diketone **44** and 170 mg of unseparable isomers. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.42 - 7.36 (band, 6H), 7.27 (d, J = 8.5Hz, 2H), 6.88 (d, J = 8.5Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.69 (m, 1H), 3.65 (M, 1H), 3.43 (t, J = 6.61Hz, 2H), 2.70 (dd, J = 14.8, 4.9Hz, 1H)2.58 - 2.35 (band, 4H), 2.08 (m,1H), 1.99 (m, 1H), 1.77 - 1.68 (band, 2H), 1.62 - 1.50 (band, 4H), 1.40 - 1.10 (band,

10H), 1.04 (s, 9H), 0.88(t, J = 6.7Hz, 1H); ^{13}C NMR (125Hz, $CDCl_3$) δ 218.8, 210.2, 159.1, 135.5, 133.6, 130.7, 129.7, 129.2, 127.7, 113.7, 72.5, 70.1, 61.0, 55.3, 52.8, 45.9, 44.2, 43.0, 41.8, 39.6, 37.8, 35.0, 32.8, 29.8, 29.7, 26.8, 26.2, 19.2; LRMS m/e calcd for $C_{42}H_{56}O_5Si$ 668.4, found 691.2 ($M + Na^+$)

Contribution from [a]The Department of Chemistry, Columbia University, Havemeyer Hall, New York, N.Y. 10027, [b]The Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., Box 106, New York, N.Y. 10021, USA and The Department of Chemistry, Butler University, 4600 Sunset Avenue, Indianapolis, IA 46208.

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