DEVELOPMENT OF METHODOLOGY BASED ON THE USE OF THE 7-OXABICYCLO[2.2.1]HEPTANYL SYSTEM FOR THE PREPARATION OF CARBOHYDRATE DERIVATIVES‡[1]

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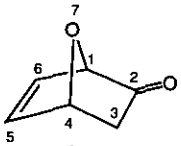
Abstract- The 7-oxabicyclo[2.2.1]heptanyl system provides a rapid entry to carbohydrate derivatives in a stereoselective manner by virtue of the rigid framework. The formation of this bicyclic system through a Diels-Alder reaction of furan with a number of dienophiles is influenced by the substitution on the dienophile. Use of an anion stabilising group as a carbonyl equivalent has previously led to a ring opening reaction of the bicyclic system. However, anion chemistry can be used to functionalise the bicyclic system, and used for the introduction of a hydroxy group that allows, in turn, a method for the preparation of hexose derivatives.

As part of our work to investigate the reactions of the 7-oxabicyclo[2.2.1]heptanyl system for the preparation of tetrahydrofuran derivatives,[2] it came to our attention that, as others have seen,[3-6] this bicyclic system has great potential for the synthesis of carbohydrate derivatives, other natural products, and their analogues[3,7-9] but not all of the latent functionality was being put to good use. We, therefore, set out to investigate the use of the 7-oxabicyclo[2.2.1]heptanyl system for the preparation of carbohydrate analogues, and to augment the chemistry of these systems to allow the preparation of hexose derivatives. The pivotal compound to our strategy became the ketone (**1**), as used by Vogel, because of the flexibility available for the introduction of functionality at carbon atoms C-5, and -6.[3,5,10]

‡ Dedicated to Professor Alan Katritzky on the occasion of his 65th birthday.



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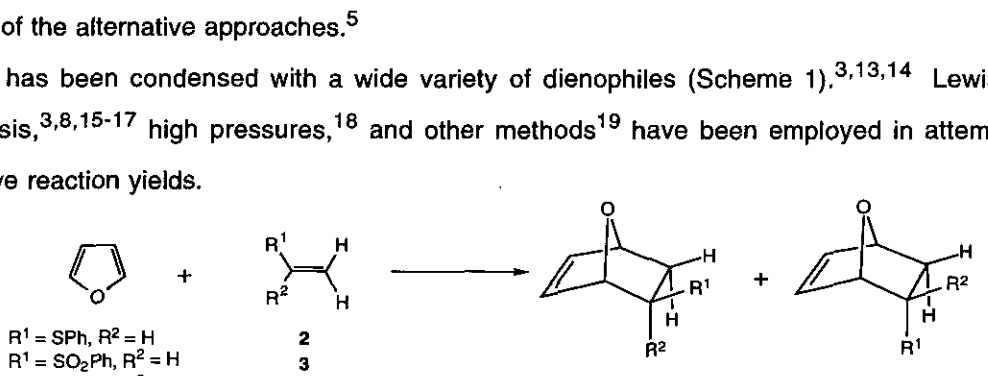
To complete the repertoire of reactions, functional groups need to be introduced at carbon atom 3. The attack from the exo-face could be achieved through an enolate intermediate,[6] but the inversion necessary to achieve functionalisation on the endo-face was not known at the commencement of this work. The key reaction for the conversion of the six-membered carbon ring to the acyclic analogue of a hexose is the Baeyer-Villiger reaction.[11]

As one of the goals of this work was to investigate new routes to carbohydrates that could then be used as new members of the chiral pool, reactions had to be high yielding, and amenable to scale-up. The study, therefore, fell into the following areas: definition of the best methods for the preparation of the 7-oxabicyclo[2.2.1]heptanyl system and development of relevant synthetic transformations within that bicyclic system[12] through the stereospecific introduction of a hydroxy group at the C-3 position of the bicyclic system.

Furan Diels-Alder Reactions: The original concept demanded that the approach should allow for the introduction of chiral influences, such as through ester formation, so that an asymmetric approach to the ketone (**1**) could be realised without the tedious separations and low yields of the alternative approaches.[5]

Furan has been condensed with a wide variety of dienophiles (Scheme 1).[3,13,14] Lewis acid catalysis,[3,8,15-17] high pressures,[18] and other methods[19] have been employed in attempts to improve reaction yields.

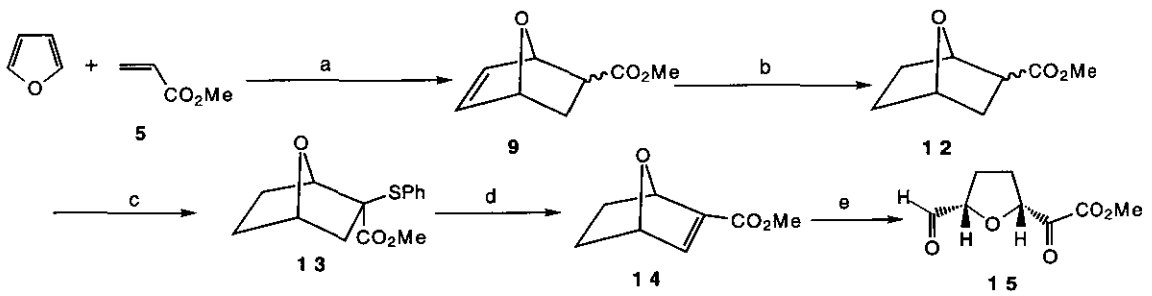


Scheme 1.

A number of potential dienophiles and conditions were investigated to achieve the condensation.[20] For this work, we concentrated on sulphur and carbonyl based dienophiles (**2-7**) (Scheme 1) that contained functionality that could be easily converted to a ketone.[21]

In the sulphur series, only the sulphone (**4**) *led to the formation of the cycloadduct* (**8**) *in good* yield.[13,22,23] In a similar manner, methyl acrylate (**5**) afforded the condensation product (**9**) in moderate yield as a mixture of the <u>exo-</u> and <u>endo-</u> isomers.[14,15] In contrast, the disubstituted alkene, α-phenylthioacrylic acid (**6**), gave only trace amounts of (**10**). The chemistry of the adducts (**8**) and (**9**) containing a sulphone or carboxylate group was investigated in the achiral series, as incorporation of a chiral group into these systems would seem to be relatively straightforward.

Reactions of 7-Oxabicyclo[2.2.1]heptanyl compounds: Our initial goal of this work was to prepare <u>cis</u>-tetrahydrofuran derivatives (Scheme 2).[2]

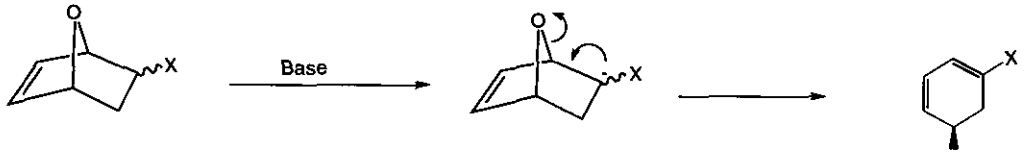


a) ZnI_2. *b)* H_2, *10% Pd-C. c) i. LDA,* C_6H_{14}, *-90°C; ii. PhSSPh. d) i. MCPBA; ii.* Δ. *e) i.* O_3; *ii.* Me_2S

Scheme 2.

The key step in this sequence is the introduction of the double bond to give the unsaturated ester (**14**), which is then oxidatively cleaved to produce the <u>cis</u>-tetrahydrofuran (**15**), and exists as a bicyclic acetal.[2] To accomplish this, formation of an anion is necessary. Both the ester and sulphone groups stabilise an α-carbanion and are, thus, amenable for use in this transformation. However, when the sulphone (**13**) was treated with base (sodium hydride, lithium diisopropylamide or lithium aluminium hydride), ring opening to the cyclohexenol (**16**) occurred, even at low temperature and with very short reaction times (<u>ca</u>. 1 min) (Scheme 3).[13]

The analogous reaction had been reported for the methyl ester (**9**) and its saturated analogue (**12**).[15] In these cases, the ester enolate was formed at -78°C and then allowed to warm to ambient temperature so that the β-elimination occurred. It was surmised that use of very low temperature would minimize the potential for this unwanted ring-opening reaction.



X = SO_2Ph **8**
CO_2Me **9**

16
17

Scheme 3.

The initial Diels-Alder adduct (**9**) was reduced in high yield to the saturated ester (**12**) (Scheme 2). Initial studies were performed with the ester (**12**) in THF at -78°C (Scheme 4). When the ester enolate was formed with lithium diisopropylamide (LDA) over a 30 min period, and then quenched with methyl iodide or a deuterium source, the cyclohexenol (**18**) was formed exclusively. However, when the temperature was lowered to -90°C, reaction with the same electrophiles led to a mixture of the alcohol (**18**) and the desired adduct. By shortening the reaction time to 10 min, the β-elimination pathway could be completely suppressed. Some representative electrophiles are given in the Table.

Table

Reactions of Electrophiles with the Anion Derived from **12**

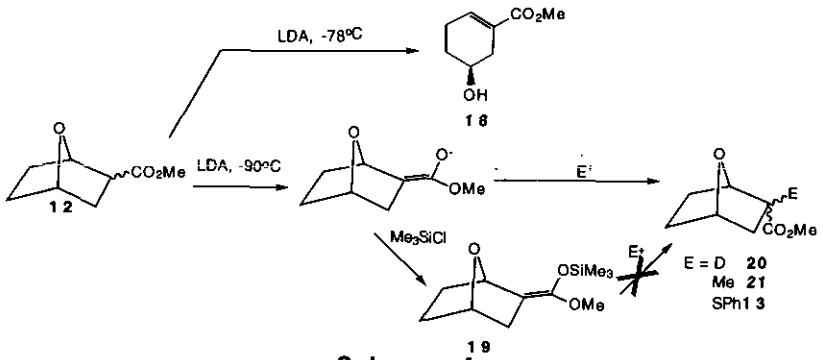
Electrophile	Solvent	Product	Yield (%)	Exo:Endo Ratio
D_2O	THF	**20**	80	2:1
MeI	THF	**21**	76	2:1
PhSSPh	THF	**13**	65	2:1
	Et_2O	**13**	65	4:1
	hexane	**13**	65	>20:1[a]
Me_3SiCl	THF	**19**	90	-

[a] No endo isomer was detected by nmr or chromatography.

The silyl enol ether (**19**) was formed in high yield. However, subsequent reaction with an electrophile in the presence of a Lewis acid,[24] did not provide an alternative method for the

introduction of an electrophile at C-2; no reaction was observed and the ester (**12**) was recovered *in high yield after aqueous work up.*

Even with these new reaction conditions for anion formation, the sulphone derivative (**8**) still gave rise to exclusively ring opened products.



Scheme 4.

In all cases, a mixture of exo- and endo-isomers was formed. Subsequent work on the elimination of the sulphoxide derived from the sulphide (**13**), showed that the presence of the endo-isomer was detrimental to the formation of the α,β-unsaturated ester (**14**) (*vide infra*). When ether or hexane was used in place of THF, the exo:endo ratio of the adducts was not changed significantly except for the case of diphenyl disulphide. In ether, the formation of the exo-isomer was favoured by 4:1, while in hexane the endo-isomer could not be detected. There is no obvious explanation for why the sulphur electrophile undergoes a stereospecific reaction in the hydrocarbon solvent. As enolates form aggregates in almost all solvents (*vide infra*), one plausible explanation is that the disulphide acts as a ligand for the hexane complex, which then ensures stereoselectivity. If the disulphide is added in a relatively large amount of THF, a mixture of the exo- and endo- isomers results, suggesting that the aggregates are extremely sensitive to the solvent present.[25-27]

Oxidation of the sulphide (**13**) to the sulphoxide proceeded smoothly, as expected. When the sulphoxide was a mixture of isomers, only one was eliminated to afford the unsaturated ester (**14**) on heating, the other could be recovered unchanged if mild conditions were employed.[28] Use of *vigorous conditions led to the degradation of the endo-sulphoxide rather than the required*

elimination. Thus, the finding that hexane led to only the exo-sulphide, and hence sulphoxide, alleviated the stereochemical problems associated with this step.

As noted above, studies were performed to find alternative routes to the ketone (**1**), but these were thwarted by both a retro-Diels-Alder reaction and a failure of the dianion derived from the acid (**22**) to react with an oxygen electrophile. As the dianion was insoluble in the reaction medium, failure to observe reaction could have been due to a combination of the low solubility and slow reaction rate due to the low temperature.

Ester Hydrolysis Reactions: Conversion of a carbon atom with a carboxylate or sulphone substituent requires the formation of a carbanion at that centre.[21] The bicyclic system has already been shown to be too unstable for this to be a viable option in the sulphone series. The conversion in the carboxylate series requires the use of the acid (**23**), potentially available by hydrolysis of the corresponding ester (**9**). The literature revealed a disparity for this transformation with yields ranging from 40-98%, under essentially identical conditions, the only difference being in the isolation procedure;[14,29] we felt that this reaction was worthy of further investigation.

With the knowledge that the 7-oxabicyclo[2.2.1]heptanyl system undergoes facile ring opening, it was felt that basic hydrolysis of the ester (**9**) could be accompanied by enolate formation which could then undergo β-elimination. Treatment of the mixture of esters (**9**) derived from the Diels-Alder reaction between furan and methyl acrylate with a variety of reagents that have been advocated for the mild hydrolysis of methyl esters ($MgSO_4$ in benzene, LiBr in DMF or 2,6-lutidine, and hydrochloric acid in THF) resulted in recovery of **9**. All of these reactions were performed at room temperature because of the thermal instability of the esters (**9**). These reactions showed that the oxygen bridge of the bicyclic system is not particularly susceptible to Lewis or Brönsted acid catalysed cleavage.

Under basic conditions, preliminary studies with one equivalent of base indicated that hydrolysis was slow. In the presence of excess sodium hydroxide, with THF as cosolvent, about 20% saponification was observed after 24 h. When the cosolvent was omitted, the yield of the acid (**23**) increased to 58% but no unreacted ester (**9**) was detected. Thus, the hydrolysis is solvent

dependent. When potassium, rather sodium, hydroxide was used with THF as cosolvent at reflux, a 40% yield of **23** was isolated with no ester (**9**) being detected. Despite numerous attempts, the maximum yield of the acid (**23**) never exceeded 58%. Our procedure did not utilise continuous extraction, but control experiments did show that greater than 90% of the acid was extracted from the aqueous phase. No ring opened products were detected in any of these hydrolysis experiments. Thus, the moderate yields were not due to this reaction pathway, nor the extractive procedure.

The most attractive, alternative explanation for the lack of material balance is a retro-Diels-Alder reaction. Distillation of the ester (**9**) even at reduced pressure, resulted in considerable degradation, and the formation of polymeric materials. To test this hypothesis, the esters (**12**) and (**24**) were treated with potassium hydroxide. The corresponding acids from these esters were isolated in over 90% yields. As the double bond is no longer available in these examples, the retro-Diels-Alder reaction is not a feasible degradation pathway. Again, no ring opened products were detected.

The acid (**23**) is only formed in low yield (*ca.* 10%) by reaction of furan with acrylic acid even in the presence of a Lewis acid catalyst.[30] When **23** was treated with base for 24 h at ambient temperature, 80% of the acid was recovered. Both of these observations suggest that the retro-Diels-Alder reaction is the plausible degradation pathway, but offer no conformation.

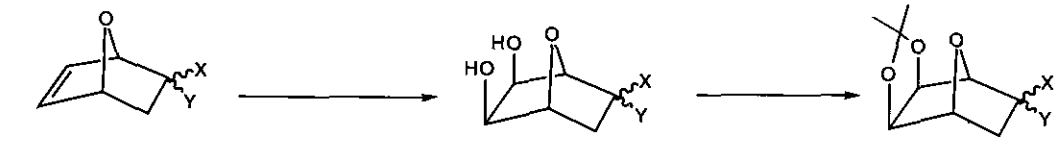
It was not possible to trap either the furan or acrylate anion by chemical means, nor detect either by spectroscopic methods. When the reaction of **9** with sodium methoxide in deuterated methanol was followed by proton nmr, the <u>exo</u> to <u>endo</u> ratio of **9** remained unchanged after 4 days; only transesterification was observed. Certainly, isomerisation of either the <u>exo-</u> or <u>endo-</u>esters to a mixture of the two isomers occurs on standing under these conditions.

Although direct evidence for a retro-Diels-Alder reaction was not obtained in these studies, there is indirect evidence that a reaction of the acid (**23**) was the reason for the low yields observed in the saponification procedure. In the one equivalent of sodium hydroxide experiment, the recovered ester (**9**) was only present as the <u>endo</u>-isomer. Thus, the <u>exo</u>-isomer must be hydrolysed preferentially, presumably because it is less sterically hindered. It was not possible to

detect whether the carboxylate ion formed by the subsequent saponification undergoes isomerisation to the endo-isomer before degradation occurs. From molecular model studies, complexation of a metal counterion by an exo-carboxylate group and the bridgehead oxygen atom is clearly feasible in an intramolecular manner; the metal ion could then catalyse the retro-Diels-Alder reaction.[31]

Consequently, hydrolysis or saponification of an ester moiety in the 7-oxabicyclo[2.2.1]heptanyl series is not practical until the 5,6-unsaturation has been removed by hydrogenation or functionalisation to avoid the possibility of a retro-DielsAlder reaction occurring.

Introduction of a Hydroxyl Group at C-3.[32] Conversion of the Diels-Alder adducts to the oxygenated species was achieved by literature methods (Scheme 5).[11,33-35] Conversion of the diols to the acetals with 2,2-dimethoxypropane was straightforward.



X,Y=O	**1**	**25**	**28**
X = CN, Y = OAc	**11**	**26**	**29**
X = CO_2Me, Y = H	**9**	**27**	**24**
X = CO_2H, Y = H	**23**		

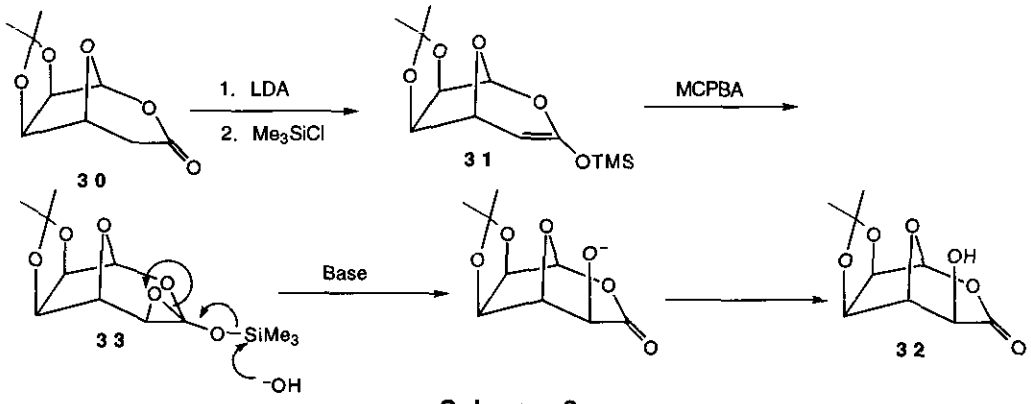
Scheme 5.

Hydrolysis of the acetyl moiety of the cyanohydrin derivative (**29**) was accomplished by treatment with sodium methoxide in methanol. The ketone (**28**) was then formed by reaction of the cyanohydrin with aqueous formaldehyde.

Baeyer-Villiger oxidation of the ketone (**28**) with m-chloroperoxybenzoic acid (MCPBA) gave the lactone (**30**) in good yield (Scheme 2).[11] The lactone (**30**) has been shown to undergo methylation of the derived enolate from the exo-face; the adduct was then hydrolysed under acidic conditions to the hydroxy acid.[6] Thus, the bicyclic system seems to react with electrophiles on the exo-face, as expected.[36]

Formation of the ester enolate of the lactone (**30**) with LDA followed by trapping with chlorotrimethylsilane afforded the silyl enol ether (**31**). Subsequent oxidation with MCPBA, followed by rearrangement, provided the hexose derivative (**32**) (Scheme 6).[37-39]

The epoxide (**33**) was surprisingly stable, and was readily detected by nmr spectroscopy in the crude reaction extracts. This highly oxygenated compound, however, could not be purified. The epoxide did, however, convert readily to the alcohol (**32**) upon stirring with dilute base. As the m-chlorobenzoic acid had been removed from the reaction mixture, the pathway for the conversion of the epoxide (**33**) to the alcohol (**32**) cannot be analogous to that proposed by Rubottom and Boeckman for the oxidation of ketones to α-hydroxy ketones.[39] Assuming exo-face attack by the

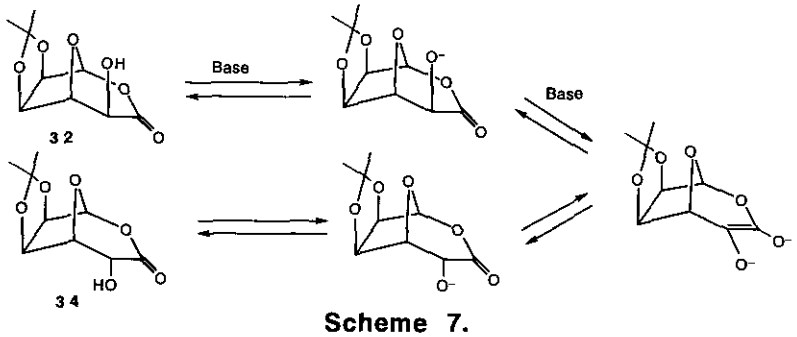


Scheme 6.

peroxy acid, the stereochemical integrity of the oxygen substituent is preserved at C-3, as evidenced by the subsequent transformations to carbohydrate derivatives,[20] during the formation of the hydroxy lactone (**32**). Attack by hydroxide ion from the endo-face of **33** is certainly hindered, so attack at the silicon centre seems a viable alternative pathway (Scheme 6).

Attempted cleavage of the lactone (**32**) with a variety of acidic reagents failed to provide the required hydroxyacid. This is in direct contrast to Vogel's report that used very mild conditions [trace $MeSO_3H$ in anhydrous methanol at -15°C for 15 min] to open 5-endo-chloro-3-exo-methyl-2,8-dioxabicyclo[3.2.1]octane.[6] The acids used in our study were methanesulphonic, p-toluenesulphonic and trifluoroacetic. However, the recovered starting material did show a small, new signal in the nmr spectrum with the original signal assigned to the proton at C-3 diminished. The new signal was assigned to the endo alcohol (**34**). This compound results from enol formation followed by reprotonation of the α-carbon from the more accessible exo-face.

As we were investigating new routes to carbohydrates, an attempt was made to protect the free hydroxyl group of **32** by reaction with benzyl bromide in the presence of aqueous base and a phase transfer catalyst, but only 50% of the desired ether was isolated. Again, formation of the endo alcohol (**34**) was evident. When other bases, such as LDA or sodium hydride were employed for the etherification, little *O*-alkylation was observed but isomerisation was apparent from the nmr spectra. The reaction pathway for isomerisation is presumably through a dianion that is reprotonated at C-3 from the less hindered exo-face (Scheme 7). When the alcohol (**32**) was treated with LDA followed by an aqueous work up, the endo-alcohol (**34**) was formed



Scheme 7.

(*ca* 19% by nmr).[40] The amount of the endo-alcohol could be increased by repetition of the base treatment to 57% after 4 cycles. After this, degradation became a major problem. In these cases, the endo-alcohol is presumably deprotonated faster than the exo-isomer, but solubility could well play an important role as the dianion formed is insoluble in the reaction solvent while even the mono-anion is not completely soluble. The use of additives such as TMEDA or HMPA promoted degradation products to form, presumably through ring opening reactions. Other hydroxyl group inversion procedures may give higher yields, but none were attempted.[41] Indeed, standard inversions of the ring opened products would remove the problems associated with the steric demands of the bicyclic system.

Although the 7-oxabicyclo[2.2.1]heptanyl and 8-oxabicyclo[3.2.1]octanyl systems are prone to ring opening reactions under basic conditions, we have shown that a careful choice of reaction

conditions and substitution can allow chemistry to be performed while keeping the bicyclic systems intact.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

All nmr spectra were recorded on Varian T60A, JEOL FX90Q or GE QE300 spectrometers with tetramethylsilane as internal standard in deuteriochloroform solution, unless stated otherwise. Isomer ratios were determined by integration of the relevant signals. Infrared spectra were performed on Perkin Elmer 137 or 621, or Nicolet 5DXC spectrophotometers. Melting points and boiling points are uncorrected. Some of the elemental analyses and high resolution mass spectra were performed by Bowling Green State University Chemistry Department.

Tetrahydrofuran and ether were freshly distilled from sodium and benzophenone. Methanol and hexane were dried over 4Å molecular sieves. *t*-Butanol was purified by distillation from potassium permanganate.

7-Oxabicyclo[2.2.1]hept-2-phenylsulphonyl-5-ene(**8**): Phenyl vinyl sulphone (1.68 g,10 mmol), furan (10 ml, 9.4 g, 138 mmol) and zinc iodide (1.3 g, 4 mmol) were placed in a flask and sealed under nitrogen. The reaction mixture was placed in the freezer (-4°C) for 48-96 h. The reaction mixture was quenched with water (25 ml), and extracted with ether (3 x 25 ml). The combined extracts were washed with saturated sodium chloride (2 x 25 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The adduct was isolated in a 95% yield and was purified on a silica gel column ($CHCl_3$) to afford **8** (2.13 g, 90%); ν_{max}(thin film) 1330 and 1160 cm^{-1} (SO_2); δ($CDCl_3$) 7.8 (5H, m, C_6H_5), 6.6 (2H, m, CH=CH), 5.0 (2H, m, C-H (1,4)), 3.8 and 3.2 (1H, m, C-$H_{endo\ and\ exo}$), and 1.9 (2H, m, CH_2). Anal. Calcd for $C_{12}H_{12}SO_3$: C, 60.7; H, 5.1. Found: C, 60.85; H, 5.1.

Methyl 7-Oxabicyclo[2.2.1]hept-5-ene-2-carboxylate(**9**):[15] Furan (131 g, 1.96 mol), methyl acrylate (110 g, 1.28 mol), and anhydrous zinc chloride (52 g, 0.79 mol) were heated under reflux for 48 h. The mixture was diluted with water (150 ml) and extracted with dichloromethane (3 x 250 ml). The organic extracts were washed with water (200 ml) and saturated aqueous sodium chloride solution (2 x 100 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the ester (**9**) (64.2 g, 49%) as a pale yellow oil (purity >95% by nmr): ν_{max}(thin film) 1720 cm^{-1} (C=O); δ($CDCl_3$) 6.4-6.0 (2H, m, CH=CH), 5.1-4.8 (2H, m, OCH), 3.7 and 3.6 (3H, 2s, CO_2Me, endo:exo = 1:2), 3.2-2.2 (1H, m ,C<u>H</u>CO_2Me) and 2.2-1.4 (2H, m, CH_2).

2-Exo- and 2-Endo-Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl Acetates (**11**):[16] A solution of 1-cyanovinyl acetate (**7**)[42] (55.5 g, 0.5 mol) and zinc iodide (48.9 g, 0.15 mol) in furan (68 g, 1 mol) was stirred in the dark at 20°C in a stoppered flask. Some of the zinc iodide remained suspended in the light yellow solution after 24 h at which time more furan (34 g, 0.5 mol) was added. The mixture was stirred for an additional 5 days before it solidified. The white solid was dissolved in a mixture of ether (1000 ml), water (500 ml) and saturated aqueous sodium chloride solution (500 ml). After separation of the layers, the aqueous fraction was extracted with ether (5 x 100 ml). The combined etheral extracts were washed with 5% aqueous sodium hydrogen carbonate (4 x 100 ml) and saturated aqueous sodium chloride (4 x 100 ml), dried ($MgSO_4$), filtered and concentrated to yield a yellow oily solid (73.85 g). The aqueous solutions were combined and extracted again with ether (3 x 100 ml) which was then washed, dried ($MgSO_4$), and concentrated as above to yield additional product [6.8 g; in total 80.65 g (90% crude)], ν_{max}(thin film) 1700 cm^{-1}, $\delta(CDCl_3)$, 6.65 (1H, dd, J = 6 and 1.5 Hz, C-H (5)) , 6.2 (1H, dd, J = 6 and 2 Hz, C-H(6)) , 5. 55 (1H, d, J = 2 Hz, C-H(1)), 5.11 (1H, dd, J = 5 and 1.5 Hz, C-H(4)), 2.7 (1H, dd, J = 12 and 5 Hz, C-H_{exo} (3)), 2.05 (3H, s, CH_3), 1.75 (1H, dd, J = 12 and 1 Hz, C-H_{endo}(3)).

Methyl 7-Oxabicyclo[2.2.1]heptane-2-carboxylate (**12**):[14] Hydrogen gas was bubbled through a solution of (**9**) (20 g, 0.13 mol) in methanol (100 ml) in the presence of 10% palladium on charcoal catalyst (0.4 g) for 24 h. The solution was filtered, concentrated under reduced pressure and distilled (bulb to bulb), 110°C(bath temperature)/15 mm Hg, to yield **12** as a colorless oil (20 g, 95%): ν_{max}(thin film) 1700 cm^{-1} (C=O); $\delta(CDCl_3)$ 4.9 (2H, m, OCH), 3.9 (3H, s, OMe), 3.4-2.6 (1H, m, C(O)CH), and 2.5-1.5 (6H, m, CH_2's and CH).

General Anion Reaction of Methyl 7-Oxabicyclo[2.2.1]heptane-2-carboxylate(12) at -90°C:[2] Diisopropylamine (2 ml, 1.44 g, 14 mmol) was added to dry THF (20 ml) and cooled to -30°C under nitrogen. *n*-Butyllithium (8.75 ml, 14 mmol) was added and the mixture cooled to -90±5°C (internal temperature) (N_2/hexane). A solution of **12** (2.0 g, 13 mmol) in dry THF (3 ml) was added dropwise to the mixture over a period of 2 min and the solution stirred for 10 min (trial experiments from 5–30 min had shown this to be the optimum time). After this time the electrophile was added, after a further 0.5 h the reaction mixture was quenched by the addition of saturated ammonium chloride (30 ml). The solution was extracted with ether (3 x 30 ml), washed with saturated sodium chloride (2 x 25 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude reaction mixture was examined by nmr and ir spectroscopy.

Purification of adducts:

Endo- and Exo-Methyl 7-Oxabicyclo[2.2.1]heptane-2-methyl-2-carboxylate(**21**): The crude product was fractionally distilled giving the adduct (1.3 g, 60%) bp 85°C/0.5 mm Hg as a pale yellow oil, ν_{max}(thin film) 1765 cm^{-1} (C=O), $\delta(CDCl_3)$ 4.6 (1H, m, C-H (1)), 4.2 (1H, m, C-H (4)), 3.7 (3H, s, CO_2CH_3), 2.2 (2H, d, J = 13 Hz, CH_2(3)), 1.5 (4H, m, CH_2 (5,6)), 1.25 (3H, s, CH_3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.5; H, 8.3. Found: C, 63.6; H, 8.3.

Endo- and Exo-Methyl 7-Oxabicyclo[2.2.1]heptane-2-phenylthio-2-carboxylate (**13**):[2] The crude product was dissolved in hexane (10 ml) and poured onto a dry flash column previously washed with hexane (50 ml). The column was washed with hexane (250 ml) to remove any excess diphenyl disulphide. The column was then washed with ether to elute the product and the ethereal solution evaporated. The crude product was distilled (bulb to bulb) (bp 112°C (bath temperature)/15 mM Hg), ν_{max}(thin film) 1765 cm^{-1} (C=O), $\delta(CDCl_3)$, 7.3 (5H, m, C_6H_5), 5.0 and 4.6 (2H, m, C-H (1,4), 3.6 and 3.5 (3H, s, CH_{3exo}, CH_{3endo}) 2.9-1.2 (6H, m, oxabicyclo system).

Trimethylsilyl Enol Ether of Methyl 7-Oxabicyclo-[2.2.1]heptane-2-carboxylate (**19**): After the addition of the electrophile to the reaction mixture, the solution was allowed to warm to room temperature and evaporated under reduced pressure. Dichloromethane (20 ml) (dried over silica) was added and the solution filtered under nitrogen. The solution was evaporated under reduced pressure and the crude mixture examined by nmr spectroscopy contained few impurities (>90% by nmr): $\delta(CDCl_3)$ 5.0 (2H, m, CH(5,6)), 3.5 (3H, s, CH_3), 3.2-0.9 (4H, m, overlaid with d, 0.9 C-H_{exo}(3) oxabicyclo system).

Methyl 2-Exo-Phenylthio-7-oxabicyclo[2.2.1]heptane-2-endo-carboxylate (**13-exo**):[2] *n*-Butyllithium (21.3 ml of a 1.6 M solution in hexane, 34 mmol) was added to diisopropylamine (4.8 ml, 3.45 g, 34 mmol) in dry hexane (100 ml) at 0°C, under nitrogen. After 0.25 h, the solution was cooled to -90°C (internal temperature) and methyl 7-oxabicyclo[2.2.1]heptane-2-carboxylate (**12**) (5.0 g, 32.5 mmol) added. The mixture was stirred at -90°C for 10 min when diphenyl disulphide (6.2 g, 33 mmol) was added. After a further 0.5 h at -90°C, the mixture was poured into saturated aqueous ammonium chloride solution (100 ml), and extracted with dichloromethane (2 x 50 ml). The combined extracts were washed with 2M aqueous sodium hydroxide solution (2 x 50 ml), and saturated aqueous sodium chloride solution (2 x 50 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give the sulphide (**13-exo**) as a pale yellow oil, (5.58 g, 66%), bp 130°C (bath temperature)/1 mm Hg; ν_{max}(thin film) 1720 (C=O) and 1550 cm^{-1} (Ar C=C); $\delta(CDCl_3)$ 7.3 (5H, br s, Ph), 4.9 ((1H, m, 1-H), 4.6 (1H, m, 4-H), 3.5 (3H, s OMe), 2.6 (2H, m, 3-H_2), and 1.7 (4H, m, 5-H_2 and 6-H_2). Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.6; H, 6.1. Found: C, 63.45; H, 5.95.

Methyl 7-Oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (**14**):[43] m-Chloroperoxybenzoic acid (2.5 g of 80% peroxyacid, 14.2 mmol) in dichloromethane (25 ml) was added to a solution of **13** (3.0 g, 11.4 mmol) in dichloromethane (50 ml) at 0°C over 1 h. After stirring for a further 1 h, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 50 ml) and saturated aqeuous sodium chloride solution (50 ml), dried (Na_2SO_4), evaporated under reduced pressure and distilled from calcium carbonate (10 g) in a Kugelrohr apparatus at 110°C(bath temperature)/1 mm Hg to give **14** as a colorless liquid (1.58 g, 91%): ν_{max}(thin film) 1700 (C=O) and 1590 cm^{-1} (C=C), $\delta(CDCl_3)$ 7.0 (1H, d J = 2 Hz, C3-H), 5.3 (1H, m , C_1-H), 5.2 (1H, m, C_4-H), 3.75 (3H, s, OMe), 1.9 and 1.3 (4H, 2m, C_5-H_2 and C_6-H_2); m/z 154.06304, calcd. for $C_8H_{10}O_3$ 154.06299; Anal. Calcd for $C_8H_{10}O_3$: C, 62.3; H, 6.55. Found: C, 62.1; H, 6.3.

General Methods For Hydrolysis of 7-Oxabicyclo[2.2.1]heptanyl-2-carboxylic Acid Esters.

Hydrolysis With Base: The ester (20 mmol) was dissolved in water (25 ml) and THF (25 ml), or THF (50 ml) only. The base was added to this solution. After completion of the reaction, the solution was extracted with ether (3 x 50 ml). The ethereal extracts were washed with saturated aqueous sodium chloride solution (2 x 25 ml), dried ($MgSO_4$) and evaporated under reduced pressure to provide recovered ester. The aqueous layer was acidified with 2 M hydrochloric acid to pH 2, extracted with ether (3 x 50 ml), washed with saturated aqueous sodium chloride solution (2 x 25 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Product ratios were determined by nmr spectroscopy of the total, combined extracts.

7-Oxabicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (**23**):[14] The acid was isolated from the above experiments as a pale yellow oil: ν_{max}(thin film) 1725 and 1705 cm^{-1} (C=O), $\delta(CDCl_3)$ 9.2 (1H, s, CO_2H), 6.3 (2H, m, CH=CH), 5.0 (2H, m, OCH), 3.1-2.1 (1H, m, C<u>H</u>CO_2) and 2.1-1.1 (2H, m, CH_2).

7-Oxabicyclo[2.2.1]heptane-2-carboxylic Acid (**22**):[14] The acid was isolated as a colorless liquid: ν_{max}(thin film) 1720 and 1700 cm^{-1} (C=O); $\delta(CDCl_3)$ 11 (1H, br s, CO_2H), 4.8 (2H, m, OCH), 3.2 (0.3H, m, endo C<u>H</u>CO_2), 2.7 (0.7H, m, exo C<u>H</u>CO_2) and 2.4 (6H, m, CH_2's).

7-Oxabicyclo[2.2.1]hepta-2,3-diol-5-carboxylic Acid, Isopropyl Acetal:[9] The acid was isolated as a colorless oil: ν_{max}(thin film) 1690 cm^{-1} (C=O); $\delta(CDCl_3)$ 4.4 (4H, m, OCH), 2.8 (1H, m, C(O)CH), 1.7 (2H, m, CH_2), and 1.4 and 1.2 (6H, 2s, MeC's).

7-Oxabicyclo[2.2.1]hept-5-en-2-one (**1**):[16] To a solution of cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate (**11**) (14.64 g, 81.8 mmol) in dry methanol (75 ml), stirred at 20°C under nitrogen was added sodium methoxide (0.75 ml of a 30% solution in MeOH, 5.4 M solution; 4.5 mmol). After 2 h, the resultant equilibrium mixture of the corresponding cyanohydrins was treated with formalin (25 ml, of a 40% solution in H_20; 10.8 g, 0.35 mol) and then stirred for an additional 1 h. The mixture was diluted with water (75 ml), saturated aqueous sodium chloride solution (75 ml) and dichloromethane (50 ml). The layers were separated, and the aqueous fraction was extracted with dichloromethane (7 x 20 ml). The combined organic fractions were washed with saturated aqueous sodium chloride solution (5 x 25 ml), dried ($MgSO_4$), and concentrated by distillation at atmospheric pressure to yield a light yellow liquid which gave, after bulb-to-bulb distillation (90°C/15 mm Hg), (**1**) as a colorless oil (8.0 g, 89%), ν_{max}(thin film) 1775 cm^{-1} (C=O), $\delta(CDCl_3)$; 6.75 (1H, dd, J = 6 and 1.5 Hz, C-H(5)), 6.5 (1H, dd, J = 6 and 2 Hz, C-H(6)), 5.3 (1H, dd, J = 4 and 1.5 Hz, C-H(4)) , 4.5 (1H, d, J = 2 Hz, C-H(1)), 2.15 (1H, dd, J = 16, 4 Hz, C-H_{exo}(3)), 1.85 (1H, d, J = 16 Hz, C-H_{endo}(3)).

5-Endo- and 5-Exo-cyano-7-oxabicyclo[2.2.1]hepta-2,3-diol-5-yl Acetate, Isopropyl Acetal (**29**):[11] To a solution of 2-endo- and 2-exo-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetates (**11**) (14.6 g, 81 mmol) in THF (150 ml) was added osmium tetroxide (2.0 ml in *t*-butyl alcohol, 0.04 mmol), pyridine (2.0 ml, 2.1 g, 26 mmol) and 30% hydrogen peroxide (12.5 ml, 0.11 mmol). After 48 h the solution

was examined by nmr spectroscopy. If any alkene was present, the percentage being calculated by integration, the equivalent amount of hydrogen peroxide was added. After all of the alkene was consumed the solution was evaporated under reduced pressure. To this viscous oil was added 2,2-dimethoxypropane (50 ml, 42.4 g, 0.4 mol), p-toluenesulphonic acid (0.1 g, 0.5 mmol) and the solution stirred for 0.5 h. The solution was evaporated under reduced pressure and 2,2-dimethoxypropane (50 ml, 42.4 g, 0.4 mol) was added and the solution stirred for a further 12 h. The solution was diluted with water (50 ml) and extracted with ether (3 x 100 ml), washed with saturated sodium chloride solution (2 x 75 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give an oily solid. Recrystallisation (ether/hexane) gave white solid mp 98-102°C: ν_{max}(nujol mull) 1770 cm^{-1} (C=O); $\delta(CDCl_3)$, 4.9 and 4.35 (2H, dd, J = 6 and 6 Hz, 5-H, 6.H), 4.7 (1H, s, 4-H), 4.6 (1H, m, 1-H), 2.17 (2H, m, 3-H), 2.15 (3H, s, CH_2), 1.3 and 1.45 (6H, 2 x s, $C(CH_3)_2$).

7-Oxabicyclo[2.2.1]hepta-2,3-diol-5-one, Isopropyl Acetal(**28**) from (**29**):[11] To a solution of 5-cyano-7-oxabicyclo[2.2.1]hepta-2,3-diol-5-yl acetate, isopropyl acetal (**29**) (6 g, 20 mmol) in dry methanol (40 ml), under nitrogen, was added sodium methoxide (0.75 ml of a 30% in methanol, 5.4 M, 4.5 mmol). After 2 h, the resultant equilibrium mixture of the corresponding cyanohydrins was treated with formaldehyde (20 ml, 40% solution in H_2O; 8.6 g, 280 mmol) and stirred for an additional 1 h. The mixture was diluted with water (75 ml), saturated sodium chloride solution (75 ml) and extracted with dichloromethane (4 x 50 ml). The combined organic fractions were washed with saturated sodium chloride solution (2 x 75 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The white solid was recrystallized from ether/hexane mp 78-80°C.

2,8-Dioxabicyclo[2.2.1]octane-6,7-diol-3-one, Isopropyl Acetal (**30**):[11] To 7-oxabicyclo[2.2.1]hept-2,3-diol-5-one, isopropyl acetal (**28**) (5.0 g, 27 mmol) in dichloromethane (100 ml) was added sodium bicarbonate (10 g, 120 mmol) and 3-chloroperbenzoic acid (tech 80-85%; 5.8 g, 27 mmol). The solution was stirred for 12 h, diluted with water (100 ml) and extracted with dichloromethane (3 x 75 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (4 x 100 ml), saturated sodium chloride solution (2 x 100 ml) and evaporated under reduced pressure to give a white solid. Recrystallisation from ether/hexane gave 4.8 g, 88%, mp 125-127°C: ν_{max}(nujol mull) 1790 cm^{-1}, $\delta(CDCl_3)$, 5.75 (1H, s, 1-H), 4.6-4.95 (3H, m, 2-H, 3-H, 4-H), 3.1 (1H, dd, J = 6 and 1.5 Hz, 5-exo-H), 2.5 (1H, d, J = 6 Hz, 5-endo-H), 1.35 and 1.5 (6H, 2 x s, $C(CH_3)_2$).

2,8-Dioxabicyclo[3.2.1]octane-6,7-diol-4-exo-hydroxy-3-one, Isopropyl Acetal (**32**): *n*-Butyllithium (10.8 ml of a 1.6 M solution in hexane, 17 mmol) was added to diisopropylamine (2.4 ml, 1.74 g, 17 mmol) in dry THF (40 ml) at -10°C under nitrogen. After 15 min, the solution was cooled to -78°C and a solution of **38** (3.8 g, 16 mmol) in dry THF (3 ml) was added dropwise. The mixture was stirred for 0.5 h when trimethylsilyl chloride (2.1 ml, 1.8 g, 20 mmol) was added. The solution was allowed to warm to room temperature and then evaporated under reduced pressure. Dry

dichloromethane (30 ml) was added and the solution filtered under nitrogen. The solution was cooled to -20°C and m-chloroperoxybenzoic acid (80-85%; 1.7 g, 16 mmol) in dry dichloromethane (30 ml) was added slowly. The solution was allowed to warm to room temperature and stirred for an additional 0.5 h. The solution was poured into saturated sodium hydrogen carbonate (75 ml) and extracted with dichloromethane (3 x 50 ml). The organic layer was washed with saturated sodium hydrogen carbonate (2 x 75 ml), saturated sodium chloride solution (2 x 100 ml), dried ($MgSO_4$) and evaporated under reduced pressure, to give a waxy solid, which gave **32** after recrystallisation (2.84 g, 72%), mp 105-106°C (ether/hexane): ν_{max}(KBr) 3490 (br, OH) and 1760 cm^{-1} (C=O); δ($CDCl_3$) 5.7 (1H, br, OH), 4.9 (2H, m, C-H(1,5)), 3.0 (1H, m, CH(OH)) ,2.8 (2H, m, C-H(6,7)), 1.45 (3H, s CH_2), 1.38 (3H, s, CH_3), ^{13}C, 164.5 (C=O), 113.5 (C-4), 103.4 (C-1), 99.6 (C-5), 83.9 and 81.9 (C-6, C-7), 35.2 (C-CH_3)$_2$), 25.9 and 24.9 ((CH_3)$_2$). Anal. Calcd for $C_9H_{12}O_6$ C, 50.0; H, 5.6. Found: C, 49.9; H, 5.6.

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