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# Sequential Ring-Opening/Cyclisation Reactions of Bicyclo[4.2.0]oct-7-enes for the Synthesis of Cyclooctadiene Fused Lactones: Model Studies Towards the Total Synthesis of Pachylactone

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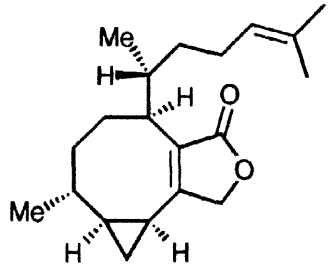
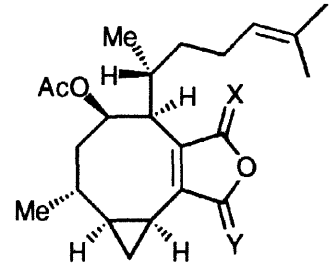
***Abstract:*** *Substituted bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylic acid derivatrives undergo facile electrocyclic ring opening to give fused cyclooctadiene lactone ring systems in excellent yield on thermolysis in xylene. Use of this reaction as the key step in an approach to the marine diterpene pachylactone 1 is described.* 

## Introduction

Pachylactone **1** is a marine diterpene which was isolated[1] in 1983 from the brown alga *Pachydictyon coriaceum* and is part of family of natural products known as the crenulides whose members also include acetoxycrenulide **2** and the isomeric isoacetoxycrenulatin **3**. These compounds are toxins which are thought to be produced as part of a defence mechanism to avoid predation by marine organsims. The complex butenolide-fused 3,8,5-ring system presents a number of difficult structural and stereochemical problems for the synthetic chemist. Only recently has a member of this family yielded to total synthesis with Paquette *et al* [2] reporting an enantioselective synthesis of **2** using an elegant Claisen ring expansion strategy.




**Pachylactone 1**




**2** X = $H_2$, Y = O
**3** X = O, Y = $H_2$

**Scheme 1**

In our studies[3] towards pachylactone **1** we envisioned utilising the electrocyclic ring opening of a suitably functionalised [4.2.0]bicyclooctene hydroxy acid such as **4** as the key step in the construction of the cyclooctane ring. It was thought that the cyclooctadiene-lactone **6** would be formed directly *via* spontaneous lactonisation of the intermediate hydroxy-acid **5**. This cyclooctadiene-lactone **6** could then be elaborated to the main skeleton of pachylactone **1** by regio- and diastereoselective cyclopropanation of the non-butenolide alkene (Scheme 2).

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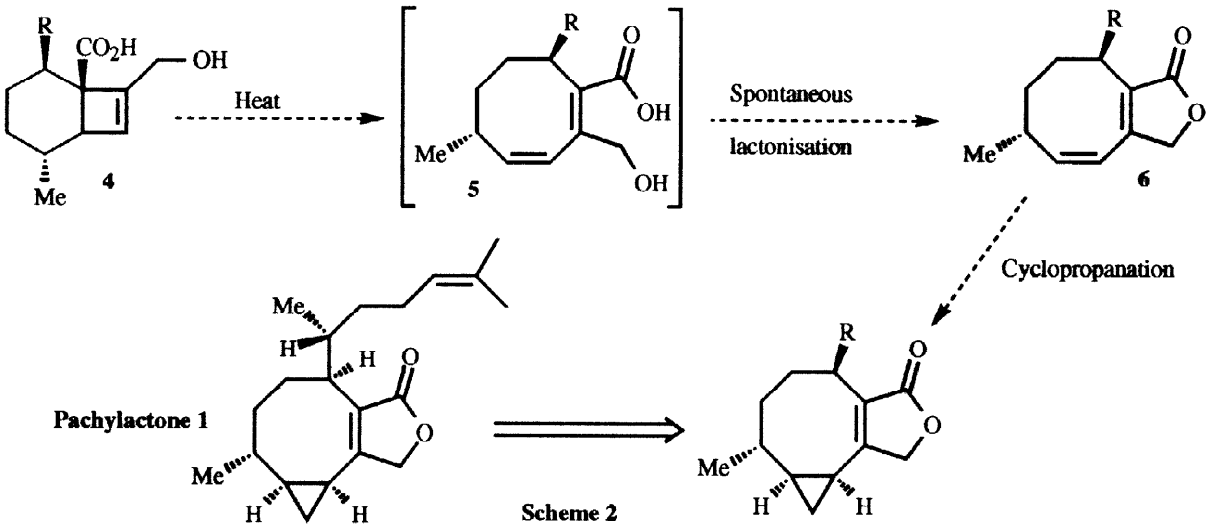
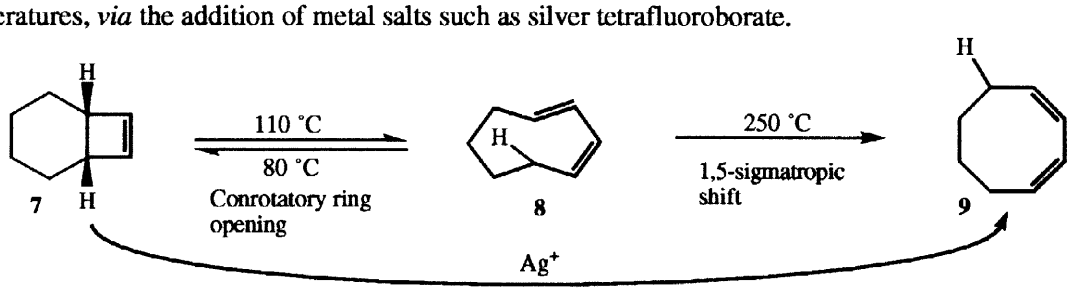


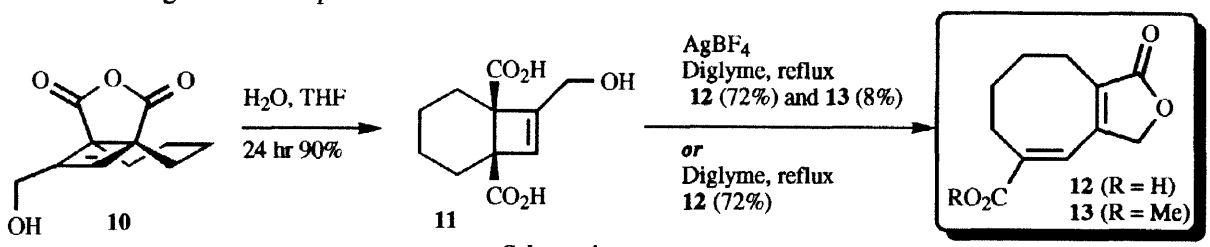

Although the thermal ring opening of cyclobutenes is well documented in the literature,[4] ring opening of the corresponding [4.2.0]bicyclooctenes is more complex and is thought to occur *via* a two step process. For example, with the parent cyclobutene **7** a thermally allowed conrotatory ring opening initially gives a highly strained *cis,trans*-1,3-cyclooctadiene **8** which then isomerises by a 1,5-sigmatropic hydrogen shift to the *cis,cis*-isomer **9**. The direct formation of this product would have to proceed by a disallowed disrotatory ring opening. McConaghy and Bloomfield[5] have proved this mechanism and have shown that the initial ring-opening can occur at temperatures as low as 110°C but the highly reactive intermediate **8** cannot be isolated due to the reversibility of the first step. However the synthetic value of the overall process is somewhat limited due to the very high temperatures required for efficient conversion to the *cis,cis*-1,3-cyclooctadiene. Fortunately Pettit[6] has shown that the *cis,cis*-isomer **9** can be formed directly, and at much lower temperatures, *via* the addition of metal salts such as silver tetrafluoroborate.




Scheme 3

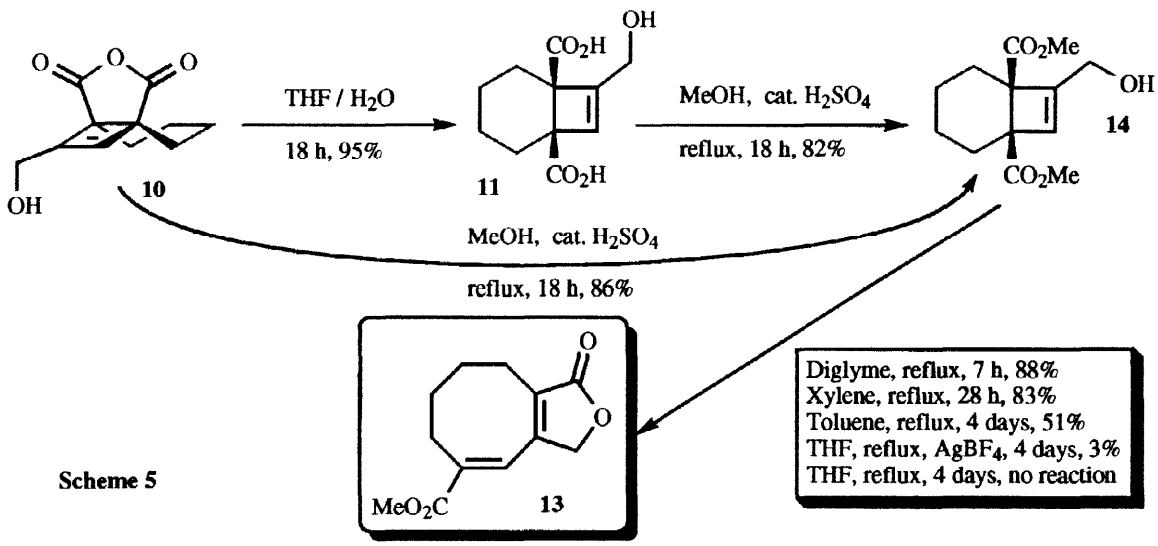
In the preceeding paper[7] we described an efficient preparation of the cyclobutene **10** *via* a highly efficient intermolecular [2+2] photocycloaddition between tetrahydrophthalic anhydride and propargyl alcohol. Hydrolysis of the anhydride gave the cyclobutene-diacid **11** (90%) as a suitable ring opening substrate for our pachylactone model studies. Utilising Pettit's procedure of stirring the cyclobutene in diethyl ether with one equivalent of siver tetrafluroborate gave no reaction; this was thought to be due to the insolubilty of diacid **11** and therefore a number of solvents and reaction temperatures were investigated. The optimum conditions

were one equivalent of silver tetrafluoroborate in diglyme in a sealed tube at 180°C which afforded the desired cyclooctadiene **12** in good yield (72%). A small amount (8%) of methyl ester **13** was also obtained, which is a result of a silver catalysed transetherification reaction between the acid OH group and the diglyme solvent. In view of the high temperature used we decided to investigate the reaction without the use of the silver salt. It was found that simply heating **11** in diglyme for 7 hours resulted in the formation of the cyclooctadiene **12** in comparable yield (72%). Thus the reaction was occurring by a purely thermal pathway but at much lower temperatures than that expected from previous work with [4.2.0]bicyclooctenes. Clearly this result needed further investigation and explanation.



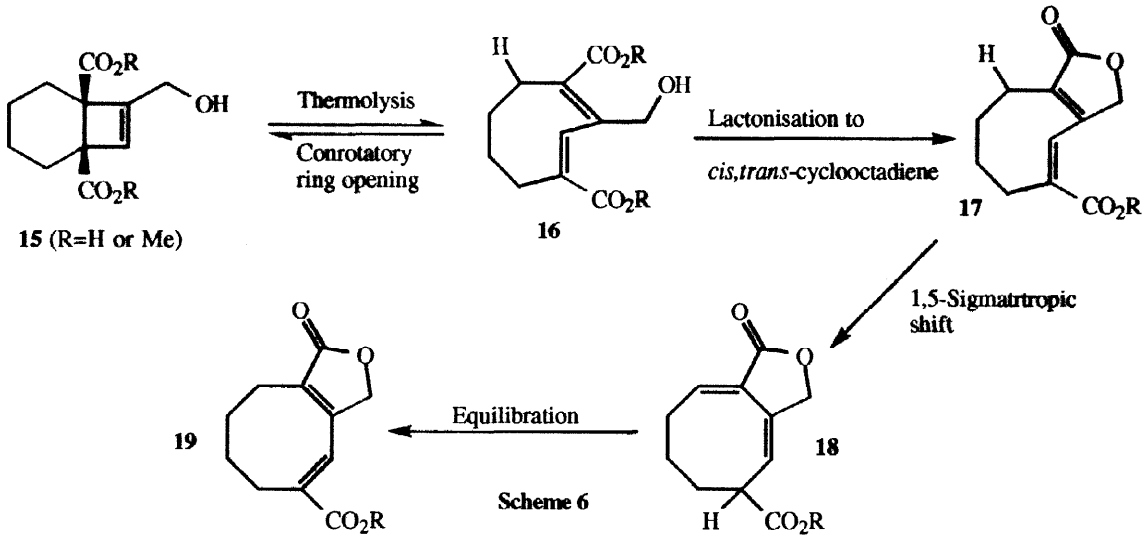

**Scheme 4**

Due to major solubility problems with the diacid **11**, further studies on these electrocyclic ring openings were carried out on the more soluble diester **14**. This was easily prepared either by esterification of **11** (82%) or more convieniently by direct alcoholysis of anhydride **10** (86%). Ring opening was conveniently achieved by heating **14** in refluxing diglyme for 7 h to afford the cyclooctadiene **13** in excellent yield (88%). Changing the solvent to xylene, and thereby lowering the reflux temperature, gave a comparable yield of **13** (83%) but with a reaction time of 28 h. Although longer reaction times were required, we have found that xylene is the solvent of choice because, unlike diglyme, it can be removed on the rotary evaporator at the end of the reaction. Lowering the temperature by using toluene increased the reaction times still further and after 4 days a moderate yield of **13** (51%) was obtained with recovery of **14** (89% yield based on recovery of starting material). With THF as the solvent no product was isolated and starting material was recovered. Using THF with one equivalent of silver tetrafluoroborate resulted in a very low yield of **13** (3%).



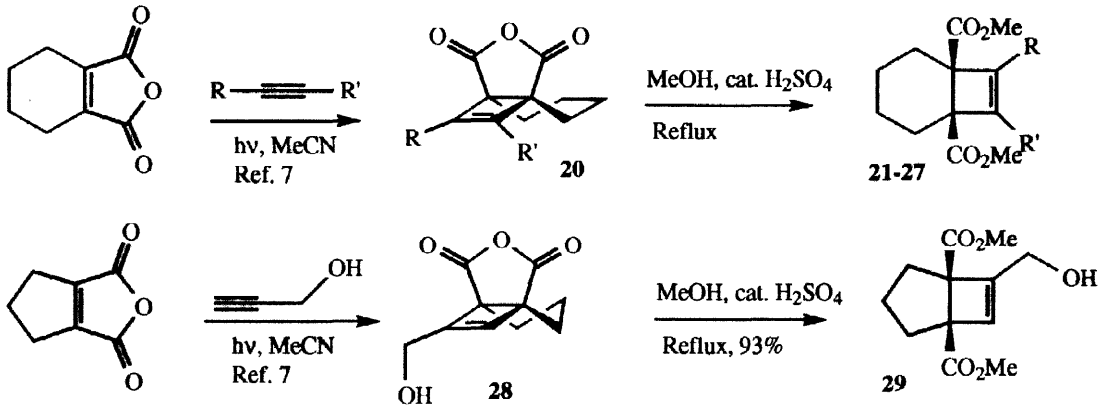

**Scheme 5**

From the above results it would appear that in our case the whole sequence of conrotatory ring opening and *trans*→*cis* isomerisation takes place at temperatures as low as 110°C. Our explanation for this is that after the initial conrotatory ring opening of **15** the resulting highly strained *cis,trans*-1,3-cyclooctadiene **16** is trapped out by lactonisation to give the *cis,trans*-1,3-cyclooctadiene-lactone **17**. This presumably cannot cyclise back to the cyclobutene, due to strain, and thus a 1,5-sigmatropic shift takes place giving **18** which then isomerises to the more stable conjugated cyclooctadiene **19** (possibly by another 1,5-sigmatropic shift).



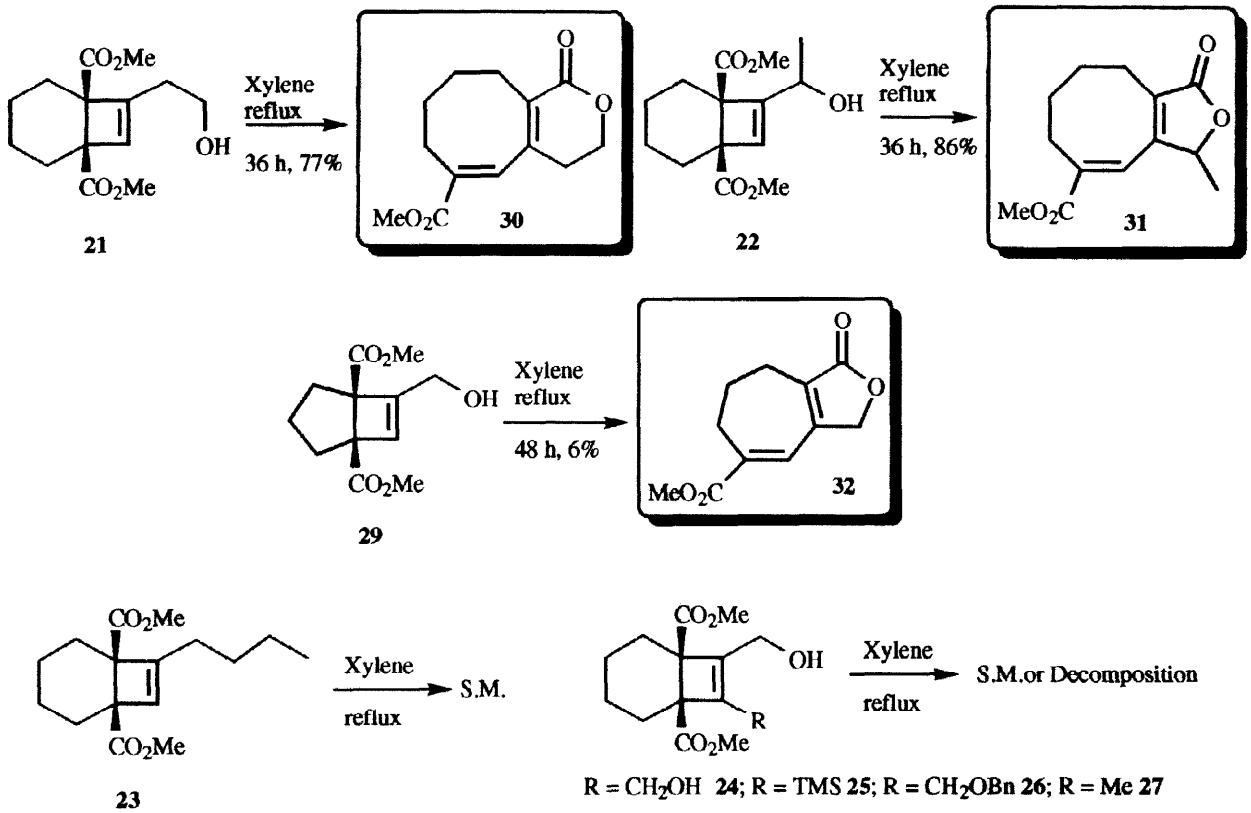

Scheme 6

These results obviously merited further study in order to investigate whether the 'low temperature' sequence could be generalised for the preparation of other cyclooctadienes. A series of ring-opening precursors were synthesized as described in the preceeding paper.[7] Thus, tetrahydrophthalic anhydride was irradiated with a variety of alkynes, resulting in the desired photoadducts **20** in good yields. As before these products were converted to the ring-opening precusors **21-27** in high yields by direct methanolysis. The 5-ring homologue **29** was obtained from alcoholysis of the bicyclo[3.2.0]heptene **28** (Scheme 7).




Scheme 7

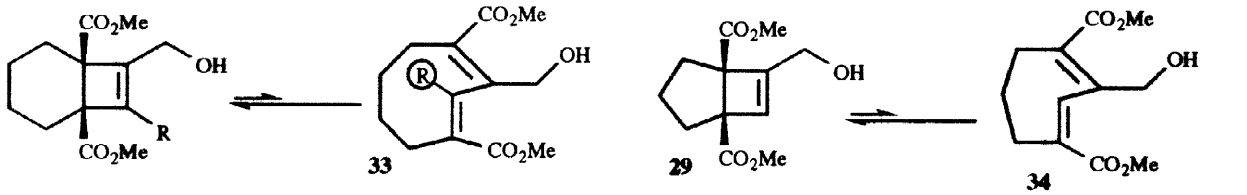
The series of diesters thus produced were each subjected to the earlier optimised ring-opening conditions of heating in refluxing xylene. The one-carbon extended homologue **21** of our previous example behaved as predicted and a good yield (77%) of the expected cyclooctadiene fused pyranone **30** was obtained on thermolysis. Similarly the 3-methyl derivative **22** afforded an 86% yield of the corresponding lactone, thus demonstrating substituent tolerance in the alkenol side chain. A low yield (6%) of cycloheptadiene **32** was obtained by heating bicycloheptene **29** in xylene at reflux for 48 h, with the majority of starting material being recovered unscathed. Prolonged heating of **29** in diglyme resulted in decomposition. Not surprisingly the 7-butyl derivative **23**, gave no reaction and starting material could be recovered untouched after a 24 h reflux. This result corroborates our proposed mechanism and proves that lactonisation, which is not possible in this case, is a key step in the overall process and essential for the reaction to take place at relatively low temperatures. In the cases of the bis(hydroxymethyl) **24** and the trimethylsilyl-hydroxymethyl **25** compounds none of the desired products were obtained and rapid decomposition was observed. More surprising were the results from the benzyloxymethyl and methyl derivatives **26** and **27**, which were inert to thermolysis and even after prolonged periods of reflux only starting materials were recovered (Scheme 8).




**Scheme 8**

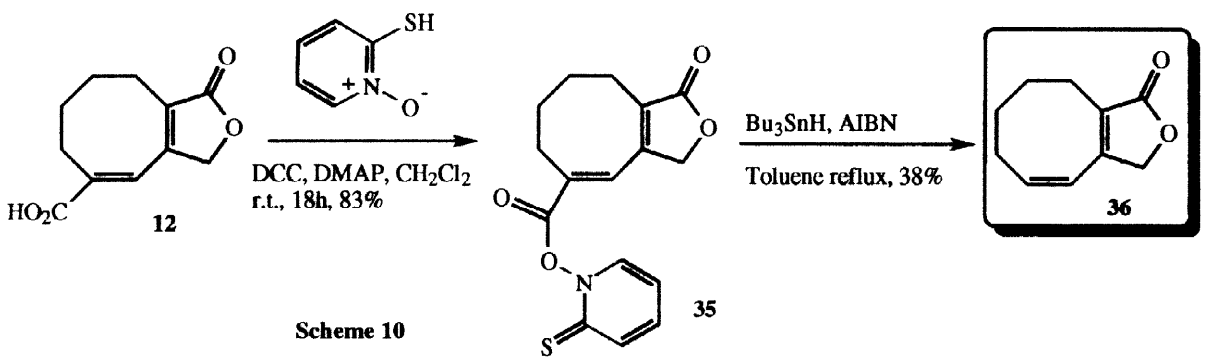
A plausible explanation for these results would appear to be quite straightforward and is outlined in Scheme 9. Any R group (where R≠H) in the 8-position of the diester stops the ring-opening occurring due to severe transannular interactions in the initial ring opened intermediate **33** and therfore the equilibrium lies wholly in

favour of the starting cyclobutene. When R = H the reaction can proceed as explained earlier with laconisation being the driving force. In the case of the bicyclo[3.2.0]hept-6-ene derivative **29** ring opening gives the *cis,trans*-cycloheptadiene **34** which is even more stained than the analogous cyclooctadienes and therefore equilibrium would, not too surprisingly, favour the starting cyclobutene (Scheme 9).




**Scheme 9**

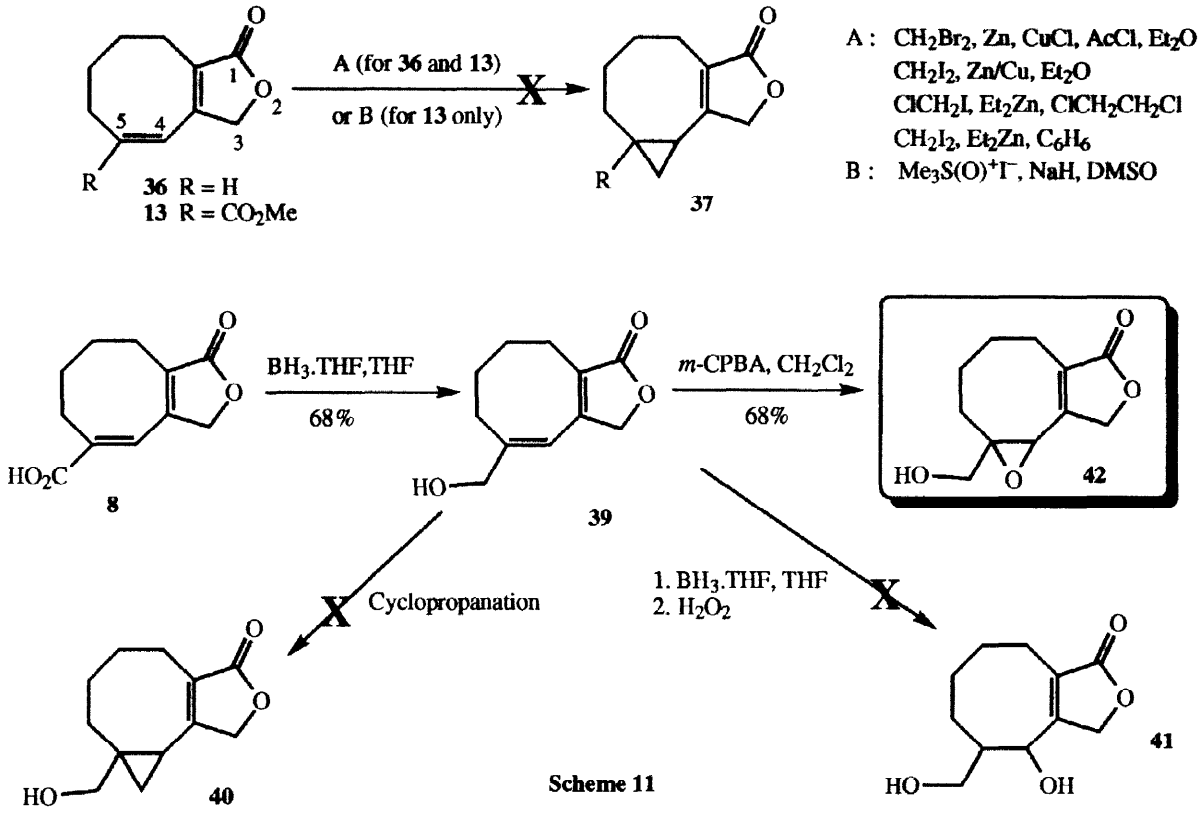
On returning to our pachylactone model study we needed to remove the unwanted 5-carboxy moiety in order to investigate the insertion of the cyclopropane ring. This was achieved by a two-step Barton decarboxylation[8] by first converting the carboxylic acid **12** to the thiopyridyl ester **35** by DCC coupling with 2-mercaptopyridine-N-oxide. This was then subjected to the usual tributyltin hydride reducing conditions to give the desired cyclooctadiene **36**, in a modest overall yield of 32% (Scheme 10).




**Scheme 10**

The conversion of cyclooctadiene **36** to cyclopropane **37**, however, proved to be a real stumbling block in our study. A variety of cyclopropanation attempts using the classic Simmons-Smith reaction and a number of well known variants[9] all resulted in recovery of starting material. Cycloctadiene **36** also proved inert to dibromocarbene prepared by treatment of bromoform with potassium *t*-butoxide.[10] Attempts to convert cyclooctadiene-ester **13** to cyclopropane **38** were equally unsuccessful using both the Simmons-Smith reaction as well as the trimethylsulfoxonium ylide described by Corey,[11] and only starting material could be recovered in all cases. Since it is well documented that cyclopropanation of alkenes are accelerated by an adjacent hydroxyl group[12] the 5-hydroxymethyl derivative **39** was prepared by reduction of the carboxylic acid **12** with borane.[13] However, once again all attempts to cyclopropanate **39** resulted in recovery of starting material and no formation of the desired hydroxymethyl-cyclopropane **40** was ever observed. As it was

recently reported[14] that 1,3-diols can be converted into cyclopropanes, we attempted to synthesise the required 1,3-diol **41** by hydroboration of the 5-hydroxymethyl derivative **39**. Unfortunately in practice only starting material **39** was isolated from the attempted hydroboration. It would thus appear that the 4,5-double bond in our cyclooctadiene systems is inert to most reaction conditions. The only reaction that this double bond would appear to undergo was epoxidation. For example treatment of the 5-hydroxymethyl derivative **39** with *m*-CPBA in dichloromethane[15] afforded epoxide **42** in 68% yield (Scheme 11).




It is posssible (in the case of **36**) that this unreactivity could simply be attributed to the fact that the double bond is electrophilic, due to extended conjugation with the lactone, and hence inert to carbenoid methods of cyclopropanation. This argument, however, does not explain why the nucleophilic sulphoxonium method failed and conversely why electrophilic epoxidation was successful. A more reasonable explanation can be obtained from the energy minimised structure shown in Figure 1. This indicates the preference for a conformer where the $C_4$-$C_5$ double bond is twisted out of coplanarity with the butenolide and where the hydrogen atoms indicated (*) would appear to shield the $\pi$-system in such a way that it may be hindered to attack by the cyclopropanating reagents used in this study.

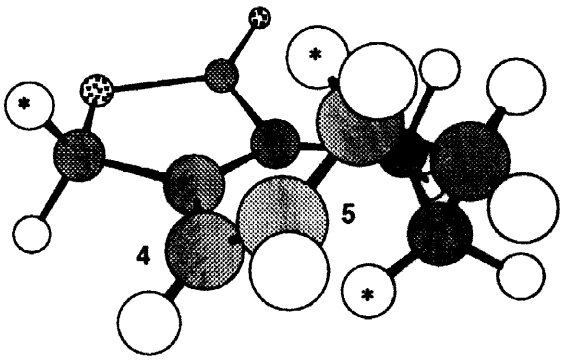



**Figure 1**
**Chem3D minimised conformer of 36**

**Conclusion:** A novel sequential ring-opening/lactonisation sequence of bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylic acid derivatives has been shown to provide rapid access to a select number of fused cyclooctadiene-lactone systems. The unusually low temperatures required for these ring openings, compared with the parent bicyclo[4.2.0]oct-7-ene, have been rationalised by the assumption that in the present study the reactions are driven by an irreversible lactonisation. The reaction has been shown to provide rapid and simple access to the pachylactone **1** skeleton, although all attempts so far to introduce the cyclopropane ring have been thwarted due to the sluggish reactivity of the C4-C5 double bond. Future studies will be aimed at investigating alternative methods of introducing the cyclopropane ring in order that this methodology can ultimately be used in a short synthesis of pachylactone.

## Experimental

For the general experimental procedures used in this study and the preparation of the [2+2] adducts **10, 20** and **28** see the preceeding paper (Ref 7.)

**7-Hydroxymethylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylic acid 11** A solution of 10-hydroxymethyl-8-oxa-tricyclo[4.3.2.$0^{1,6}$]undec-10-ene-7,9-dione **10** (1.94 g, 9.33 mmol) in THF/water (70 mL/30 mL) was stirred at room temperature for 18 hours. Removal of the solvent *in vacuo* resulted in a white solid, 1.90 g, 90%; $R_f$=0.48, EtOAc. $\delta_H$ ($D_2O$) 1.33-1.62 (4H, m), 1.74-1.86 (2H, m), 2.01-2.11 (2H, m), 4.11 (1H, dd, *J* 16.2Hz, *J* 1.0Hz), 4.16 (1H, dd, *J* 15.8Hz, *J* 1.3Hz), 6.18 (1H, app.t, *J* 1.3Hz); $\delta_C$ ($CD_3OD$) 17.03 (2 x $CH_2$), 27.22 (2 x $CH_2$), 56.30 (quat C), 58.54 (quat C), 59.49 ($CH_2$), 132.00 (CH), 152.47 (quat C), 177.23 (quat C), 177.71 (quat C); *m/z* 208 [{M–$H_2O$}$^+$] (24), 190 (14), 179 (14), 162 (18), 136 (58), 108 (100), 91 (44), 79 (47); analysis calculated for $C_{11}H_{14}O_5$: C, 58.41%; H, 6.19%; found: C, 58.40%; H, 6.20%.

**Dimethyl 7-Hydroxymethylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 14** To a solution of 7-hydroxymethylbicyclo[4.2.0.]oct-7-ene-1,6-dicarboxylic acid **11** (0.6 g, 2.88 mmol) in methanol (40 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 18 h after which the methanol removed *in vacuo* and the residue dissolved in ethyl acetate (150 mL). The organic layer was washed with sodium bicarbonate solution (50 mL), brine (50 mL), dried over magnesium sulphate and

concentrated *in vacuo*. Chromatography on silica (30-60% EtOAc/petrol) afforded the pure product as a yellow oil, 0.6 g, 82%; $R_f$ 0.45, EtOAc.$\upsilon_{max}$ /cm$^{-1}$ 3301, 1734 and 1645; $\delta_H$ 1.42-1.70 (4H, m), 1.77-1.93 (2H, m), 2.11-2.24 (2H, m), 2.59-2.64 (1H, br.s, OH), 3.65 (3H, s), 3.67 (3H, s), 4.24 (2H, m), 6.15 (1H, t, *J* 1.5Hz); $\delta_C$ 15.85 ($CH_2$), 15.89 ($CH_2$), 25.55 ($CH_2$), 26.29 ($CH_2$), 51.97 ($CH_3$), 52.15 ($CH_3$), 55.15 (quat C), 57.86 (quat C), 59.26 ($CH_2$), 131.97 (CH), 150.47 (quat C), 173.96 (quat C), 174.70 (quat C); *m/z* 236 [{M–$H_2O$}$^+$] (4), 222 (35), 194 (100), 162 (66), 135 (84), 117 (56), 79 (58); analysis calculated for $C_{13}H_{18}O_5$: C, 61.39%; H, 7.14%; found: C, 60.94%; H, 6.99%.

**Dimethyl 7-(2-Hydroxyethyl)bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 21** (R= $CH_2CH_2OH$, R' = H): To a solution of 10-(2-hydroxyethyl)-8-oxatricyclo[4.3.2.0$^{1,6}$]undec-10-ene-7,9-dione **20** (R = $CH_2CH_2OH$, R' = H) (1.0 g, 4.50 mmol) in methanol (30 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 18 hours. Work-up as for **14** and chromatography on silica (50-100% EtOAc/petrol) afforded pure product as a yellow oil, 1.0 g, 83%; $R_f$ 0.39, EtOAc. $\upsilon_{max}$ /cm$^{-1}$ 3446, 1733 and 1642; $\delta_H$ 1.40-1.86 (6H, m), 2.05-2.49 (4H, m), 3.64 (3H, s), 3.66 (3H, s), 3.73-3.79 (2H, m), 6.13 (1H, t, *J* 1.3Hz); $\delta_C$ 15.85 ($CH_2$), 15.89 ($CH_2$), 25.07 ($CH_2$), 26.52 ($CH_2$), 32.27 ($CH_2$), 51.90 ($CH_3$), 52.00 ($CH_3$), 55.26 (quat C), 58.06 (quat C), 59.66 ($CH_2$), 133.48 (CH), 159.09 (quat C), 174.35 (quat C), 174.39 (quat C); *m/z* 238 [{M–30}$^+$] (41), 206 (100), 177 (29), 119 (32), 91 (22). Analysis calculated for $C_{14}H_{20}O_5$: C, 62.66%; H, 7.52%; found: C, 61.90%; H, 7.45%.

**Dimethyl 7-butylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 22** (R= $^n$Bu, R'=H) To a solution of 10-butyl-8-oxatricyclo[4.3.2.0$^{1,6}$]undec-10-ene-7,9-dione **20** (R = $^n$Bu, R' = H) (1.0 g, 4.27 mmol) in methanol (25 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 4 hours. Work-up as for **14** and chromatography on silica (5-10% EtOAc/petrol) afforded pure product as a colourless oil, 1.04 g, 87%; $R_f$ 0.39, EtOAc. $\upsilon_{max}$ /cm$^{-1}$ 1735 and 1643; $\delta_H$ 0.92 (3H, t, *J* 7.3Hz), 1.31-2.23 (14H, m), 3.63 (6H, s), 5.98 (1H, t, *J* 1.7Hz); $\delta_C$ 13.91 ($CH_3$), 15.96 (2 x $CH_2$), 22.59 ($CH_2$), 25.18 ($CH_2$), 26.68 ($CH_2$), 27.69 ($CH_2$), 28.03 ($CH_2$), 51.68 ($CH_3$), 51.72 ($CH_3$), 54.54 (quat C), 57.75 (quat C), 129.95 (CH), 152.76 (quat C), 173.98 (quat C), 174.66 (quat C); *m/z* 280 [M$^+$] (9), 248 (37), 220 (100), 191 (33), 161 (44), 119 (18), 91 (27); analysis calculated for $C_{16}H_{24}O_4$: C, 68.53%; H, 8.63%; found: C, 68.54%; H, 8.57%.

**Dimethyl 7,8-bis(hydroxymethyl)bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 23** (R,R' = $CH_2OH$) To a solution of 10,11-bis(hydroxymethyl)-8-oxatricyclo[4.3.2.0$^{1,6}$]undec-10-ene-7,9-dione **20** (R,R' = $CH_2OH$) (0.6 g, 2.52 mmol) in methanol (25 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 6 h. Work-up as for **14** and chromatography on silica (50-100% EtOAc/petrol) afforded pure product as a white solid, 0.44 g, 61%; $R_f$ 0.30, EtOAc. $\upsilon_{max}$ /cm$^{-1}$ 3189, 1740; $\delta_H$ 1.42-1.70 (4H, m), 1.76-1.86 (2H, m), 2.09-2.21 (2H, m), 3.55 (2H, s), 3.65 (6H, s), 4.18-4.34 (4H, m); $\delta_C$ 15.83 ($CH_2$), 24.83 ($CH_2$), 52.06 ($CH_3$), 55.74 (quat C), 57.93 ($CH_2$), 142.77 (quat C), 174.21 (quat C); *m/z* 266 [{M–$H_2O$}$^+$] (15), 234 (100), 206 (21), 174 (34), 147 (36), 119 (21); analysis calculated for $C_{14}H_{20}O_6$: C, 59.13%; H, 7.09%; found: C, 59.18%; H, 7.05%.

**Dimethyl 7-hydroxymethyl-8-trimethylsilylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 24** (R = $SiMe_3$, R' = $CH_2OH$): To a solution of 10-hydroxymethyl-11-trimethylsilyl-8-oxatricyclo[4.3.2.$0^{1,6}$]-undec-10-ene-7,9-dione **20** (R= $SiMe_3$, R' = $CH_2OH$) (1.4 g, 5.00 mmol) in methanol (30 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 4 h. Work-up as for **14** and chromatography on silica (30-40% EtOAc/petrol) afforded pure product as a yellow oil, 1.31 g, 80%; $R_f$ 0.27, 40%EtOAc/petrol. $\upsilon_{max}$ /$cm^{-1}$ 3518, 1735, 1623 and 842; $\delta_H$ 0.12 (9H, s), 1.46-1.69 (4H, m), 1.81-1.95 (2H, m), 2.04-2.21 (2H,m), 3.44 (1H, app.t, *J* 5.6Hz), 4.22 (1H, dd, *J* 5.3Hz, *J* 14.2Hz), 4.37 (1H, dd, *J* 5.6Hz, *J* 14.5Hz); $\delta_C$ –1.02 (3 x $CH_3$), 16.02 ($CH_2$), 16.16 ($CH_2$), 24.98 ($CH_2$), 27.64 ($CH_2$), 51.68 ($CH_3$), 52.15 ($CH_3$), 56.63 (quat C), 59.12 (quat C), 59.81 ($CH_2$), 149.81 (quat C), 160.51 (quat C), 174.50 (quat C), 175.67 (quat C); *m/z* 326 [$M^+$] (6), 311 [{M–$CH_3$}$^+$] (62), 293 (53), 266 (87), 251(74), 237 (25), 177 (31), 163 (56), 117 (34), 91 (25), 73 (100); analysis calculated for $C_{16}H_{26}O_5Si$: C, 58.87%; H, 8.03%; found: C, 58.79%; H, 7.93%.

**Dimethyl 8-benzyloxymethyl-7-hydroxymethylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 25** (R = $CH_2OH$, R' = $CH_2OBn$): To a solution of 11-benzyloxymethyl-10-hydroxymethyl-8-oxa-tricyclo[4.3.2.$0^{1,6}$]undec-10-ene-7,9-dione **20** (R = $CH_2OH$, R' = $CH_2OBn$) (2.50 g, 7.62 mmol) in methanol (100 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 18 h. Work-up as for **14** and chromatography on silica (20-40% EtOAc/petrol) afforded pure product as a yellow oil, 2.40 g, 84%; $R_f$ 0.29, 40%EtOAc/petrol. $\upsilon_{max}$ /$cm^{-1}$ 3443, 1732 and (s) 1497; $\delta_H$ 1.45-1.77 (4H, m), 1.80-1.87 (2H, m), 2.08-2.19 (2H, m), 3.61 (3H, s), 3.65 (3H, s), 3.87-3.92 (1H, m), 4.00-4.25 (4H, m), 4.56 (1H, d, *J* 11.9Hz), 4.63 (1H, d, *J* 11.9Hz), 7.28-7.40 (5H, m); $\delta_C$ 15.83 ($CH_2$), 15.88 ($CH_2$), 24.69 ($CH_2$), 25.25 ($CH_2$), 51.89 ($CH_3$), 52.04 ($CH_3$), 55.42 (quat C), 56.15 (quat C), 58.02 ($CH_2$), 65.43 ($CH_2$), 73.42 ($CH_2$), 127.76 (2 x CH), 127.99 (CH), 128.55 (2 x CH), 137.19 (quat C), 139.80 (quat C), 144.09 (quat C), 173.53 (quat C), 174.30 (quat C).

**Dimethyl 7-hydroxymethyl-8-methylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate acid 26** (R = H, R' = Me): To a solution of 10-hydroxymethyl-11-methyl-8-oxatricyclo[4.3.2.$0^{1,6}$]undec-10-ene-7,9-dione **20** (R = H, R' = Me) (1.0 g, 4.50 mmol) in methanol (40 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 5 h. Work-up as for **14** and chromatography on silica (40% EtOAc/petrol) afforded pure product as a white solid, 0.94 g, 78%; $R_f$ 0.27, 40%EtOAc/petrol. M.Pt. 80-83°C; $\upsilon_{max}$ /$cm^{-1}$ 3490 and 1729; $\delta_H$ 1.35-1.66 (4H, m), 1.70 (3H, s), 1.76-1.89 (2H, m), 2.05-2.21 (2H, m), 3.16 (1H, dd, *J* 6.3Hz, *J* 4.6Hz), 3.64 (3H, s), 3.67 (3H, s), 4.05-4.12 (1H, m), 4.32 (1H, dd, *J* 13.5Hz, *J* 5.9Hz); $\delta_C$ 11.23 ($CH_3$), 15.79 (2 x $CH_2$), 23.58 ($CH_2$), 25.47 ($CH_2$), 51.70 ($CH_3$), 52.01 ($CH_3$), 56.53 (quat C), 56.66 ($CH_2$), 56.70 (quat C), 141.10 (quat C), 142.23 (quat C), 173.58 (quat C), 175.60 (quat C); *m/z* 268 [$M^+$] (3), 236 (9), 222 (9), 208 (100), 191 (12), 148 (40), 131 (17), 91 (20); analysis calculated for $C_{14}H_{20}O_5$: C, 62.66%; H, 7.52%; found: C, 62.73%; H, 7.48%.

**Dimethyl 7-(1-hydroxyethyl)bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate 27** (R = H, R' = CH(Me)OH) To a solution of 10-(1-hydroxyethyl)-8-oxatricyclo[4.3.2.$0^{1,6}$]undec-10-ene-7,9-dione **20** (R

= H, R' = CH(Me)OH) (1.0 g, 4.50 mmol) in methanol (40 mL) was added concentrated sulphuric acid (1 mL). The mixture was heated at reflux for 4 h. Work-up as for **14** and chromatography on silica (40-60% EtOAc/petrol) afforded pure product (1:1 mixture of diastereomers) as a yellow oil, 1.11 g, 92%; $R_f$ 0.27, 40%EtOAc/petrol. $\upsilon_{max}$ /cm$^{-1}$ 3457, 1728 and 1646; $\delta_H$ 1.35 and 1.39 (d, *J* 6.6Hz), (3H), 1.41-1.69 (4H, m), 1.74-2.30 (4H, m), 2.69 (d, *J* 5.3Hz) and 3.43 (d, *J* 4.9Hz) (1H), 3.64 (3H, s), 3.67 (s) and 3.68 (s) (3H), 4.29-4.35 (m), 4.51-4.56 (m), (1H), 6.08 (d, *J* 1.3Hz) and 6.09 (d, *J* 1.7Hz) (1H); $\delta_C$ 15.85, 15.89 ($CH_2$), 15.85, 16.10 ($CH_2$), 20.16, 21.08 ($CH_3$), 25.62, 26.20 ($CH_2$), 26.36, 26.83 ($CH_2$), 51.90, 51.95 ($CH_3$), 52.04 , 52.22 ($CH_3$), 54.55 (quat C), 57.97, 58.17 (quat C), 63.83, 65.35 (CH), 131.09, 131.18 (CH), 154.03, 154.36 (quat C), 173.94, 174.12 (quat C), 174.64, 175.27 (quat C). Analysis calculated for $C_{14}H_{20}O_5$: C, 62.66%; H, 7.52%; found: C, 62.29%; H, 7.62%.

**Dimethyl 6-hydroxymethylbicyclo[3.2.0.]hept-6-ene-1,5-dicarboxylate 29** To a solution of 9-hydroxymethyl-7-oxatricyclo[3.3.2.0$^{1,5}$]dec-9-ene-6,8-dione **28** (0.95 g, 4.90 mmol) in methanol (30 mL) was added concentrated sulphuric acid (1 mL). Work-up as for **14** and chromatography on silica (50% EtOAc/petrol) afforded pure product as a colourless oil, 1.1 g, 93%; $R_f$ 0.29, 60%EtOAc/petrol. $\upsilon_{max}$ /cm$^{-1}$ 3458, 1734 and 1654; $\delta_H$ 1.60-1.76 (3H, m), 1.86-2.01 (4H, m), 3.68 (3H, s), 3.70 (3H, s), 4.20-4.21 (2H, m), 5.95-5.96 (1H, m); $\delta_C$ 23.99 ($CH_2$), 28.43 ($CH_2$), 28.86 ($CH_2$), 51.95 ($CH_3$), 52.15 ($CH_3$), 58.24 ($CH_2$), 63.60 (quat C), 65.84 (quat C), 128.84 (CH), 147.21 (quat C), 172.83 (quat C), 173.49 (quat C); *m/z* 240 [M$^+$] (7), 208 (46), 180 (100), 148 (55), 121 (58), 91 (66). Analysis calculated for $C_{12}H_{16}O_5$: C, 59.98%; H, 6.72%; found: C, 59.40%; H, 6.76%.

**1-Oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan-5-carboxylic acid 12** A solution of 7-hydroxymethylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylic acid **11** (2.4 g, 10.6 mmol) in diglyme (20 mL) was heated at reflux under a nitrogen atmosphere for 7 h. The solvent was removed *in vacuo* and chromatography on silica (50-100% EtOAc/petrol) followed by recrystallisation from ethyl acetate/petrol yielded the pure product as a cream solid, 1.6 g, 72%; $R_f$ 0.40, EtOAc. M.Pt. 188-192°C; $\upsilon_{max}$ /cm$^{-1}$ 3050, 1722 and 1621; $\delta_H$ 1.71-1.89 (4H, m), 2.18-2.68 (4H, m), 4.71 (2H, t, *J* 2.5 Hz), 7.29 (1H, s); $\delta_C$ 20.66 ($CH_2$), 25.23 ($CH_2$), 25.48 ($CH_2$), 26.04 ($CH_2$), 71.01 ($CH_2$), 131.01 (CH), 131.64 (quat C), 137.23 (quat C), 150.17 (quat C), 171.25 (quat C), 174.21 (quat C); *m/z* 208 [M$^+$] (100), 190 (53), 179 (50), 162 (62), 135 (30), 119 (51), 105 (44), 91 (65), 77 (44), 43 (83); analysis calculated for $C_{11}H_{12}O_4$: C, 63.44%; H, 5.81%; found: C, 63.66%; H, 5.74%.

**Methyl 1-oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan-5-carboxylate 13** A solution of dimethyl 7-hydroxymethylbicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate **14** (0.9 g, 3.54 mmol) in xylene (10 mL) was heated at reflux under a nitrogen atmosphere for 36 h. The solvent was removed *in vacuo* and chromatography on silica (20-40% EtOAc/petrol) afforded pure product as a pale yellow oil, 0.65 g, 83%; $R_f$ 0.50, 60% EtOAc/petrol. $\upsilon_{max}$ /cm$^{-1}$ 1756, 1717 and 1634; $\delta_H$ 1.67-1.76 (2H, m), 1.80-1.89 (2H, m), 2.45-2.55 (2H, m), 2.62-2.67 (2H, m), 3.84 (3H, s), 4.68 (2H, t, *J* 2.5 Hz), 7.15 (1H, s); $\delta_C$ 20.68 ($CH_2$), 25.34 ($CH_2$), 25.43 ($CH_2$), 26.31 ($CH_2$), 52.40 ($CH_3$), 71.05 ($CH_2$), 128.93 (CH), 130.82 (quat C), 137.95 (quat C),

150.58 (quat C), 166.74 (quat C), 174.32 (quat C); *m/z* 222 [M+] (100), 190 (86), 162 (73), 135 (28), 119 (48), 105 (49), 91 (64), 77 (42); analysis calculated for $C_{12}H_{14}O_4$: C, 64.84%; H, 6.35%; found: C, 64.87%; H, 6.39%.

**Methyl 1-oxo-3,4,7,8,9,10-hexahydro-1H-cycloocta[*c*]pyran-6-carboxylate 30** A solution of dimethyl 7-(2-hydroxyethyl)bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate **21** (1.0 g, 3.73 mmol) in xylene (12 mL) was heated at reflux under a nitrogen atmosphere for 40 h. The solvent was removed *in vacuo* and chromatography on silica (20-40% EtOAc/petrol) afforded pure product as a cream solid, 0.68 g, 77%; $R_f$ 0.37, 40% EtOAc/petrol. M.Pt. 79-82°C $\upsilon_{max}/cm^{-1}$ 1712 and 1629; $\delta_H$ 1.40-1.72 (4H, m), 2.10-2.60 (4H, m), 2.48 (2H, t, *J* 6.1 Hz), 3.81 (3H, s), 4.40 (2H, t, *J* 6.1 Hz), 7.13 (1H, s); $\delta_C$ 22.37 ($CH_2$), 23.27 ($CH_2$), 26.96 ($CH_2$), 27.57 ($CH_2$), 27.91 ($CH_2$), 52.24 ($CH_3$), 65.77 ($CH_2$), 128.52 (quat C), 134.74 (CH), 136.23 (quat C), 145.57 (quat C), 165.26 (quat C), 167.37 (quat C); *m/z* 236 [M+] (88), 204 (25), 177 (100), 131 (44), 91 (86), 77 (37); analysis calculated for $C_{13}H_{16}O_4$: C, 66.07%; H, 6.83%; found: C, 66.12%; H, 6.77%.

**3-Methyl-1-oxo-1,3,6,7,8,9-hexahydro-cycloocta[*c*]furan-5-carboxylic acid 31** A solution of dimethyl 7-(1-hydroxyethyl)bicyclo[4.2.0]oct-7-ene-1,6-dicarboxylate **27** (0.8 g, 2.99 mmol) in xylene (12 mL) was heated at reflux under a nitrogen atmosphere for 36 h. The solvent was removed *in vacuo* and chromatography on silica (20% EtOAc/petrol) afforded pure product as a cream solid, 0.62 g, 85%; $R_f$ 0.44, 40% EtOAc/petrol. $\upsilon_{max}/cm^{-1}$ 1751, 1715, 1653 and 1630; $\delta_H$ 1.41 (3H, d, *J* 6.6 Hz), 1.62-1.87 (4H, m), 2.47-2.68 (4H, m), 3.82 (3H, s), 4.87-4.93 (1H, m), 7.14 (1H, s); $\delta_C$ 18.85 ($CH_3$), 20.61 ($CH_2$), 25.18 ($CH_2$), 25.37 ($CH_2$), 26.36 ($CH_2$), 52.40 ($CH_3$), 78.31 (CH), 128.04 (CH), 130.53 (quat C), 137.91 (quat C), 155.00 (quat C), 166.72 (quat C), 173.29 (quat C); *m/z* 236 [M+] (89), 204 (42), 193 (51), 176 (38), 133 (54), 105 (100), 91 (43), 77 (50); analysis calculated for $C_{13}H_{15}O_4$: C, 66.07%; H, 6.83%; found: C, 66.15%; H, 6.78%.

**Methyl 3-Oxo-3,4,5,6-tetrahydro-[1*H*]-cyclohepta[*c*]furan-7-carboxylate 32** A solution of dimethyl 6-hydroxymethylbicyclo[3.2.0]hept-6-ene-1,5-dicarboxylate **29** (1.0 g, 4.17 mmol) in xylene (10 mL) was heated at reflux under a nitrogen atmosphere for 42 hours. The solvent was removed *in vacuo* and chromatography on silica (30-50% EtOAc/Petrol) afforded pure product as a yellow solid, 0.05 g, 6%; $R_f$=0.38, 40% EtOAc/Petrol (0.7 g of starting material was also isolated). M.Pt. 73-76°C; $\upsilon_{max}/cm^{-1}$ 1751, 1707, 1653 and 1622; $\delta_H$ 1.89-1.98 (2H, m), 2.62-2.67 (2H, m), 2.81-2.85 (2H, m), 3.81 (3H, s), 4.78 (2H, t, *J*=2.8Hz), 7.03 (1H, s); $\delta_C$ ppm 21.85 ($CH_2$), 27.37 ($CH_2$), 29.90 ($CH_2$), 52.60 ($CH_3$), 71.12 ($CH_2$), 125.93 (CH), 132.70 (quat C), 142.37 (quat C), 150.13 (quat C), 167.22 (quat C), 174.21 (quat C); *m/z* 208 [M+] (100), 179 (26), 148 (23), 119 (28), 105 (35), 91 (59); analysis calculated for $C_{11}H_{12}O_4$: C, 63.44%; H, 5.81%; found: C, 63.11%; H, 5.95%.

**1-Oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan 36** To a stirred solution of 1-oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan-5-carboxylic acid **12** (1.2 g, 5.77 mmol) in dry dichloromethane (50 mL) under a nitrogen atmosphere was added 2-mercaptopyridine-*N*-oxide (0.88 g, 6.92 mmol) and 4-dimethylaminopyridine (1.05 g, 8.65 mmol). Dicyclohexylcarbodiimide (1.78 g, 8.65 mmol) in dichloromethane (10 mL) was added dropwise and the reaction mixture stirred at room temperature for 18 h after which the resulting suspension was filtering through celite, washing with dichloromethane (150 mL). The filtrate was washed sucessively with 2M hydrochloric acid (30 mL), sodium bicarbonate solution (30 mL), brine (30 mL) and then dried over magnesium sulphate. The solvent was removed *in vacuo*. and chromatography on silica (50-100% EtOAc/petrol) afforded the 2-mercaptopyridine ester **35** as a yellow foam, 1.6 g, 83%; $R_f$ 0.61, 100% EtOAc/petrol. To this product (1.6 g, 4.78 mmol) in dry toluene (40 mL) at reflux, under a nitrogen atmosphere, was added a solution of AIBN (0.08 g, 0.478 mmol) and tributyltin hydride (1.3 mL, 4.78 mmol) in toluene (10 mL) and reaction mixture heated at relux for a further 18 h. The solvent was removed *in vacuo*; the residue was dissolved in acetonitrile (50 mL) and washed with petrol (50 mL) and the acetonitrile layer separated and concentrated *in vacuo*. Chromatography on silica (10-20% EtOAc/Petrol) yielded pure product as a yellow oil, 0.30 g, 38%; $R_f$ 0.50, 40% EtOAc/petrol. $\upsilon_{max}$ /cm$^{-1}$ 1751 and 1667; $\delta_H$ 1.55-1.68 (2H, m), 1.80-1.89 (2H, m), 2.32-2.51 (4H, m), 4.62 (2H, t, *J* 2.3 Hz), 5.99 (1H, d, *J* 11.5 Hz), 6.07 (1H, dd, *J* 11.2, 7.3 Hz); $\delta_C$ 21.06 ($CH_2$), 24.49 ($CH_2$), 24.96 ($CH_2$), 27.05 ($CH_2$), 71.23 ($CH_2$), 120.81 (CH), 126.90 (quat C), 137.95 (quat C), 138.42 (CH), 153.03 (quat C), 175.17 (quat C); *m/z* 164 [M$^+$] (100), 135 (43), 119 (32), 105 (22), 91 (43); (Accurate elemental analysis could not be obtained due to organotin residues).

**5-Hydroxymethyl-1-oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan 39** To a solution of 1-oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan-5-carboxylic acid **8** (1.0 g, 4.81 mmol) in THF (40 mL) cooled to 0°C was added dropwise borane/THF complex (5.8 mL, 5.77 mmol, 1.0 M solution in THF). The reaction mixture was allowed to warm to room temperature for 2.5 h. Work-up consisted of addition of water (20 mL), extraction with ethyl acetate (100 mL), washing with brine (20 mL), separation of the organic layer, drying over magnesium sulphate, filtering, and removal of the solvent *in vacuo*. Chromatography on silica (30-60% EtOAc/petrol) yielded pure product as a white solid, 0.61 g, 65%; $R_f$ 0.30, 60% EtOAc/petrol.M.Pt. 94-97°C; $\upsilon_{max}$ /cm$^{-1}$ 3506, 1729 and 1637; $\delta_H$ 1.61-1.71 (2H, m), 1.79-1.89 (3H, m), 2.28-2.33 (2H, m), 2.44-2.47 (2H, m), 4.22 (2H, d, *J* 1.3 Hz), 4.62 (2H, t, *J* 2.3 Hz), 6.14 (1H, s); $\delta_C$ 21.10 ($CH_2$), 24.71 ($CH_2$), 25.21 ($CH_2$), 27.62 ($CH_2$), 65.25 ($CH_2$), 71.52 ($CH_2$), 113.96 (CH), 126.00 (quat C), 149.79 (quat C), 153.60 (quat C), 175.67 (quat C); *m/z* 194 [M$^+$] (76), 176 (28), 165 (27), 147 (24), 135 (30), 119 (51), 105 (34), 91 (100), 79 (78). Anal. calcd. for $C_{11}H_{14}O_3$: C, 68.01%; H, 7.27%. Found: C, 67.54%; H, 7.46%

**5-Hydroxymethyl-1-oxo-4,5-oxy-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan 42** To a solution of 5-hydroxymethyl-1-oxo-1,3,6,7,8,9-hexahydrocycloocta[*c*]furan **39** (0.2 g, 1.03 mmol) in dichloromethane (5 mL) was added a solution of *m*-CPBA in dichloromethane (20 mL) dried over magnesium sulphate. The reaction mixture was stirred at room temperature for 18 h. Work-up consisted of extraction with

dichloromethane (100 mL), alternate washing with sodium hydrogencarbonate solution (3 x 25 mL) and sodium metabisulphite solution (3 x 25 mL), separation of the organic layer, drying over magnesium sulphate, filtering, and removal of the solvent *in vacuo*. Chromatography on silica (50% EtOAc/petrol) yielded pure product as a white solid, 0.16 g, 74%; $R_f$ 0.35, EtOAc. M.Pt. 120-124°C; $\upsilon_{max}$ /cm$^{-1}$ 3478 and 1746 ; $\delta_H$ 1.26-1.40 (1H, m), 1.59-1.90 (6H, m), 2.05-2.26 (2H, m), 2.60-2.71 (1H, m), 2.44-2.47 (2H, m), 3.80 (1H, s), 3.82 (1H, d, *J* 12.2 Hz), 3.90 (1H, d, *J* 12.5 Hz), 4.79 (2H, t, *J* 2.5 Hz); $\delta_C$ 21.53 ($CH_2$), 25.57 ($CH_2$), 27.53 ($CH_2$), 52.24 (CH), 61.46 ($CH_2$), 63.72 (quat C), 70.87 ($CH_2$), 130.31 (quat C), 150.31 (quat C), 174.30 (quat C); *m/z* 210 [M$^+$] (3), 156 (100), 139 (76), 111 (43), 91 (52), 79 (39). Anal. calcd. for $C_{11}H_{14}O_4$: C, 62.84%; H, 6.72%. Found: C, 62.67%; H, 6.91%.

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