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Synthetic studies on the DEF-rings of FR182877 and hexacyclinic acid☆

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Abstract—A synthesis of model DEF-rings of the polyketide anti tumor natural products FR182877 and hexacyclinic acid has been achieved. The key steps in the synthesis are an intramolecular Pd(0) catalyzed allylic substitution reaction, which was used to generate a 9-membered carbocycle, and a novel transannular iodocyclization reaction which furnished the DF-rings of both natural products.

1. Introduction

As part of a screening program searching for new antimitotic compounds the Fujisawa Pharmaceutical Company isolated FR182877 **1**, from the culture broth of *Streptomyces* sp. no. 9885.[1] This compound has an unprecedented hexacyclic ring system, with a bridgehead double bond as part of a vinylogous carbonate unit, and has been shown to have potent anti-tumor activity. In biological assays FR182877 was shown to have IC_{50} values of between 73 and 21 ng/ml depending on the cell line, and it has been shown to prolong the life of tumor bearing mice. The mode of action of FR182877 has been shown to be that of an antimitotic agent as HT-29 cells treated with FR182877 were determined to be in the G2/M phase and microtubule assembly was detected.[2,3] These findings are consistent with other known antimitotic agents such as taxol and the epothilones. Originally the structure was assigned as the enantiomer of **1**.[4] This error was realized by the efforts of Sorensen when he achieved the first total synthesis of the unnatural enantiomer.[5] Total synthesis of the natural enantiomer, by the group of Evans, followed closely behind.[6] Both of these elegant total syntheses utilized a similar approach, which involved the synthesis of a macrocyclic precursor followed by spontaneous tandem transannular Diels–Alder/hetero Diels–Alder reactions to install five of the six rings. The final E-ring was installed by lactonization.

Several other groups have also targeted FR182877 for synthesis, with Prunet,[7] Nakada[8] and Roush[9] reporting syntheses of the A-, AB- and ABC-rings, respectively. Prunet adopted a ring closing metathesis approach to the A-ring. Nakada utilized an intramolecular Diels–Alder reaction to furnish an AB-ring system, while Roush employed a Morita–Baylis–Hilman reaction to construct the ABC-rings of FR182877. The DEF-rings of FR182877 have also been the subject of synthetic study, with Armstrong reporting a procedure for the synthesis of a number of DE-ring analogues.[10]

Another new natural product, hexacyclinic acid **2**, which bears remarkable similarity to FR182877, was isolated contemporaneously from the culture broth of *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013) following an OSMAC (one strain/many compounds) cultivation program.[11] The structure of hexacyclinic acid was determined by NMR studies and X-ray crystallography. Hexacyclinic acid shows weak cytotoxic activity when tested against HM02, HEPG2 and MCF7 cell lines with GI_{50} values up to 14.0 $\mu mol\,L^{-1}$. The structural similarity between FR182877 and hexacyclinic acid suggests that these two molecules may have a similar biogenetic origin. Comparison of both structures show that they differ only in the oxidation state of C13, the stereochemistry of the AB- and BC-ring junctions, acylation of the C9 hydroxyl and the level of hydration of the DE-ring junction. This similarity was noted by Evans, who proposed that the different stereochemistry around the B-ring could result from

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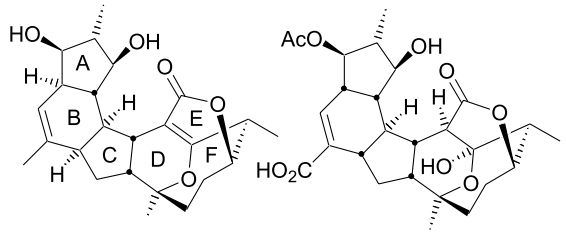
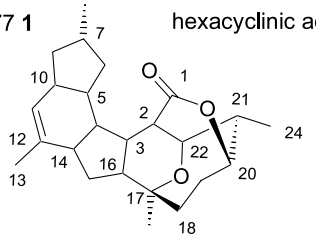
differing modes of intramolecular Diels–Alder cyclization. However, extensive studies by Evans yielded only the diasteroisomer which led to FR182877.[6] We too were intrigued by the prospect of developing a common strategy for the synthesis of both FR182877 and hexacyclinic acid, however, we decided to focus our initial endeavors on the challenging DEF-ring systems of these natural products.[12,13]



FR182877 **1** hexacyclinic acid **2**

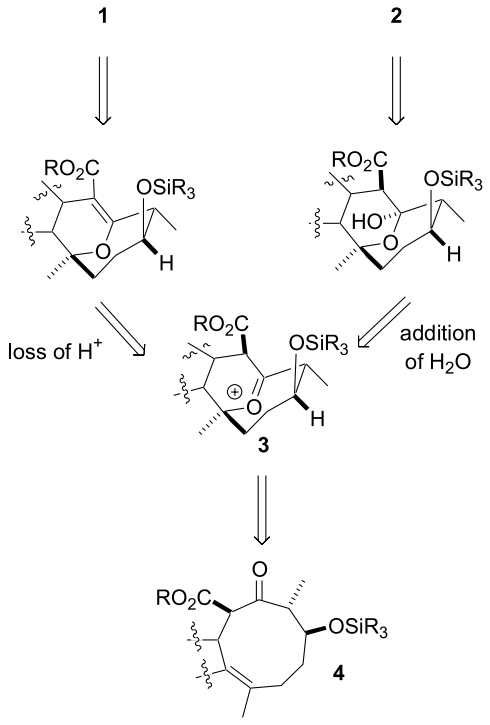


2. Results and discussion

Our alternative strategy for the synthesis of the DEF-rings does not involve their formation through an intramolecular hetero Diels–Alder reaction. Instead we proposed an approach in which the DEF-rings are constructed from a common carbocyclic precursor by means of a transannular cationic cyclization event. As such cationic cyclisations are known in the biosynthesis of other natural products, this approach provides an alternative biosynthetic hypothesis for the construction of the DEF-ring cores of these natural products.

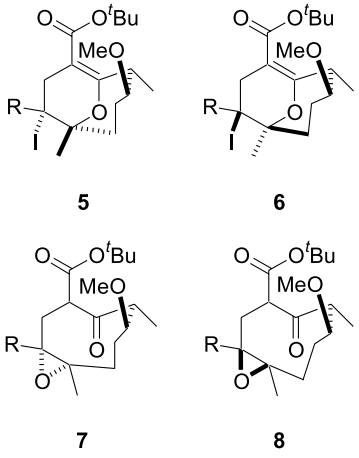
Retrosynthetic analysis of the DEF-rings of both FR182877 and hexacyclinic acid is outlined in Scheme 1. We reasoned that both the FR182877 and the hexacyclinic acid DEF-ring systems could be accessed from the same oxocarbenium ion **3**. In the synthetic direction the FR182877 DEF-rings would arise from the loss of a proton from **3**, while the hexacyclinic acid DEF-ring system would result from the addition of water to **3**. In turn, **3** would be formed from the transannular intramolecular cationic cyclization of the ketone carbonyl of a β-ketoester on to an appropriately positioned double bond. This disconnection reveals 9-membered carbocycle **4** as the immediate precursor to **3**.

There are a number of key stereochemical concerns arising from this strategy. The primary one being whether the transannular cationic cyclization event would occur on the desired α-face or undesired β-face of the carbon–carbon double bond. In order to generate confidence that the correct mode of cyclization would ensue molecular modelling studies were conducted. We initially modelled the two possible diastereomers resulting from iodocyclization on to both an α- and β-iodonium ion, **5** and **6**, respectively.[14]



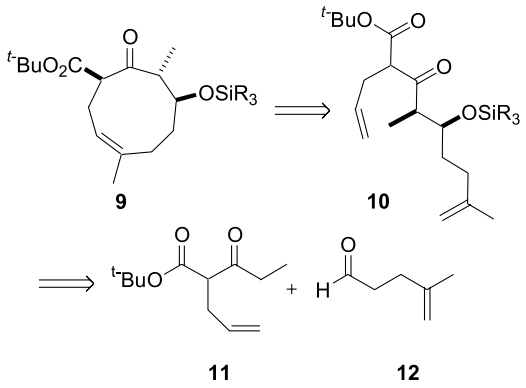
Scheme 1.

Molecular modelling studies on these ring systems indicated that the desired diastereomer **6** was some 4.5 kcal mol^{-1} lower in energy than **5**. Since the intermediate iodonium ions were not parameterized for in our version of Macromodel the corresponding epoxides **7** and **8** were modelled. The results of this study suggested that the energy difference between the two epoxides were minimal, at only 0.35 kcal mol^{-1}. If the difference in energy between the cyclized products is reflected in the energies of their respective transition states, and the difference in the epoxides is carried through to the corresponding iodonium ions then, given the reversibility of iodonium ion formation we anticipated that conditions could be found to favor formation of the desired thermodynamic product **6**.



Encouraged by the results of the molecular modelling studies, we embarked upon the synthesis of a model 9-membered carbocycle to test the synthetic utility of our

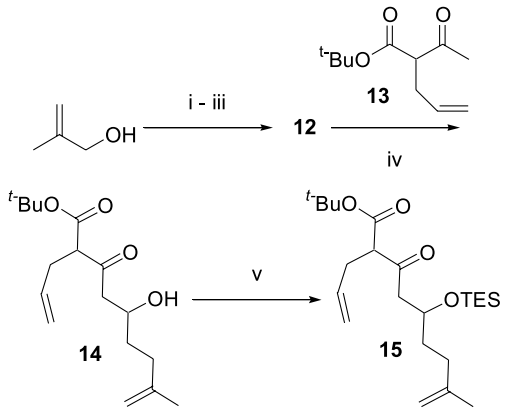
transannular cationic cyclization approach to the DEF-rings of FR182877 and hexacyclinic acid. Our initial retrosynthetic plan is given in Scheme 2. Scission of the trisubstituted double bond in **9** reveals diene **10**, which can be constructed from the aldol reaction of β-ketoester **11** with aldehyde **12**. However, due to the general lack of diastereoselectivity in the aldol reactions of γ-substituted β-ketoesters,[15] and the desire to test our key transannular cationic cyclization strategy, we opted to synthesize a 9-membered ring without the α-methyl group.



Scheme 2.

2.1. Synthesis of the cationic cyclization precursor 17

Aldehyde **12** was synthesized in 3 steps in 91% yield from methallyl alcohol by Johnson orthoester Claisen rearrangement and lithium aluminium hydride reduction, followed by a Swern oxidation. *tert*-Butyl acetoacetate was allylated with NaH and allyl bromide with the reaction being quenched after 6 min to avoid formation of the *bis*-allylated product. Diene **14** was formed in 78% yield as an inseparable mixture of diastereomers by the slow addition of aldehyde **12** to a solution of the dianion of **13**. The free hydroxyl was protected as the TES ether by the action of TESCl and DMAP in pyridine to provide **15** in 90% yield (Scheme 3).



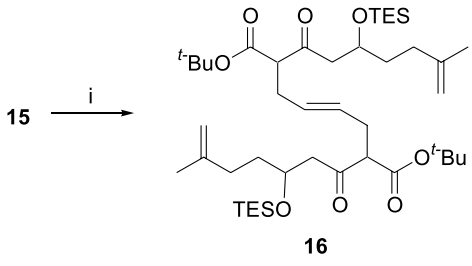
Scheme 3. Reagents and conditions: (i) propionic acid, triethyl orthoacetate, 120 °C, 98%; (ii) $LiAlH_4$, Et_2O, 0 °C, 99%; (iii) DMSO, oxalyl chloride, triethylamine, CH_2Cl_2, −78 °C, 94%; (iv) NaH, 0 °C, THF then *n*BuLi, 0 °C, THF; −78 °C, addition of **12**, 78%; (v) TESCl, DMAP, pyridine, 90%.

Given the recent advances in ring closing olefin metathesis (RCM) we investigated the possibility of closing the 9-membered carbocycle by this reaction. Fürstner has reported the use of Grubbs' second generation catalyst to achieve the formation of 5 and 6 membered rings containing either a tri- or tetra-substituted double bond.[16] Contemporaneously with our studies Clark reported the use of the RCM reaction for the formation of a 9-membered carbocycle in his synthesis of the cornexistin core.[17] In addition to these studies, Granja used Grubbs' second generation catalyst to form a tri-substituted double bond in an 8-membered carbocyle.[18]

When our metathesis precursor **15** was subjected to typical metathesis conditions of 1 mol% Grubbs' second generation catalyst, 0.32 M concentration in toluene at 80 °C it resulted in removal of the TES group (Table 1, entry 1). With 10 mol% catalyst and higher dilution no reaction was observed. Upon extending the reaction time to 5–10 days, dimerization at the least substituted double bond to give **16** was seen (Table 1, entry 2), (Scheme 4). Although this was not the desired result it did show that the metathesis reaction was occurring. In order to promote cyclization over dimerization the reaction concentration was reduced (Table 1, entries 3 and 4), however, this led to the formation of reduced quantities of dimer **16** over a longer time. Further dilution resulted in no reaction (Table 1, entries 5–8).

Table 1. Results of concentration studies on the metathesis reaction

Entry	Concn. (M)	Catalyst (mol%)	Result
1	0.32	1	Loss of TES
2	0.036	10	Dimer **16**
3	0.0036	10	Dimer **16**
4	0.0030	10	Trace dimer **16**
5	0.0024	10	No reaction
6	0.0016	10	No reaction
7	0.0008	10	No reaction
8	0.0004	10	No reaction

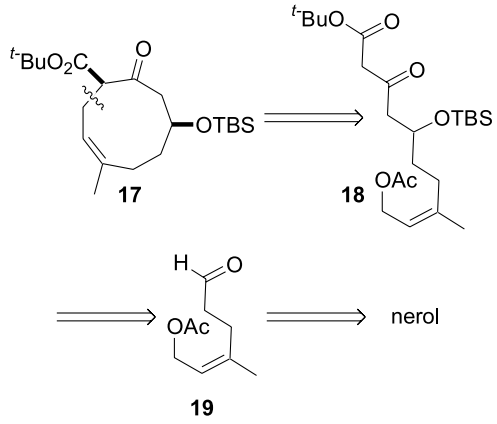


Scheme 4. Reagents and conditions: (i) Grubbs' second generation catalyst, toluene, 80 °C, 5–10 days.

Following the failure of the metathesis strategy to deliver the 9-membered carbocycle a recent hypothesis came to light.[19] This hypothesis suggested that substrates with an oxygen atom five or six atoms away from the alkylidene carbene are more susceptible to the problem of chelation rendering the catalyst unreactive. Since chelation is possible in our substrate regardless of which double bond reacts first,

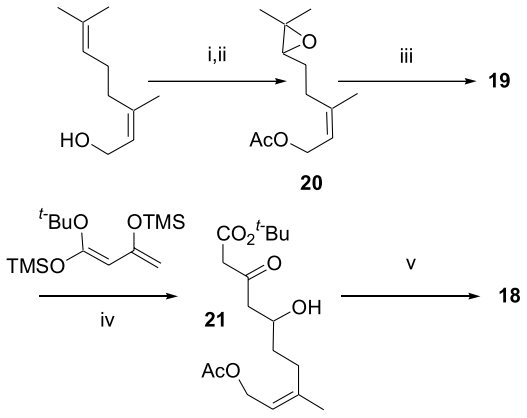
the need for vastly extended reaction times may not be surprising.

Due to the failure of the RCM approach to yield any of the desired 9-membered carbocycle an alternative approach to its synthesis was developed. Scission of the indicated bond in **17** reveals acyclic precursor **18**. In the synthetic direction it was envisaged that an intramolecular allylation reaction would close the ring and furnish **17**. Cyclization precursor **18** would arise from the aldol reaction of *tert*-butyl acetoacetate on aldehyde **19**, which is derived from nerol (Scheme 5).



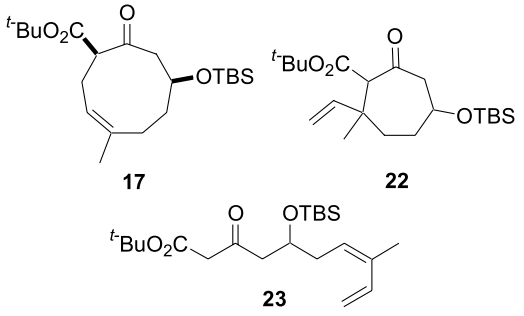
Scheme 5.

Aldehyde **19** was prepared from nerol by acylation with acetic anhydride in pyridine in 100% yield, followed by epoxidation of the terminal double bond with *m*CPBA in 85% yield, and periodic acid oxidative cleavage to generate the desired aldehyde **19** in 81% yield.[20] Mukaiyama aldol reaction of the *bis*-silyl enolether of *tert*-butyl acetoacetate and aldehyde **19** in the presence of $TiCl_4$ gave the desired aldol product **21** in 79% yield. The free hydroxyl group of **21** was further protected in 98% yield as the TBS ether with TBSOTf in pyridine at −30 °C to provide **18** (Scheme 6).



Scheme 6. Reagents and conditions: (i) DMAP, acetic anhydride, pyridine, 18 h, 100%; (ii) *m*CPBA, 2 h, CH_2Cl_2, 0 °C, 85%; (iii) periodic acid, THF/water, 2 h, 0 °C, 81%; (iv) $TiCl_4$, CH_2Cl_2, −78 °C, 3 h, 79%; (v) TBSOTf, py, −35 °C, 8 h, 97%.

As the formation of 9-membered carbocyclic rings via S_N^2 displacement is notoriously troublesome, we decided to investigate the use of an intramolecular Pd(0) catalyzed allylic substitution reaction. Trost has shown that cyclisations wherein 9- and 7-membered ring formation compete, the reaction is finely balanced, with bulkier nucleophiles favoring attack at the terminus of the π-allyl system generating the 9-membered ring.[21] In cases where the nucleophile is a β-ketoester problems of competing *O*-alkylation arise.[22] Theoretically the product of *O*-alkylation may be converted to the desired carbocycle by a sigmatropic rearrangement. Initial trials of the Pd(0) catalyzed allylic substitution reaction using the conditions reported by Trost led to a complex mixture of products, from which 3 compounds were isolated in poor yields. These were later identified as 9-membered ring **17** (trace amounts), 7-membered ring **22** (18%) and diene **23** (72%). While **17** and **22** arise from attack of the nucleophile on the opposite ends of the π-allyl system, **23** arises from its elimination. Although elimination was not unexpected, the extent to which it occurred was. Indeed, only two examples of this process could be found in the literature and then elimination occurred because no nucleophile was present.[23] Performing the reaction without first pre-forming the anion did not result in diene formation, demonstrating that deprotonation of the π-allyl system by the pre-formed anion was responsible for the elimination. Syringe pump addition of the anion to a solution of the catalyst significantly reduced the amount of diene **23** formed. To favor the formation of **17** over **22**, a number of different diphosphine ligands and stoichiometries were screened. The most significant of these results are displayed in Table 2.



As can be seen in Table 2, entry 3 the formation of **17** peaked with the use of dppe as a ligand. This could be attributed to the diphosphine ligand affecting the rate of formation of the π-allyl complex. Slowing the formation of

Table 2. Optimization of the Pd(0) catalyzed π-allyl substitution reaction

Entry[a]	Ligand	Yield (%)[b]	Ratio **17**:**22**:**23**[c]
1	Ph_3P	91	trace:1:4
2	dppm	97	trace:1:8
3	dppe	93[d]	2:trace:1
4	dppp	94	1:1:2
5	dppf	90	3:2:8

[a] Reagents and conditions: (i) **18**, NaH, $Pd(PPh_3)_4$ (5 mol%), ligand (10 mol%), THF, reflux.
[b] Combined yield. All compounds co-ran and exhaustive flash column chromatography provided only small amounts of purified products.
[c] By ^1H NMR (400 MHz).
[d] Isolation of **17** (61%) and **23** (32%) proved possible by flash column chromatography on $AgNO_3$ impregrated silica gel.[24,25]

the complex due either to the rates of diphosphine chelation (entries 2 and 4), or to sterics (entry 5) would result in an increase in pre-formed anion concentration, and hence subsequent increase in diene production. Despite optimization of the reaction, the three major products proved difficult to separate; with exhaustive chromatography furnishing only milligram quantities of each product. However, silver nitrate absorbed onto silica gel could be used to aid chromatographic separation.[24] Trials of this method successfully separated the 9-membered ring **17** from the mixture but the 7-membered ring **22** and diene **23** remained mixed. Small quantities of **23** were eventually purified by extensive chromatography.[26] Optimization of the Pd(0) catalyzed allylic substitution reaction resulted in the desired 9-membered ring product **17** being isolated in 61% yield as a single diastereomer. To our knowledge this is the first report of this type of Pd(0) catalyzed allylic substitution reaction where the β-ketoester nucleophile is internal to the ring being formed. ^{1}H NMR and gradient NOE experiments determined that the relative stereochemistry of the substituents on the 9-membered ring were *cis*. Interestingly, this also highlighted that the 9-membered ring existed in a chair–boat conformation (Fig. 1).[27]

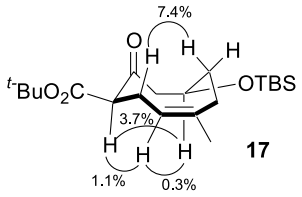


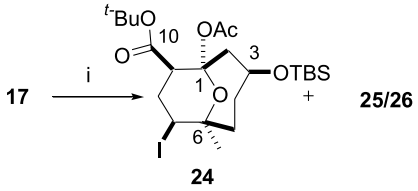
Figure 1. Key NOEs indicating the chair–boat conformation of **17**.

2.2. Synthesis of a model DEF-ring core of hexacyclinic acid

With quantities of **17** now available we could study the crucial transannular cationic cyclization reaction. We were initially attracted to the work of Gopalan[28] who showed that internal nucleophiles, such as carbonyl groups of esters, can trap the cation generated by the addition of $Hg(OTf)_2$ to a proximal double bond in an acyclic polyene. Gopalan also showed that when the nucleophile was a β-ketoester, cyclization occurred through the oxygen of the ketone carbonyl rather than through the ester carbonyl. In this case loss of a proton generated a double bond to give a cyclic enol ether. This is applicable to the formation of the DEF-rings of FR182877, but examples of the addition of an external nucleophile required to generate the hexacyclinic acid system were not reported.

Attempts at cyclizing **17** with $Hg(OTf)_2$ using the procedures of either Gopalan[28] or Nishizawa[29] resulted in a complex mixture of products. It was thought that the TfOH formed was causing decomposition of the desired product, however, when the cyclizations were performed in the presence of an amine base no reaction resulted. Disappointed at this lack of success, we turned our attention to halocyclization reactions. The use of iodine reagents, such as I_2,[30] NIS,[31] NIP[32] and AcOI,[33] for iodolactonization and iodoetherification have been widely reported in the literature, but these have usually involved cyclization of a carboxylic acid or of a free hydroxyl group onto an iodonium ion. At the time of these studies we could find no examples of a transannular iodocyclisation of a ketone carbonyl group. The most relevant conditions were reported for the use of AcOI by Cambie and co-workers, who perform a transannular iodoetherification across an 8-membered ring.[33]

Trial reactions with AcOI in AcOH gave our first promising cyclization results. When **17** was treated with AcOI in glacial acetic acid a new product was formed, which was assigned as the DF-ring system **24**, similar to that in hexacyclinic acid. The formation of this product implies the intermediacy of an oxocarbenium ion, which is quenched by the addition of the AcOH solvent (Scheme 7).[27]



Scheme 7. Reagents and conditions: (i) iodine, silver acetate, AcOH, rt, 1 h, **24** (61%), **25/26** (30%).

Two additional side products which proved inseparable from each other were also isolated from the reaction. The structures of these were determined by X-ray crystallography as a 1:1 co-crystal of iodolactones **25** and **26** (Fig. 2), resulting from a 5-*exo* and 6-*endo* cyclization, respectively of the ester carbonyl group.

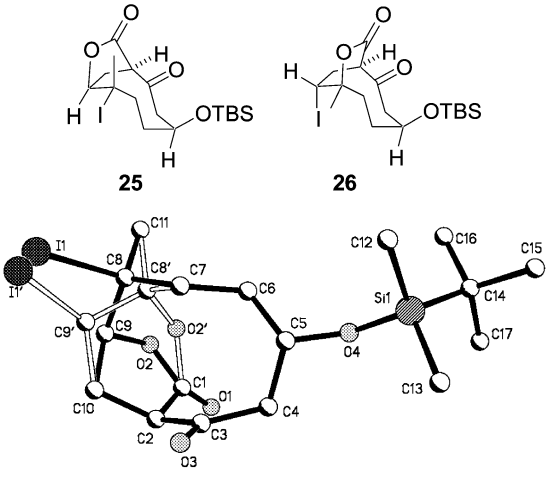
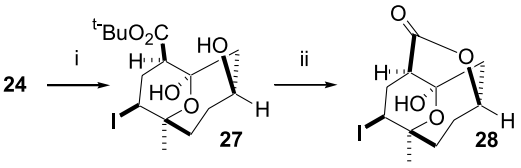
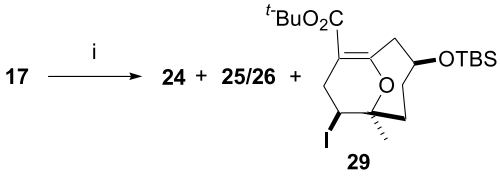


Figure 2. Structure of the 1:1 co-crystal of the 5-*exo* **25** and 6-*endo* **26** products arising from cyclization through the ester carbonyl. The open bonds and primed atom labels represent where the 6-*endo* product **26** deviates from the structure of the 5-*exo* product **25**.

With the DF ring system **24** available, removal of the protecting groups was necessary (Scheme 8). Treatment of **24** with two equivalents of HF in MeCN gave the hemi-ketal **27** as a white crystalline solid in 97% yield. A single crystal X-ray structure of **27** (Fig. 3) showed the desired relative stereochemistry and confirmed our earlier NMR assignment of **24**. No unusual features were observed in the crystal.



Scheme 8. Reagents and conditions: (i) HF, MeCN, rt, 18 h, 97%; (iv) TFA, CH_2Cl_2, rt, 4 days 100%.



Scheme 9. Reagents and conditions: (i) iodine, silver acetate, AcOH, rt, 1 h, **24** (61%), **25/26** (30%) and **29** (5%).

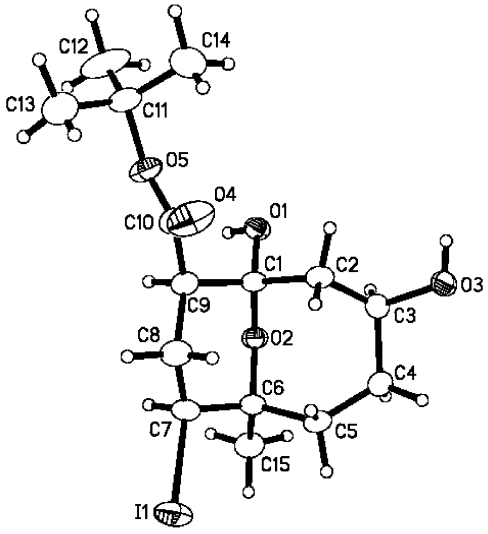


Figure 3. Crystal structure of the hexacyclinic acid DF ring intermediate **27**.

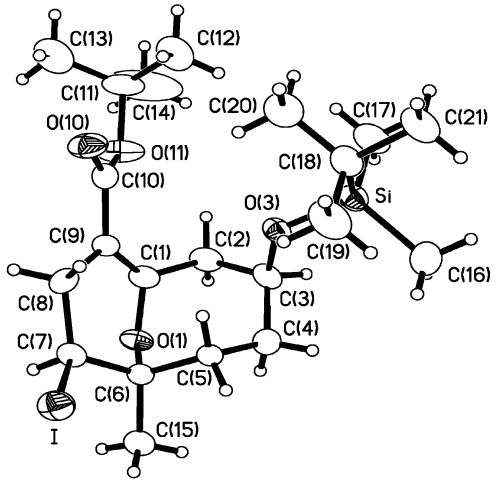


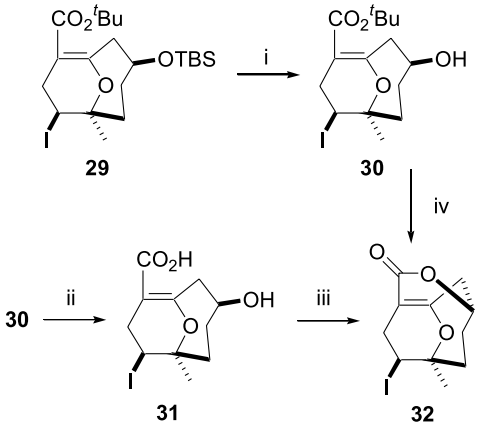
Figure 4. Crystal structure of the FR182877 DF ring intermediate **29**.

Removal of the *tert*-butyl ester proved troublesome. Exposure of hemi-ketal **27** to TFA in CH_2Cl_2 could be seen, by TLC, to remove the *tert*-butyl group but isolation of the resulting acid proved to be difficult. Isolation of a product was finally achieved by exposure of the hemi-ketal **27** to TFA in CH_2Cl_2 for an extended time period. This resulted in removal of the ester and subsequent lactonization in one reaction. Isolation of the model DEF system of hexacyclinic acid **28** was achieved quantitatively from hemi-ketal **27** (Scheme 8). The ^{1}H NMR spectrum of the model DEF-ring system **28**, as well as showing that the protecting groups had been removed, gave key evidence for the lactonization, in the form of the carbinol resonance H-3, which had shifted to a higher frequency (δ 5.52) as is expected by lactonisation.[27]

2.3. Synthesis of a model DEF-ring core of FR182877

When performed on quantities greater than 0.5 g, the reaction of **17** with AcOI in AcOH delivered around 5% of a previously undetected white crystalline solid. The ^{1}H NMR spectrum of this solid showed retention of the TBS group, the *tert*-butyl ester and the methyl group although, it did not show incorporation of an acetate group. Ten other distinct resonances with relative integrals of one were also present. The spectrum was assigned as the FR182877 model DF-ring system **29**[27] (Scheme 9). This assignment was confirmed by a single crystal X-ray analysis of **29** (Fig. 4). The crystal structure showed no unusual features or strain in the bridgehead double bond. Obtaining both **27** and **29** from the same reaction proved that our concept of generating both ring systems from a common oxocarbenium ion intermediate was a valid one.

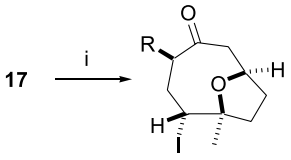
In a similar manner to the hexacyclinic acid route, removal of the TBS group from **29** was achieved using HF in MeCN to give the free alcohol **30**. Treatment of the alcohol **30** with TFA in CH_2Cl_2 resulted in removal of the *tert*-butyl ester and isolation of the acid **31** in 96% yield. Closure of the lactone was possible by either resubmitting **31** to TFA or by using Mukaiyama's reagent as the group of Evans had done.[6] It was later found that the DEF ring system **32** was formed in the initial TFA promoted removal of the *tert*-butyl



Scheme 10. Reagents and conditions: (i) HF, MeCN, rt, 6 h, 100%; (ii) TFA, CH_2Cl_2, rt, 8 h, 96%; (iii) TFA, CH_2Cl_2, rt, 4 h, 96%; or Mukaiyama's reagent, Et_3N, MeCN, CH_2Cl_2, 75%; (iv) TFA, CH_2Cl_2, rt, 8 h, 100%.

ester, but chromatography resulted in opening the lactone ring. By careful purification of the reagents and solvents used in the reaction,[34] the DEF-ring system **32** could be isolated from the TFA mediated reaction in quantitative yield (Scheme 10). Interestingly, this DEF-ring unit is stable in air unlike the natural product. Solutions of **32** of varying concentrations have been stored, open to the air, for periods of up to four weeks without decomposition or epoxidation.

Although we had proved our initial concept that both DEF-ring systems are available via the same method, the yield of the FR182877 system was not particularly pleasing. In an attempt to induce loss of a proton we carried out the reaction in a non-nucleophilic solvent. When $CHCl_3$ was used as a solvent iodolactones **25** and **26** were formed exclusively. Treatment of **17** with AcOI in Et_2O proceeded smoothly to give a single product. Unfortunately, this product was identified as the [5.2.1]bicycloiodoketone **33** (Scheme 11). The related compound **34** was isolated when THF, MeCN or MeOH were used as solvents. The use of benzene, hexane, CCl_4, EtOAc, DMF, DMSO, pyridine, TFA or 1,1,1,3,3,3-hexafluoro-*iso*-propanol all resulted in re-isolation of **17**. In the case where **33** was formed it was believed that the desired iodonium ion was being generated but since the reaction was not anhydrous an equivalent of HI was formed. We believed that this HI promoted the removal of the TBS group with subsequent cyclization through the free alcohol. The TBSI generated cleaved the *tert*-butyl ester with subsequent decarboxylation. We, therefore, performed the reaction under anhydrous conditions and in the presence of a variety of bases with the intention of sequestering any HI formed and hence leaving the TBS group intact. The presence of base only served to inhibit all cyclization reactions.



33 R=H, **34** R=$CO_2{}^t$Bu

Scheme 11. Reagents and conditions: (i) AcOI, Et_2O, 100%.

These solvent studies showed that cyclization was possible through each of the oxygen containing functionalities in 9-membered carbocycle **17**. We were understandably interested in this range of reactivity and in how each of these products was formed. A number of possible explanations are feasible; (1) keto–enol tautomers of the 9-membered carbocycle **17** could react in different manners; (2) epimerization at C2 of **17** would result in diastereomers, each of which could react differently; or (3) different solvents may lead to population of different conformations of **17**, which could result in different reactivity. These possibilities were investigated by the use of ^{1}H NMR spectroscopy, in both $CDCl_3$ and d_3-acetic acid which showed; (1) no detectable enol tautomer; (2) no detectable epimerization of **17**; and (3) no conformational change of **17** on changing solvent from $CDCl_3$ to d_3-acetic acid. The NOE data in both $CDCl_3$ and d_3-acetic acid showed the same ground state chair–boat conformation (Fig. 1) discussed earlier.

It is obvious that a change in conformation of **17** was required to satisfy any of the observed modes of reactivity. In the ground state chair–boat conformation, none of the oxygen containing functionalities are in sufficiently close proximity to the double bond to react on formation of an iodonium ion. As such none of the observed reaction pathways can occur via the observed chair–boat conformation. The observed reactivity can be rationalized as arising from conformational differences of the two possible iodonium ions (either α- or β-). As such the formation of each of the observed products can be rationalized through an appropriate conformation of either the α- or β-iodonium ion. The formation of the iodolactones **25** and **26** arise from an α-iodonium ion reacting through a chair–chair conformation **35** (Fig. 5). This conformation of the α-iodonium ion results in the ester carbonyl group being in a suitable position to attack the iodonium ion resulting in the products **25** and **26** shown.

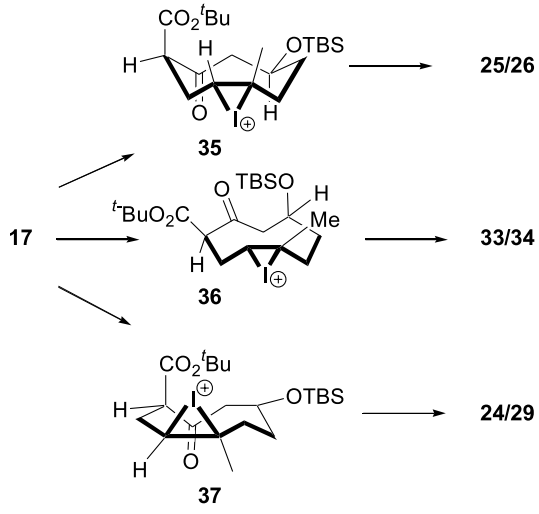


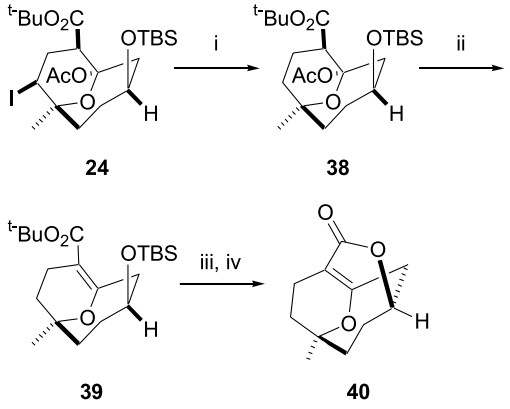
Figure 5. Proposed reacting conformations of **17**.

The bicyclic ethers **33** and **34** also arise from the reaction of an α-iodonium ion, this time through a boat–boat reacting conformation **36** (Fig. 5), placing the OTBS oxygen in a suitable position for attack on the iodonium ion. The hexacyclinic acid and FR182877 DF-ring systems arise from a β-iodonium ion reacting via a boat–boat conformation **37** (Fig. 5) with cyclization occurring through the ketone carbonyl. Conformations **35**, **36** and **37** of the 9-membered ring **17** are all presumably within about 2 kcal mol^{-1} of the ground state chair–boat conformation.

Since the products **25/26**, **33/34** and **24/29** arise from the cyclization of the different functionalities, onto the two diastereotopic iodonium ions (either α- or β-), through different conformations, we conclude that the solvent in some way stabilizes one of these iodonium ion conformations to a greater extent than the others. This increased stability of one iodonium ion conformation could lead to an increase in the population of this conformation and that this

population distribution governs which of the products is the major one formed.

As we were unable to influence the course of the iodocyclisation reaction to favor the formation of **29**, we sought to convert **24** into a FR182877 DEF-ring system. This was achieved by the reductive removal of the iodine, either via Bu_3SnH and catalytic AIBN or via catalytic transfer hydrogenation in a disappointing, although unoptimized 23% yield. The dehalogenated DF-ring **38** was treated with DBU[35] which provided 93% yield of **39**. The DF-ring **39** now contained the vinylogous carbonate unit required for the construction of the DEF-rings of FR182877. The synthesis of a FR182877 DEF-ring **40** was achieved by deprotection and lactonization by sequential treatment of **39** with aq HF in MeCN followed by TFA in CH_2Cl_2 in 100% yield over the two steps (Scheme 12).



Scheme 12. Reagents and conditions: (i) $Pd(PPh_3)_4$, Bu_3N, HCO_2H, DMF, 23%; (ii) DBU, MeCN, reflux, 93%; (iii) 40% aq HF, MeCN, 100%; (iv) TFA, CH_2Cl_2, 100%.

3. Conclusions

We have developed a novel intramolecular Pd(0) allylic substitution, transannular iodocyclization approach to the DEF-ring cores of both hexacyclinic acid and FR182877, utilizing the formation of a common oxocarbenium ion intermediate. We believe that this transannular cationic cyclization provides support for a possible alternative biosynthetic hypothesis to the one previously advanced.[5,6] Interestingly, the nature of the transannular cyclization is highly solvent dependant, and conditions were discovered that allowed for cyclization through any of the oxygen functionalities in the 9-membered ring precursor. We believe that this is due to the solvent subtly affecting the population of different conformations of similar energy of the 9-membered ring. Work is ongoing in an attempt to apply this transannular iodocyclisation reaction to the total synthesis of both hexacyclinic acid and FR182877.

4. Experimental

4.1. General

All melting points are uncorrected. Reaction progress was monitored using glass-backed TLC plates pre-coated with silica UV_{254} and visualized by using either UV radiation (254 nm), ceric ammonium molybdate or anisaldehyde stains. Column chromatography was performed using silica gel 60 (220–240 mesh), with the solvent systems indicated in the relevant experimental procedures. Silver nitrate impregnated silica gel and TLC plates were prepared according to standard procedures.[24] Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl, dimethyl formamide was stirred with calcium hydride and distilled prior to use. Benzene, DMSO and MeCN were all distilled from calcium hydride prior to use. Hexane was distilled prior to use. All other reagents were used as received from commercial suppliers unless stated otherwise in the appropriate text. For the sake of journal space experimental and characterization data for key compounds only is presented here. Full details of other procedures and compounds can be found in the accompanying supporting information.

4.2. Pd(0) Catalyzed cyclization reaction of 18. Synthesis of 17, 22 and 23

A solution of *tert*-butyl-10-acetoxy-8-methyl-5-(*tert*-butyl, dimethylsilanyloxy)-3-oxo-dec-8-enoate **18** (240 mg, 0.550 mmol) in THF (6 ml) was added to a flask containing sodium hydride (22 mg, 0.56 mmol) and the solution was stirred for 15 min. The yellow solution was drawn into a syringe and the syringe was equipped with a needle fitted with a small glass wool plug. The solution was added to a solution of *tetrakis*triphenylphosphine palladium (32 mg, 0.027 mmol) and dppe (10 mol%) in THF (5 ml) under reflux, at a rate of 4.76 ml/h via syringe pump. The resulting mixture was maintained under reflux for a further 1 h before being allowed to cool to room temperature. The mixture was filtered through a plug of silica with ether (75 ml) and concentrated in vacuo. The resulting oil was subjected to chromatography on silver nitrate impregnated silica (9:1 hexane–ether elution) to give the 9-membered carbocycle **17** (61%), the 7-membered carbocycle **22** and diene **23**.

4.2.1. 1-Oxo-8-(*tert*-butyl dimethylsilanyloxy)-5-methyl-2-(carbo-*tert*-butoxy)-cyclonon-4-ene (17). ν_{max} (solution; $CHCl_3$) 2956 (CH stretch), 2931 (CH stretch), 1738 (C=O stretch), 1705 (C=O stretch), 1472 (CH bend), 1277 (C–O stretch), 1257 (C–O stretch), 1070 (Si–O stretch) and 837 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.33 (1H, t, $J=8.0$ Hz, H4), 4.09 (1H, tt, $J=9.1$, 3.1 Hz, H8), 3.39 (1H, dd, $J=10.8$, 3.1 Hz, H2), 2.92 (1H, dd, $J=14.3$, 9.1 Hz, H9), 2.73 (1H, m, H3), 2.59 (1H, dd, $J=14.3$, 3.0 Hz, H9), 2.46 (1H, ddd, $J=14.3$, 8.0, 3.1 Hz, H3), 2.28 (1H, ddd, $J=14.0$, 12.0, 4.5 Hz, H7), 1.89 (1H, app tt, $J=14.0$, 4.5 Hz, H6), 1.79 (1H, dt, $J=14.0$, 4.5 Hz, H7), 1.70 (1H, m, H6), 1.69 (3H, s, 5Me), 1.57 (9H, s, ^{t}Bu), 0.89 (9H, s, TBS), 0.11 (3H, s, TBS) and 0.9 (3H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 207.8 (s, C10), 168.5 (s, C1), 139.2 (s, C5), 121.4 (d, C4), 82.0 (s, ^{t}Bu), 68.2 (d, C8) 59.9 (d, C2), 50.3 (t, C9), 35.6 (t, C7), 28.1 (q, ^{t}Bu), 27.2 (t, C3), 26.9 (t, C6), 25.9 (q, TBS), 22.8 (q, 4Me), 18.1 (s, TBS), −4.7 (q, TBS) and −4.7 (q, TBS) ppm. MS (CI NH_3) *m/z* 400 $(M+NH_4)^+$, 383 $(M+H)^+$ and 344 $(M+NH_4, -{}^tBu)^+$; found M+H 383.2622, $C_{21}H_{39}O_4Si$ requires M+H 383.2618.

4.2.2. 1-Oxo-6-(*tert*-butyl dimethylsilanyloxy)-3-methyl-3-(eth-2-enyl)-2-(carbo-*tert*-butoxy)-cycloheptane (22). ν_{max} (solution; $CHCl_3$) 2955 (CH stretch), 2930 (CH stretch), 1738 (C=O stretch), 1694 (C=O stretch), 1258 (C–O stretch), 1145 (C–O stretch), 1075 (Si–O stretch) and 835.3 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.87 (1H, dd, $J=17.5$, 10.8 Hz, 3 vinyl), 5.04 (1H, dd, $J=17.5$, 0.6 Hz, 3 vinyl), 5.02 (1H, dd, $J=10.8$, 0.6 Hz, 3 vinyl), 4.16 (1H, m, H6), 3.95 (1H, s, H2), 2.75 (1H, ddd, $J=17.6$, 5.9, 1.3 Hz, H7), 2.63 (1H, dd, $J=17.6$, 3.2 Hz, H7), 2.11 (1H, ddd, $J=11.6$, 3.2, 3.2 Hz, H5), 1.90 (1H, m, H5), 1.77 (1H, m, H4), 1.55 (1H, m, H4), 1.43 (9H, s, ^{t}Bu), 1.24 (3H, s, 3Me), 0.92 (9H, s, TBS) and 0.08 (6H, t, $J=1.6$ Hz, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 206.3, 168.2, 146.2, 112.0, 80.9, 68.0, 66.0, 52.3, 40.1, 36.6, 32.2, 27.9, 25.7, 20.4, 18.0, 1.0, −4.9 and −5.1 ppm. MS (CI NH_3) *m/z* 383 $(M+H)^+$; found M+H 383.2627, $C_{21}H_{39}O_4Si$ requires M+H 383.2618.

4.2.3. *tert*-Butyl-8-methyl-5-(*tert*-butyl dimethylsilanyloxy)-3-oxo-dec-7,9-dienoate (23). ν_{max} (solution; $CHCl_3$) 2930 (CH stretch), 2884 (CH stretch), 1713 (C=O stretch), 1607 (C=O stretch), 1411 (CH bend), 1256 (C–O stretch), 1224 (C–O stretch), 1060 (Si–O stretch) and 830 (=CH oop bend) cm^{-1}. δ_H (400 MHz; DMSO) 6.34 (1H, dd, $J=10.7$, 17.4 Hz, H9), 5.51 (1H, t, $J=7.0$ Hz, H7), 5.10 (1H, d, $J=$ 17.4 Hz, H10 *cis*), 4.95 (1H, d, $J=10.7$ Hz, H10 *trans*), 4.17 (1H, app pentet, $J=5.6$ Hz, H5), 3.44 (2H, s, H2), 2.66 (1H, dd, $J=16.2$, 6.5 Hz, H4), 2.58 (1H, dd, $J=16.2$, 4.0 Hz, H4), 2.28 (2H, dd, $J=7.0$, 6.5 Hz, H6), 1.68 (3H, s, 8Me), 1.40 (9H, s, ^{t}Bu), 0.82 (9H, d, $J=1.6$ Hz, TBS), 0.03 (3H, d, $J=1.3$ Hz, TBS) and 0.00 (3H, d, $J=1.3$ Hz, TBS) ppm. δ_C (100 MHz; DMSO) 202.1 (s, C3), 166.1 (s, C1), 141.2 (s, C8), 135.4 (d, C7), 128.4 (d, C9), 111.4 (t, C10), 80.7 (s, ^{t}Bu), 68.1 (d, C5), 51.2 (t, C2), 49.4 (t, C4), 35.8 (t, C6), 27.7 (q, ^{t}Bu), 25.7 (q, TBS), 17.6 (s, TBS), 11.7 (q, 8Me), −4.8 (q, TBS) and −5.0 (q, TBS) ppm. MS (ES+) *m/z* 383 $(M+H)^+$, 327 $(M+H, -{}^tBu)^+$ and 309 $(M+H, -TBS)^+$; found M+H 383.2620, $C_{21}H_{39}O_4Si$ requires M+H 383.2618.

4.2.4. Iodocyclization of 17. Synthesis of 24 and 29. To a mixture of iodine (1.92 g, 7.6 mmol) and silver acetate (1.26 g, 7.6 mmol) was added acetic acid (54 ml). The mixture was stirred for 30 min before being transferred via syringe to a solution of **17** (1.00 g, 2.5 mmol) in acetic acid (21 ml). The mixture was stirred for 1 h before being diluted with water (500 ml) and CH_2Cl_2 (100 ml), and neutralized with solid $NaHCO_3$. The resulting solution was saturated with solid sodium chloride and extracted with CH_2Cl_2 (5× 200 ml). The organic phase was washed with saturated aqueous sodium thiosulfate solution (500 ml), saturated aqueous $NaHCO_3$ solution (3×200 ml), water (3×200 ml) and brine (250 ml) before being dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was subjected to column chromatography (98:2 petrol–ether) to give **24** (816 mg, 4.6 mmol, 61%) as a colorless oil, **29** (73 mg, 0.13 mmol, 5%) as a white crystalline solid.

4.2.5. 9-(Carbo-*tert*-butoxy)-7-iodo-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-1-acetoxy-oxabicyclo[4.3.1]-nonane (24). ν_{max} (solution; $CHCl_3$) 2990 (CH stretch), 2857 (CH stretch), 1747 (C=O stretch), 1721 (C=O stretch), 1294 (C–O stretch), 1257 (C–O stretch), 1075 (Si–O stretch) and 837 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 4.33 (1H, m, H3), 4.15 (1H, dd, $J=14.0$, 4.7 Hz, H7), 4.04 (1H, dd, $J=13.1$, 4.7 Hz, H9), 2.70 (1H, ddd, $J=$ 14.5, 14.0, 13.1 Hz, H8), 2.52–2.45 (2H, m, H2, H8), 2.25–2.18 (2H, m, H4, H5), 2.04 (3H, s, Ac), 1.76–1.68 (2H, m, H2, H4), 1.57 (1H, m, H5), 1.44 (9H, s, ^{t}Bu), 1.38 (3H, s, 6Me), 0.90 (9H, s, TBS), 0.07 (3H, s, TBS) and 0.07 (3H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 168.8 (s, C10), 168.6 (s, Ac), 101.8 (s, C1), 81.3 (s, ^{t}Bu), 78.6 (s, C6), 65.1 (d, C3), 48.0 (d, C9), 39.9 (t, C2), 34.5 (t, C8), 33.0 (d, C7), 31.5 (t, C5), 29.6 (t, C4), 28.0 (q, ^{t}Bu), 28.0 (q, 6Me), 26.0 (q, TBS), 22.7 (q, Ac), 18.3 (s, TBS), −4.7 (q, TBS) and −4.8 (q, TBS) ppm. MS (CI NH_3) *m/z* 586 $(M+NH_4)^+$, 526 $(M-OAc, +NH_4)^+$, 509 $(M-OAc)^+$, 460 $(M-I, +NH_4)^+$, 327 $(M-TBS, -I)^+$, 284 $(M-TBS, -Ac)^+$; found $M+NH_4$ 586.2060, $C_{23}H_{45}IO_6SiN$ requires $M+NH_4$ 586.2061. Anal. Calcd for $C_{23}H_{41}IO_6Si$: C, 48.59, H, 7.27. Found C, 48.98, H, 7.17.

4.2.6. 9-(Carbo-*tert*-butoxy)-7-iodo-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-oxabicyclo[4.3.1]non-9-ene (29). Mp 89–90 °C. ν_{max} (solution; $CHCl_3$) 2955 (CH stretch), 2857 (CH stretch), 1698 (C=O stretch), 1432 (CH bend), 1258 (C–O stretch), 1146 (C–O stretch), 1059 (Si–O stretch) and 836 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 4.41 (1H, t, $J=8.4$ Hz, H7), 4.21 (1H, m, H3), 3.58 (1H, dt, $J=12.5$, 1.8 Hz, H2), 3.17 (1H, dd, $J=18.8$, 7.6 Hz, H8), 3.04 (1H, ddd, $J=18.8$, 8.4, 1.8 Hz, H8), 2.30 (1H, dd, $J=14.6$, 11.0 Hz, H5), 2.23 (1H, ddd, $J=12.5$, 4.7, 1.8 Hz, H2), 1.78 (1H, ddt, $J=13.0$, 12.4, 1.5 Hz, H4), 1.72 (1H, m, H4), 1.49 (1H, m, H5), 1.46 (9H, s, ^{t}Bu), 1.44 (3H, s, 6Me), 0.88 (9H, s, TBS) and 0.57 (6H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 166.6 (s, C10), 161.9 (s, C9), 128.4 (s, C1), 116.9 (s, C6), 80.2 (s, ^{t}Bu), 78.1 (d, C3), 67.4 (t, C2), 42.4 (t, C8), 36.0 (d, C7), 33.6 (t, C4), 31.9 (t, C5), 28.5 (q, ^{t}Bu), 26.2 (q, TBS),26.1 (q, 6Me), 18.4 (s, TBS), −4.7 (q, TBS) and −5.0 (q, TBS) ppm. MS (ES+) *m/z* 509 $(M+H)^+$, 453 $(M+H, -{}^tBu)^+$, 395 $(M+H, -TBS)^+$; found M+H 509.1580, $C_{21}H_{38}IO_4Si$ requires M+H 509.1579. Anal. Calcd for $C_{21}H_{37}IO_4Si$: C, 49.60, H, 7.33. Found C, 49.25, H, 7.21.

4.2.7. 7-Hydroxy-5-methyl-4-iodo-10,6-dioxatricyclo-[5.3.2.0]dodecan-1-one (28). To a solution of **27** (37 mg, 0.087 mmol) in CH_2Cl_2 (2 ml) was added TFA (0.01 ml, 0.1 mmol) and the mixture stirred for 4 days. Further portions (0.01 ml, 0.1 mmol) of TFA were added after 1, 2 and 3 days. The mixture was concentrated in vacuo to give the product (29 mg, 0.087 mmol, 100%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 3573 (br, OH stretch), 3186 (CH stretch), 2932 (CH stretch), 1780 (C=O stretch), 1453 (CH bend), 1152 (C–O stretch) and 1118 (C–O stretch) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.52 (1H, dddd, $J=12.3$, 6.5, 6.5, 3.3 Hz, H9), 4.06 (1H, m, H4), 2.74–2.62 (4H, m, H8, H8, H3, H3), 2.46 (1H, m, H11), 2.29 (1H, m, H12), 2.09 (1H, dd, $J=14.3$, 3.1 Hz, H2), 1.85 (1H, ddd, $J=15.2$, 4.2, 2.8 Hz, H12), 1.68 (1H, ddd, $J=15.2$, 7.1, 3.3 Hz, H11) 1.44 (1H, s, OH) and 1.42 (3H, s, 5Me) ppm. δ_C (100 MHz; $CDCl_3$) 172.7 (s, C1), 95.9 (s, C5), 78.1 (s, C7), 72.8 (d, C9), 54.7 (d, C4), 35.7 (t, C3 or C8), 34.5 (t, C3 or C8), 31.3 (d, C2), 29.2 (t, C12), 28.0 (q, 5Me) and 27.4 (t, C11) ppm. MS

(CI NH_3) *m/z* 356 $(M+NH_4)^+$; found $M+NH_4$ 356.0353, $C_{11}H_{19}IO_4N$ requires $M+NH_4$ 356.0353.

4.2.8. 5-Methyl-4-iodo-10,6-dioxatricyclo[5.3.2.0]dodec-2(7)-en-1-one (32). To a solution of **30** (15 mg, 0.04 mmol) in CH_2Cl_2 (5 ml) was added TFA (0.1 ml, 0.40 mmol) and the mixture stirred for 24 h. The mixture was concentrated in vacuo to give the product (14 mg, 0.04 mmol, 100%) as a white crystalline solid. Mp 190–193 °C (darkens significantly at 173 °C). ν_{max} (solution; $CHCl_3$) 2928 (CH stretch), 2856 (CH stretch), 1688 (C=O stretch), 1423 (CH bend), 1285 (C–O stretch) and 1260 (C–O stretch) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.40 (1H, m, H9), 4.43 (1H, dd, $J=9.0$, 7.5 Hz, H4), 3.97 (1H, dt, $J=13.7$, 1.7 Hz, H8), 3.23 (1H, dd, $J=19.1$, 7.5 Hz, H3), 3.16 (1H, ddd, $J=19.1$, 9.0, 1.7 Hz, H3), 2.39 (1H, ddd, $J=13.7$, 4.3, 1.7 Hz, H8), 2.22 (1H, dd, $J=15.2$, 6.7 Hz, H12), 2.02–1.95 (2H, m, H11, H11), 1.68 (1H, ddd, $J=15.2$, 6.7, 1.6 Hz, H12) and 1.53 (3H, s, 5Me) ppm. δ_C (100 MHz; $CDCl_3$) 171.1 (s), 163.0 (s), 115.3 (s), 79.0 (s), 73.7 (d), 38.7 (t), 34.8 (t), 28.5 (d), 28.0 (t), 26.8 (t) and 25.5 (q) ppm. MS (EI+) *m/z* 321 $(M+H)^+$, 193 $(M-I)^+$, 165 $(M-I, -CO)^+$; found M 320.9985, $C_{11}H_{14}IO_3$ requires M 320.9988. Anal. Calcd for $C_{11}H_{13}IO_3$: C, 41.27, H, 4.09. Found C, 41.66, H, 3.89.

4.2.9. 9-(Carbo-*tert*-butoxy)-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-1-acetoxy-oxabicyclo[4.3.1]nonane (38). A mixture of **24** (10 mg, 0.02 mmol), $Pd(PPh_3)_4$ (4 mg, 0.003 mmol), Bu_3N (10 mg, 0.05 mmol) and formic acid (2 mg, 0.03 mmol) in DMF (2 ml) was stirred together for 18 h at 60 °C. The mixture was heated under reflux for 24 h before being cooled to room temperature. The mixture was filtered through celite with ether (75 ml) and the resulting solution concentrated in vacuo. The resulting oil was subjected to column chromatography (9:1 hexane–ether elution) to give the product (2 mg, 0.005 mmol, 23%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 2981 (CH stretch), 2850 (CH stretch), 1744 (C=O stretch), 1729 (C=O stretch), 1266 (C–O stretch), 1221 (C–O stretch) and 1054 (Si–O stretch) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 4.35 (1H, m, H3), 3.79 (1H, dd, $J=12.7$, 4.7 Hz, H9), 2.50 (1H, dd, $J=15.0$, 11.7 Hz, H2), 2.26 (1H, ddd, $J=14.1$, 8.3, 2.8 Hz, H4), 2.17 (1H, dd, $J=14.1$, 2.8 Hz, H4), 2.12 (1H, m, H8), 2.04 (3H, s, Ac), 1.87 (1H, m, H5), 1.74 (1H, dd, $J=15.0$, 3.2 Hz, H2), 1.62 (1H, m, H8), 1.51 (1H, m, H5), 1.45 (9H, s, ^{t}Bu), 1.31 (1H, m, H7), 1.19 (3H, s, 6Me), 1.08 (1H, d, $J=5.5$ Hz, H7), 0.90 (9H, s, TBS), 0.08 (3H, s, TBS) and 0.07 (3H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 171.0 (s), 168.9 (s), 102.5 (s), 80.7 (s), 76.1 (s), 65.9 (d), 45.1 (d), 40.5 (t), 34.1 (t), 31.5 (t), 31.4 (t), 29.2 (q), 28.1 (q), 26.0 (q), 22.9 (q), 21.3 (t), 18.4 (s), −4.7 (q) and −4.8 (q) ppm. MS (CI NH_3) *m/z* 460 $(M+NH_4)^+$, 386 $(M+H, -{}^tBu)^+$, 328 $(M+H, -TBS)^+$, 271 $(M+H, -{}^tBu, -TBS)^+$; found $M+NH_4$ 460.3097, $C_{23}H_{46}NO_6Si$ requires $M+NH_4$ 460.3094.

4.2.10. 9-(Carbo-*tert*-butoxy)-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-oxabicyclo[4.3.1]non-9(1)-ene (39). To a solution of **38** (6 mg, 0.013 mmol) in MeCN (4 ml) was added DBU (3 mg, 0.020 mmol) and the mixture heated under reflux for 8 days. An additional portion of DBU (3 mg, 0.020 mmol) was added after 1 day. The mixture was cooled to room temperature and diluted with ether (50 ml). The resulting solution was washed successively with saturated aqueous $NaHCO_3$ solution (2×20 ml), water (2×20 ml) and brine (20 ml). The aqueous washes were extracted with ether (3×20 ml) and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was subjected to column chromatography (9:1 hexane–ether elution) to give the product (5 mg, 0.013 mmol, 93%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 2930 (CH stretch), 2856 (CH stretch), 1640 (C=O stretch), 1451 (CH bend), 1262 (C–O stretch), 1134 (C–O stretch) and 1089 (Si–O stretch) cm^{-1}. δ_H (500 MHz; $CDCl_3$) 4.16 (1H, m, H3), 3.40 (1H, dd, $J=14.0$, 4.6 Hz, H2), 2.63 (1H, ddd, $J=14.9$, 6.6, 2.1 Hz, H8), 2.60 (1H, ddd, $J=14.9$, 6.6, 2.1 Hz, H8), 1.99 (1H, m, H5 or H7), 1.92 (1H, m, H5 or H7), 1.86 (1H, ddd, $J=14.0$, 8.0, 2.1 Hz, H2), 1.75–1.64 (2H, m, H4, H4), 1.58–1.52 (2H, m, H5, H7), 1.50 (9H, s, ^{t}Bu), 1.34 (3H, s, 6Me), 0.88 (9H, s, TBS), 0.07 (3H, s, TBS) and 0.06 (3H, s, TBS) ppm. δ_C (125 MHz; $CDCl_3$) 166.5 (s), 165.3 (s), 121.3 (s), 80.4 (s), 80.1 (s), 70.2 (d), 41.3 (t), 37.4 (t), 32.3 (t), 28.5 (q), 28.2 (t), 26.0 (q), 21.3 (t), 18.2 (s), 14.2 (q), −4.5 (q) and −4.6 (q) ppm. MS (CI NH_3) *m/z* 383 $(M+H)^+$, 327 $(M+H, -{}^tBu)^+$ and 269 $(M+H, -TBS)^+$; found M+H 383.2609, $C_{21}H_{39}O_4Si$ requires M+H 383.2612.

4.2.11. 5-Methyl-10,6-dioxatricyclo[5.3.2.0]dodec-2(7)-en-1-one (40). To a solution of 9-(carbo-*tert*-butoxy)-7-iodo-6-methyl-3-hydroxy-oxabicyclo[4.3.1]non-9-ene (7 mg, 0.02 mmol) in CH_2Cl_2 (1 ml) was added TFA (0.02 ml, 0.30 mmol) and the mixture stirred for 7 h. The mixture was concentrated in vacuo to give the crude product as a white solid. The solid was subjected to column chromatography (4:1 hexane–ether elution) to give the product (2 mg, 0.01 mmol, 50%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 2929 (CH stretch), 2855 (CH stretch), 1644 (C=O stretch), 1261 (C–O stretch) and 1224 (C–O stretch) cm^{-1}. δ_H (500 MHz; $CDCl_3$) 5.35 (1H, m, H9), 3.93 (1H, dd, $J=14.2$, 1.9 Hz, H8), 2.71 (1H, ddd, $J=15.9$, 8.4, 2.4 Hz, H3), 2.52 (1H, ddd, $J=14.2$, 5.0, 1.9 Hz, H8), 2.36 (1H, t, $J=7.7$ Hz, H12), 2.20 (1H, m, H3), 2.08 (1H, ddd, $J=13.0$, 9.2, 2.4 Hz, H4), 2.05–1.91 (2H, m, H11, H11), 1.73 (1H, dt, $J=13.0$, 8.4 Hz, H4), 1.65 (1H, m, H12) and 1.40 (3H, s, 5Me) ppm. δ_C (125 MHz; $CDCl_3$) 171.1, 165.3, 117.5, 79.2, 77.6, 74.8, 37.9, 36.2, 28.0, 27.2 and 19.7 ppm. MS (EI+) *m/z* 194 $(M)^+$, 176 $(M, -H_2O)^+$ and 131 $(M, -H_2O, -CO_2)^+$.

5. Supporting information available

Experimental procedures and spectroscopic data for compounds **12**, **14**, **15**, **16**, **18**, **19**, **20**, **21**, **27**, **30**, **31** and **33**.

Discussion of spectroscopic data for compounds **17**, **24**, **28** and **29**.

Copies of NMR spectra for compounds **15**, **18**, **17**, **21**, **22**, **23**, **24**, **28**, **29**, **33**, **28**, **39** and **40**.

Supplementary crystallographic data in CIF format for compounds **25/26**, **27** and **29**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.095

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