Domino Michael-Aldol Annulations for the Stereocontrolled Synthesis of Bicyclo[3.3.1]nonane and Bicyclo[3.2.1]octane Derivatives

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Abstract: Domino Michael-aldol annulation of cycloalkane-1,3-diones with enals affords a general route to 6-hydroxybicyclo[3.3.1]nonane-2,9-diones and 2-hydroxybicyclo[3.2.1]octane-6,8-diones, notably in one-pot procedures under convenient conditions. The annulation is shown to be compatible with one or more substituents at six positions of the bicyclo[3.3.1]nonane-2,9-dione scaffold. In some cases, the relative configuration of the product can be controlled by the appropriate choice of solvent, base and temperature for the annulation. In contrast to the chair-chair conformations usually adopted, the bicyclo compounds derived from 2,4,4-trimethylcyclohexane-1,3-dione possessed boat-chair conformations. Oxidation of the annulation products gave the corresponding bicyclo triketones.

Keywords: Annulation, domino Michael-aldol addition, bicyclo[3.3.1]nonane, stereocontrolled cyclisation, boat-chair conformers

Introduction

Alicyclic frameworks often have advantageous pharmaceutical properties compared with substituted aromatic rings, principally by conferring higher aqueous solubility, lower toxicity and greater structural diversity, including stereochemistry.[1,2] Polysubstituted bicyclo compounds (*e.g.* derivatives of bicyclo[3.3.1]nonane [3] and of bicyclo[3.2.1]octane)[4] have long presented challenges for organic synthesis (Figure 1a), especially in the placement of substituents with stereocontrol, and are become increasingly important in medicinal chemistry.[2,5] In particular, several bicyclo[3.3.1]nonanes of the polyprenylated acylphloroglucinol (PPAP) family (Figure 1b) possess multiple therapeutic effects including anti-bacterial, anti-depressant, anti-viral and anti-cancer properties.[6-8]

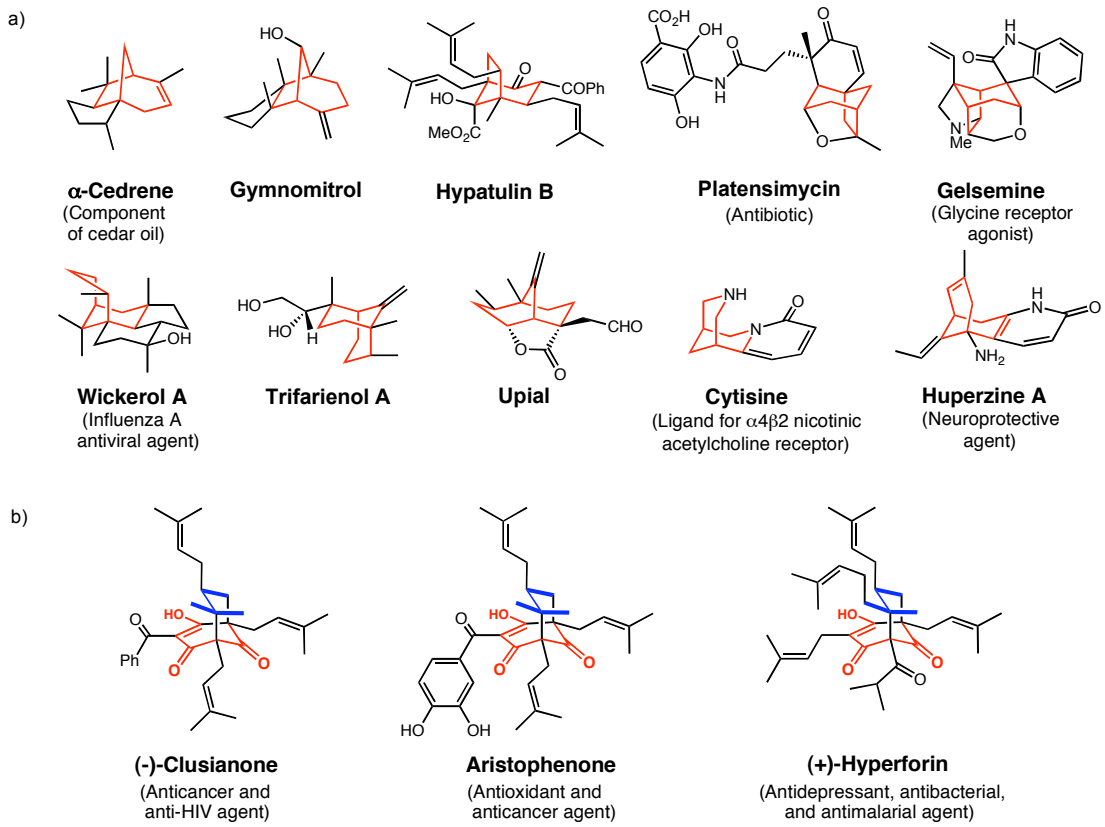
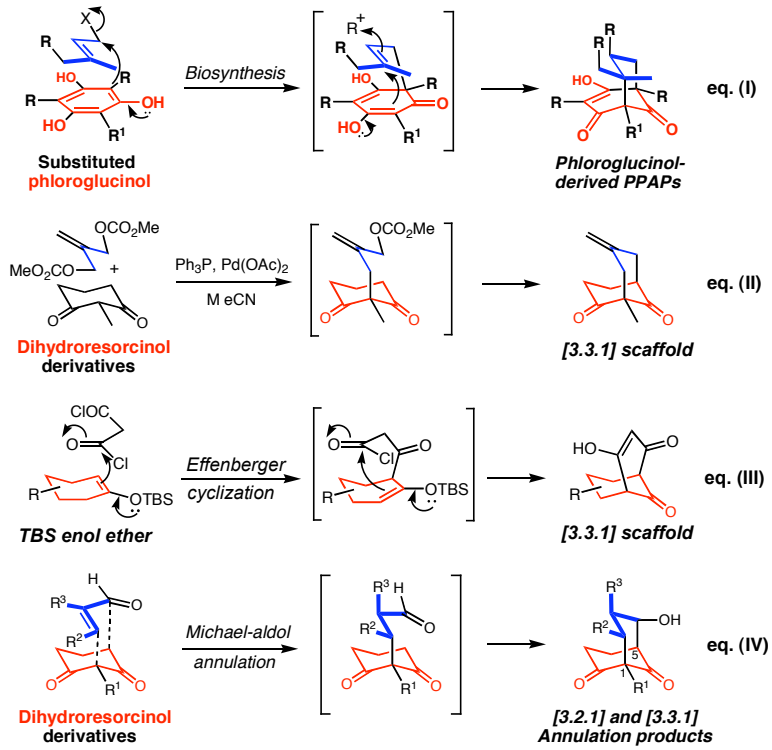


Figure 1. (a) Representative natural products featuring bicyclo[3.3.1] and [3.2.1] scaffolds. (b) Representative polyprenylated acylphloroglucinols with biological activity.

Most synthetic methodology for the construction of bicyclo[3.3.1]nonane derivatives involves a sequential process rather than a domino annulation, an excellent recent example being the alkylation of a disubstituted 1,3-dimethoxybenzene with an enantiomerically pure epibromohydrin followed by Lewis-acid ring opening of the epoxide, effecting an enantioselective desymmetrisation.[9] Subsequent oxidation enabled the Shair group to complete the synthesis of a type A PPAP natural product, (+)-hyperforin.[9] This approach established the utility of derivatives of dihydroresorcinols as key precursors of bicyclo[3.3.1]octane derivatives, with the possibility of later oxidation should a phloroglucinol-derived bicyclo[3.3.1]octane be required.

Seeking to develop a domino annulation, we had regard to the putative biosynthesis of hyperforin [7,10] and related natural products involving the annulation of a substituted phloroglucinol (Scheme 1, eq. I) by alkylative dearomatisation with a prenyl unit, then a second electrophilic attack completing the annulation. Although to the best of our knowledge a biomimetic synthesis involving both steps is not known, a biomimetic cationic cyclisation (the second step) induced by formic acid afforded a bicyclo system that was converted into (-)-clusianone.[11] Regarding domino alkylation-conjugate addition sequences, Porco and coworkers used annulating dielectrophiles comprising various allylic alcohol and 2-alkenal derivatives that contain a leaving group at the 2-position;[12] bicyclo[3.3.1]nonane derivatives of the PPAP type can be obtained, stereocontrol often being possible at the central carbon atom

of the annulating unit. Porco also achieved domino conjugate addition-alkylation sequences that proceed through a bicyclo[3.3.1]nonane scaffold but which result in adamantanone derivatives.[13] Additionally, the Porco group has developed powerful palladium-catalysed alkylative dearomatisation-annulation domino reactions of 2-acylphloroglucinol derivatives with *bis*-Boc-protected methylenepropane-1,3-diol.[14] A related palladium-catalysed Tsuji-Trost approach had already been demonstrated, as in the reaction of a dihydroresorcinol derivative with the dicarbonate of methylenepropane-1,3-diol (Scheme 1, eq. II).[15] Lastly, a succinct domino approach to the synthesis of substituted bicyclo[3.3.1]nonanes involves annulation by diacylation of a substituted cyclohexanone using malonyl chloride,[16-18] the Effenberger cyclisation (Scheme 1, eq. III). However, the reaction usually proceeds in modest yield and is largely limited to 2-unsubstituted malonyl derivatives and to the annulation of a six-membered ring.



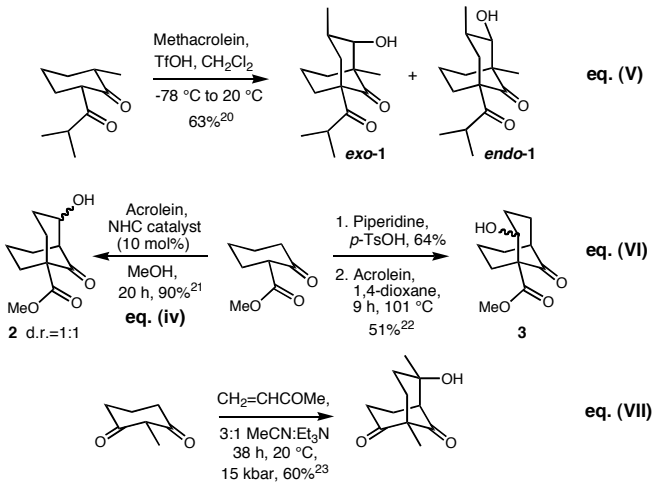
Scheme 1. Biosynthesis of PPAPs, and selected domino annulation strategies for bicyclo systems.

Given the emerging potential of bicyclo scaffolds in medicinal chemistry,[1,2,5] and the limitations of current domino annulations that afford bicyclo systems, a succinct synthetic method was sought for that could generate the maximum number of stereocentres with stereocontrol, with flexibility both in the incorporation of substituents and in the size of the ring undergoing annulation. Having regard to the above criteria of diversity, and inspired by the biosynthetic annulation of phloroglucinol derivatives, we examined the feasibility of domino Michael-aldol annulations of 2-substituted cyclohexane-1,3-diones with enals, a one-pot process that can create stereocentres at any of the three carbon atoms in the annulating unit

(Scheme 1, eq. IV). Here we report the efficacy of this domino annulation, examine its scope, and show that it can afford highly substituted bicyclo[3.2.1]octanes or bicyclo[3.3.1]nonanes, depending on the size of the cycloalkanedione used.

Results and Discussion

Michael-Aldol annulations have furnished polysubstituted cyclohexanone derivatives, in some cases with high enantioselectivity.[19] However, with few exceptions,[20] a cyclohexanone ring lacking an electron-withdrawing group at the α-position has seldom been shown to react with an enone or enal to give a bicyclo ketol. Bicyclo formation has mainly been achieved by reacting α-alkoxycarbonyl- or α-acyl-cycloalkanones with either aldehydes[21-23] or ketones.[24] One example of an acid-catalysed annulation of a substituted 2-acylcyclohexanone was described by Nicolaou,[21] and afforded a 2:1 mixture of diastereoisomers of ketol **1** (Scheme 2, eq. V). The relative configurations were not assigned but are presumably as in Scheme 2, given that oxidation afforded the corresponding trione in 81% yield, the 3-methyl group being assigned as *exo* to the bridgehead carbonyl group. Michael-aldol annulation of β-keto esters has been achieved using *N*-heterocyclic carbene catalysts, but not usually with stereocontrol (*e.g.* ketol **2** in eq. VI, Scheme 2).[22] Initial formation of the enamine enables the reverse mode of annulation to be achieved, but again with little diastereoselection (*e.g.* ketol **3** in eq. VII, Scheme 2).[23] The corresponding reaction with methacrolein proceeded with significant stereocontrol (48% of the 6-*endo*-hydroxy-7-*exo*-methyl bicyclo ketol) but was conducted over 9 days.[23]



Scheme 2. Michael-aldol annulations giving bicyclo ketols.

Given the limitations in scope and/or stereocontrol using α-alkoxycarbonyl- or α-acyl-cycloalkanones in such annulation reactions, investigation of cycloalkane-1,3-diones appeared to be a potentially useful alternative to the construction of functionalised bicyclo[3.n.1]alkane scaffolds. However, to the best of our knowledge, the only such annulations involving a cyclohexane-1,3-dione derivative were reported by Dauben, in which enones were reacted at very high pressure to give ketols (Scheme 2, eq. VII).[24] Accordingly, a pilot study of the

reaction of 2-methylcyclohexane-1,3-dione (**4**) with acrolein was made (Table 1). Given the literature precedents for the use of secondary and tertiary organic bases (*e.g.* eq. VI and VII, Scheme 2), including piperidine,[25] a selection of bases was first studied (Table 1, entries 1-9). No reaction was observed using NaOMe or pyrrolidine (entries 1 and 2) whereas triethylamine, DIPEA, imidazole or pyridine afforded exclusively the Michael adduct **5** in 62-83% yield (Table 1, entries 3-6). In contrast to pyridine, DMAP provided the desired 6-hydroxybicyclo[3.3.1]nonane-2,9-diones **6** in excellent yield and appreciable diastereoselectivity (entry 7). The strong base DBU provided a 1:1 mixture of the Michael adduct **5** and the bicyclo ketols **6** (1:1 carbinol epimers, entry 8), whereas the weaker base 1,4-diazabicyclo[2.2.2]octane (DABCO) gave complete conversion into the bicyclo ketols **6** (1:1 carbinol epimers, entry 9). Although 10 mol% DABCO afforded a mixture of products **5** and **6** (entry 10), 20 mol% DABCO provided exclusively the bicyclo products **6** (100% conversion, 65% isolated yield of 1:1 epimers, entry 11). Under the same conditions, other solvents, including more polar solvents, did not improve the yield of bicyclo compounds **6** (entries 12-15). However, at 95 °C for 16 h DABCO (20 mol%) achieved complete conversion into ketols **6** (66:34 epimeric ratio, entry 16). Under the same conditions but heating for longer (48 h) quantitative conversion into a 90:10 ratio of epimers was achieved (entry 17); optimisation of the d.r. (entries 16-18) showed that DABCO (1 equiv.) enabled full conversion solely to the *exo*-ketol **6** (entry 18). Given the literature precedent for bicyclo compound formation using acidic reagents,[18] the use of *p*-TsOH, TFA, and TfOH were examined but were found to be ineffective (entries 20, 21 and 23), except for 20% TFA in MeCN at 95 °C which afforded 36% of the ketol **6** (entry 22). Having demonstrated the benefit of heat to the selectivity of the reaction, neutral conditions were then examined; only the *exo*-ketol **6** was detected, with good to quantitative conversion (entries 24 and 25).

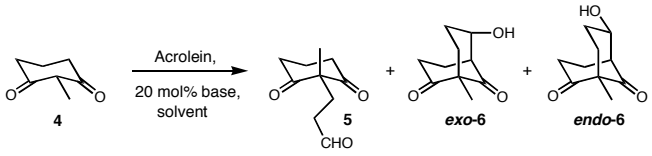


Table 1. Optimisation of bicycloketols from methylcyclohexane-1,3-dione (**4**) and acrolein.[a,b]

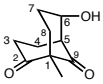
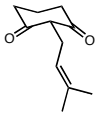
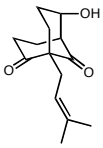
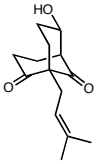
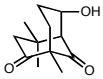
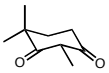
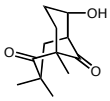
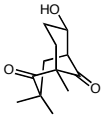
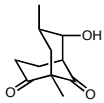
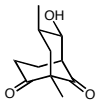
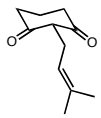
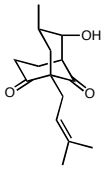
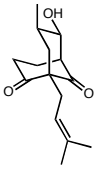
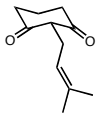
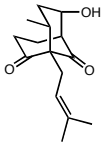
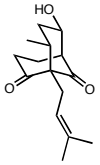
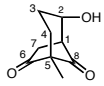
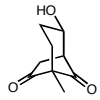
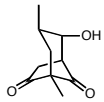
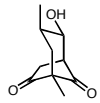
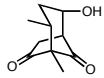
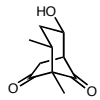
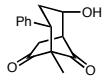
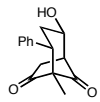
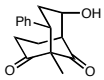
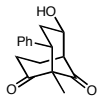
Entry	Base/Acid	Solvent	T (°C)	Time (h)	**5** (%)	*Exo*-**6**: *Endo*-**6** (%)
1	NaOMe	MeOH	25	16	-	-
2	Pyrrolidine (1 eq.)	MeCN	25	16	-	-
3	Et_3N (1 eq.)	MeCN	25	16	62	-
4	$(i\text{-Pr})_2NEt$ (1 eq.)	MeCN	25	16	62	-
5	Imidazole (1 eq.)	MeCN	25	16	83	-
6	Pyridine (1 eq.)	MeCN	25	32	83	-
7	DMAP (1 eq.)	MeCN	25	16	traces	70:30 (95)
8	DBU (1 eq.)	MeCN	25	32	50	50:50 (50)
9	DABCO (1 eq.)	MeCN	25	16	-	50:50 (100)

10	DABCO (0.1 eq.)	MeCN	25	16	50	50:50 (50)
11	DABCO (0.2 eq.)	MeCN	25	16	-	50:50 (100)
12	DABCO (0.2 eq.)	EtOH	25	16	62	traces
13	DABCO (0.2 eq.)	DMF	25	16	95	-
14	DABCO (0.2 eq.)	DMSO	25	16	50	50:50 (50)
15	DABCO (0.2 eq.)	THF	25	16	7	68:32 (93)
16	DABCO (0.2 eq.)	MeCN	95	16	-	66:34 (100)
17	DABCO (0.2 eq.)	MeCN	95	48	-	90:10 (100)
18	**DABCO (1 eq.)**	**MeCN**	**95**	**48**	**-**	**100:0 (100)**
19	DABCO (0.2 eq.)	PhMe	115	16	7	86:14 (93)
20	*p*-TsOH	CH_2Cl_2	25	16	62	-
21	TFA	MeCN	25	16	80	-
22	TFA	MeCN	95	16	-	100:0 (36)
23	TfOH	CH_2Cl_2	-78 to 25	16	-	-
24	**-**	**MeCN**	**95**	**72**	**-**	**100:0 (70)**
25	-	DMF	135	24	-	100:0 (100)

[a] Percentage of conversion was determined from the ^{1}H NMR spectra of the crude products.
[b] Diastereoisomeric ratios (d.r.) were determined from integration values in the ^{1}H NMR spectra of the products after work-up.

Although DMF at 130 °C was optimal for ketols **6** and **13** (Table 2, entries 1 and 8) in terms of yield and 6-*exo*-diastereoselectivity, DMF was found to be unsatisfactory for enals other than acrolein. All reactions were initially run using 20 mol% of (DABCO) but under those conditions only bicyclo ketols **7** and **10** were obtained in satisfactory yields and diastereoselectivity (Table 2, entries 2 and 5). In all other cases, DABCO (1 equiv.) in MeCN gave the best yields and diastereoselectivities, and most reactions were complete within 16 h. For bicyclo[3.3.1]nonane-6-hydroxy-2,9-diones lacking substitution at the 7- and 8-positions the *exo*-ketols were obtained, either predominantly (entries 2 and 4) or exclusively (entries 1 and 3); that preference was also observed in the bicyclo[3.2.1]octane series (entry 8). In contrast, the 6-*endo*-ketols predominated in bicyclo compounds that contained an equatorial substituent on the carbon atom (in the bridging unit) adjacent to the alcohol (entry 5) or on the carbon atom remote from the alcohol (entries 9, 11 and 12). However, where a 2-prenyl group was present and also either a 7-or 8-substituent, the *exo*-ketols predominated (entries 6 and 7).

Table 2. Annulation of substituted cyclohexane-1,3-diones to give bicyclo ketols.[a,b]

Entry	1,3-Dione	Bicyclo ketols and yields			
1[c,d]		 ***exo*-6**	97%		
2[c]		 ***exo*-7**	90:10 80%	 ***endo*-7**	
3[c,e]		 ***exo*-8**	66%		
4[c]		 ***exo*-9**	65:35 98%	 ***endo*-9**	
5[f]		 ***exo*-10**	20:80 96%	 ***endo*-10**	
6[f]		 ***exo*-11**	70:30 86%	 ***endo*-11**	
7[g]		 ***exo*-12**	60:40 44%	 ***endo*-12**	
8[c,d]		 ***exo*-13**	80:20 60%	 ***endo*-13**	
9[f]		 ***exo*-14**	30:70 50%	 ***endo*-14**	
10[g]		 ***exo*-15**	37:50[h] 61%	 ***endo*-15**	
11[i]		 ***exo*-16**	40:60 10%[j]	 ***endo*-16**	
12[i]		 ***exo*-17**	30:70 10%[j]	 ***endo*-17**	

[a] Reactions performed in the presence of DABCO (0.2 equiv or 1.0 equiv.) at 95 °C. [b] *Endo* and *exo* refer to the orientation of the hydroxy group. [c] Reaction with acrolein. [d] Reaction performed in DMF at 135 °C. [e] Sequential: the unpurified Michael adduct was isolated and then cyclised. [f] Reaction with methacrolein. [g] Reaction with crotonaldehyde. [h] 13% of an additional isomer was detected by ^{1}H NMR spectroscopy. [i] Reaction with cinnamaldehyde. [j] >95% conversion by ^{1}H NMR spectroscopy; low isolated yield attributed to partial decomposition of **16** and **17** during purification.

Assignment of the 6-*exo*-ketols **6** was indicated by the presence of small coupling constants (<5 Hz) for the 6-C*H*(OH) hydrogen atom, in contrast to that the 6-*endo*-ketols (*e.g.* *trans*-diaxial $J_{5,6}$ = 11.5 Hz for *endo*-**6**, and 10.5 Hz for *endo*-**10**). The isolation of *endo*-ketol **10**, together with its different NMR data from the *exo*-ketol **10** (isolated in 6% yield from a reaction in DMF at 95 °C) confirmed the assignments in entry 5 to be a mixture of *exo*- and *endo*-diastereoisomers, and excluded the possibility of equilibrating conformers as an explanation of the results. The situation is similar for the various optimisation runs in Table 2 which can only be explained by increasing predominance of *exo*-ketol **6** at higher temperatures and/or longer reaction times. The NMR data for all the bicyclo ketols comprise a pattern of chemical shifts and coupling constants consistent with the structural assignments given in Table 2. Additional support for the structures assigned by NMR spectroscopy is found in the X-ray crystal structure of the 3,5-dinitrobenzoyl derivative of *exo*-ketol **6** which shows that the C-O bond in the 6-CH(OH) moiety is axial; the relatively small couplings of 5.2 Hz and 1.6 Hz for

the equatorial C*H*-OCOAr hydrogen atom in this ester parallel the small coupling constants observed for *exo- versus endo*-epimers.

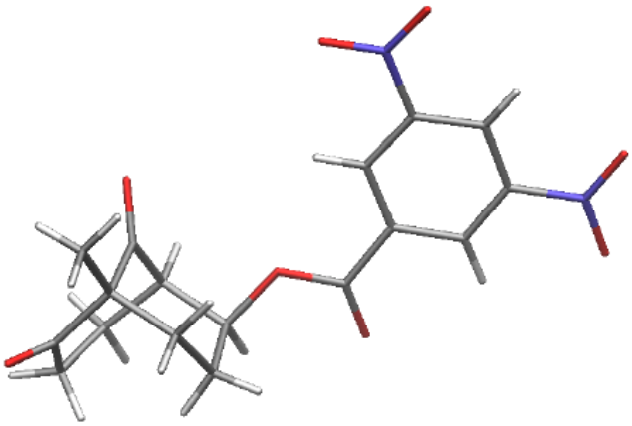
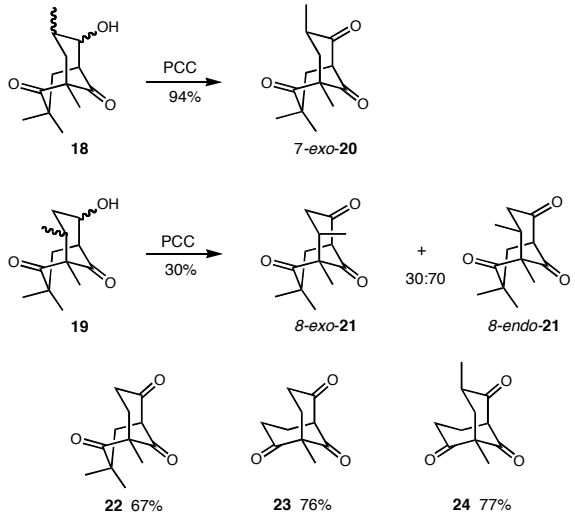


Figure 2. X-ray structure (ORTEP) of the 3,5-dinitrobenzoate ester of *exo*-ketol **6**.[23]

The annulation methodology was also found to be effective using *gem*-dimethyl-substituted cyclohexane-1,3-diones (Table 2, entries 3 and 4). In the case of 2,4,4-trimethylcyclohexane-1,3-dione, reaction with methacrolein and crotonaldehyde afforded the bicyclo ketols **18** (65%) and **19** (49%) respectively (Scheme 3); simplification of the mixtures of diastereoisomers **18** and **19** was achieved by oxidation with pyridinium chlorochromate (PCC), giving the triketones **20** and **21** respectively. Similarly, oxidation of ketols **6**, **9**, **10**, with PCC afforded the respective triketones **22**-**24** (Scheme 3).



Scheme 3. Bicyclo[3.3.1]nonane-2,6,9-triones prepared by the oxidation of ketols with pyridinium chlorochromate.

Molecular models of the *gem*-dimethyl-substituted trione **20** indicated that the usual chair-chair conformation adopted by most bicyclo[3.3.1]nonanes would suffer severe non-bonding interactions. That inference of an alternative conformation was confirmed by a single-crystal X-ray determination of the trione **20** which established the unusual boat-chair conformation

(Fig. 3a). Compared to an sp^3 carbon atom, the bridgehead carbonyl group is more able to accommodate a boat structure, and without significant flagpole interactions, for the ring containing the *gem*-dimethyl group.

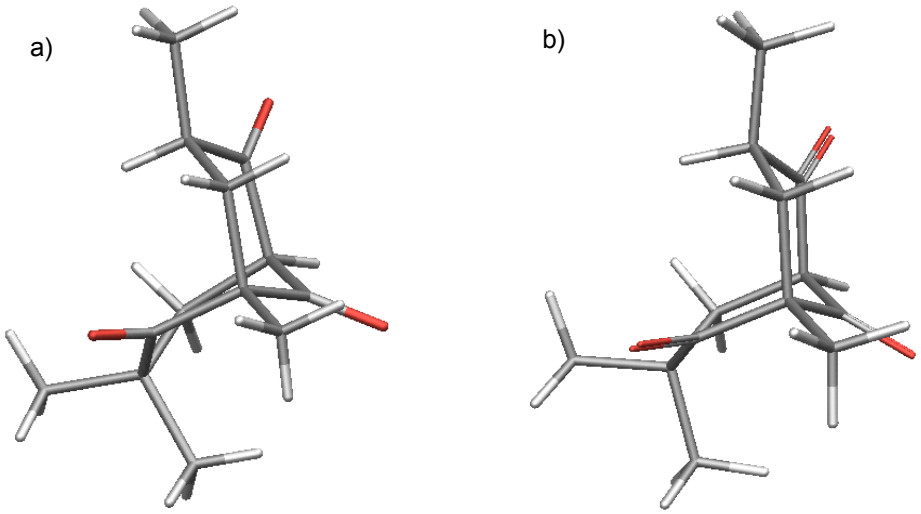


Figure 3. **(a)** X-ray structure of the trione **20** [26] and (b) lowest energy conformer obtained by OPLS3-GB/SA conformational search.

OPLS3-GB/SA conformational energy searches (Table 3)[27] and quantum mechanics calculations (Tables S1-S3, Supplementary Information) support a boat-chair conformation for the trione **20**. In addition, conformational searches on the other bicyclo compounds **21**, **22**, *exo*-**9** and *endo*-**9** that possess the same location of *gem*-dimethyl-substitution as in **20** all identified the boat-chair conformation as the lowest in energy (Table 3). Other less favourable chair-boat, twistboat-twistboat and boat-boat conformers could be detected but never the usual chair-chair conformation. The presence of a *gem*-dimethyl group excludes the chair-chair conformation from being adopted owing to the severe non-bonding interactions of the axial methyl group with the 7-methylene unit that would arise. In contrast, where such a non-bonding interaction is absent, as is the case for triones **23** and **24**, the usual chair-chair conformation for saturated, substituted bicyclo[3.3.1]nonanes is preferred.

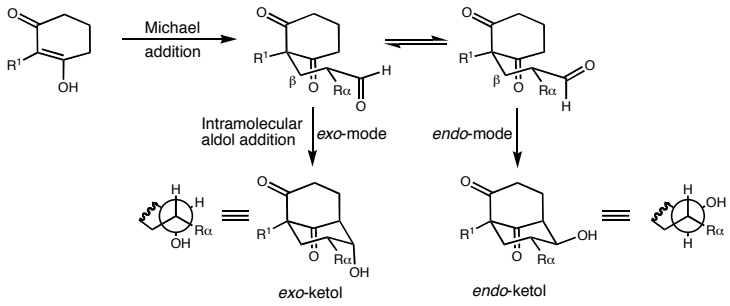
Table 3. Relative conformational energies ($kJmol^{-1}$)[a] of C3-*gem*-dimethyl-bicyclo compounds in water calculated using OPLS3-GB/SA.[27]

Compound	**7-*exo*-20**	**8-*endo*-21**	**22**	***exo*-9**	***endo*-9**
Boat-chair[b]	0	0	0	0	0
Chair-boat	16.2	-[c]	10.0	28.4	35.6
Twistboat-twistboat	23.9	27.7	19.2	33.1	34.2
Boat-boat	27.4	-[c]	21.0	-[c]	-[c]
Twistboat-twistboat 2	-[c]	-[c]	-[c]	-[c]	41.3

Chair-chair	-[c]	-[c]	-[c]	-[c]	-[c]

[a] Energies quoted are relative to the boat-chair conformation. [b] The first-named conformer refers to the ring containing the *gem*-dimethyl group. [c] Not found during the conformational search.

Trends in the mode of cyclisation are apparent. For the bicyclo[3.3.1]nonane-2,9-diones, the *exo*-ketol **6** is generally preferred over the *endo*-ketol. However, the preference for the *exo*-ketol can be overcome by substitution in some locations on the framework, especially for the bicyclo[3.2.1]octane-6,8-diones, as shown in Table 2. Regarding the effect of substitution on the aldehydic chain, an α-methyl group derived from methacrolein adopts the equatorial position prior to cyclisation, leading to a significant preference for the *endo*-alcohol, as seen by comparing entry 1 with entry 5 (Table 2), and entry 8 with entry 9. An α-substituent disfavours the formation of the *exo*-ketol because of three significant and adjacent developing synclinal interactions, compared with only two synclinal interactions for the *endo*-ketol (Scheme 4). However, a β-methyl or β-phenyl group (entries 7 and 10-12) exerts a much weaker effect than an α-methyl substituent, although both diminish the strong preference for the *exo*-isomer that is observed in cases where no α- or β-substituent is present (Table 2, entries 1, 2 and 8).



Scheme 4. Modes of cyclisation in the domino Michael-aldol annulation.

Substituents both on the cycloalkane-1,3-dione ring and on the enal can have a profound effect on the conformation on the Michael adduct, and hence on its mode of cyclisation. Thus, only *exo*-ketol **8** (Table 2, entry 3) was detected, the developing 1,3-diaxial interaction of the C=O group with the equatorial methyl group preventing the *endo*-mode of cyclisation (Scheme 4). In contrast, the location of the *gem*-dimethyl substituents in entry 4 excludes a chair-chair conformation; consequently, the dione ring adopts a boat conformation, which having smaller non-bonding interactions with the aldehydic carbonyl group leads to a significant amount of the *endo*-isomer, the preference for the *exo*-isomer (as shown for **6** and **8**) being eroded. The generally lower selectivities for the cyclopentane-1,3-dione series compared to the cyclohexane-1,3-dione series are also consistent with the flatter and less encumbering cyclopentane-1.3-dione ring that leads to the development of smaller non-bonding interactions during cyclisation.

The formation and conformations of the bicyclo ketols herein studied have implications for the potential of bicyclo compounds in medicinal chemistry. The domino Michael-aldol

annulation has been shown to be effective with substituents at many locations of the bicyclo framework. Varying degrees of control of the configuration of the hydroxy group in the ketols have been achieved through optimisation of reaction conditions or through the conformational effects exerted by substituents. The bicyclo compounds derived from cycloalkane-1,3-diones often possess well-defined configurations and conformations that can contain multiple substituents with specific directionality that overall achieves a wide coverage of chemical space for a relatively compact structure. Additionally, these non-aromatic alicyclic scaffolds satisfy two important criteria for drug-likeness: high levels of saturation and suitable logP values.[5]

Conclusions

The present study has demonstrated the considerable scope of the domino Michael-aldol annulation in obtaining access to 6-hydroxybicyclo[3.3.1]nonane-2,9-diones and 2-hydroxybicyclo[3.2.1]octane-6,8-diones from cycloalkane-1,3-diones and enals, notably in one-pot procedures under convenient conditions. In some cases, the relative configuration of the annulation product can be controlled by the appropriate choice of solvent, base and temperature. This study has shown that the annulation is compatible with one or more substituents at six positions of the bicyclo[3.3.1]nonane-2,9-dione scaffold. The bicyclo compounds provide structural diversity suitable for use in medicinal chemistry programmes and with potential for use as precursors in natural product synthesis. Oxidation of the annulation products was achieved to give a variety of stable bicyclo triones.

Experimental Section

General. All moisture-sensitive reactions were performed under an atmosphere of argon and using glassware pre-dried in an oven (100 °C). Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualised by UV (254 nm) or by staining with potassium permanganate with subsequent heating. Flash column chromatography was performed using Merck 0.040-0.063 mm, 230-400 mesh silica gel. Evaporation refers to the removal of solvent under reduced pressure. Melting points were determined using a Büchi B-540 apparatus. Infrared (IR) spectra were recorded on a Perkin−Elmer Spectrum One FT-IR spectrometer; absorptions are quoted in wavenumbers. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer and calibrated using residual undeuterated solvent as an internal reference; chemical shifts are in parts per million (δ) and coupling constants (*J*) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Equivocal assignments are denoted by an asterisk. High-resolution mass spectra (HRMS) were obtained using either an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage, or using a VG7070H mass spectrometer with Finigan Incos II data system at University College London.

The following compounds were prepared according to the literature: 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione;[28] 2,5,5-trimethyl-1,3-cyclohexanedione.[29]

2,4,4-Trimethylcyclohexane-1,3-dione. To a solution of 4,4-dimethyl-1,3-cyclohexanedione (5.0 g, 35.6 mmol) in aqueous sodium hydroxide (3M, 12.5 mL) at 0 °C was added iodomethane (4.43 mL, 71.3 mmol), dropwise over 30 min. The ice-bath was then removed and the mixture heated at 100 °C for 24 h. After cooling, the mixture was extracted with dichloromethane (3 x 30 mL), and the combined organic layers washed with water (2 x 20 mL) dried over $MgSO_4$, filtered and evaporated. Flash column chromatography (silica gel, 3:7, ethyl acetate; petroleum ether) of the residue gave **2,4,4-trimethylcyclohexane-1,3-dione** (2.84 g, 52%) as a white solid, stable for several weeks when stored at -20 °C; IR (film): 3005, 2988, 1711, 1458 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.48 (2H, t, *J* = 6.5 Hz, $COCH_2$), 1.79 (2H, t, *J* = 6.5 Hz, $C(CH_3)_2CH_2$), 1.63 (3H, s, 2-CH_3), 1.08 (6H, s, $C(CH_3)_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 110.0, 40.1, 35.8, 28.0, 25.4, 7.7; HRMS (ESI-TOF) $[M+H]^+$ $C_9H_{15}O_2$ calcd. 155.1067, found 155.1065.

6-*exo*-Hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (**6**). To a stirred solution of 2-methyl-1,3-cyclohexanedione (100 mg, 0.79 mmol) in dimethylformamide (4 mL) was added acrolein (67 mg, 81 μL, 1.18 mmol) at 25 °C. The solution was then heated at 130 °C for 24 h. After allowing the mixture to cool the solvent was evaporated. The residue was washed with chloroform (2 x 3 mL) to give *exo*-ketol **6** (142 mg, 97%) as an oil; IR (film): 3405, 2936, 1727, 1697, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, dt, *J* = 3.1, 2.6 Hz, 6-CH), 2.93 (1H, dm, *J* = 9.7 Hz, 5-CH), 2.60 (1H, m, 3-CHeq), 2.32 (1H, dt, *J* = 16.5, 9.5 Hz, 3-CHax), 2.22-2.14 (1H, m, 4-CHeq), 2.14-2.06 (2H, m, 8-CH_2), 1.84 (1H, m, 7-CHeq), 1.74-1.67 (2H, m, 4-CHax and 7-CHax), 1.15 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9 (9-CO), 211.5 (2-CO), 77.0 (6-CH), 63.2 (1-C), 52.2 (5-CH), 38.2 (3-CH_2), 37.4 (8-CH_2), 26.4 (7-CH_2), 18.9 (4-CH_2), 16.7 (CH_3); HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{15}O_3$ calcd. 183.1016, found 183.1018.

6-*endo*-Hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (**6**). From the above reaction conducted in the presence of DABCO (0.2 equiv) in acetonitrile at 20 °C was obtained a 1:1 mixture of epimers at position-6. For *endo*-ketol **6**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (1H, dt, *J* = 11.5, 5.0 Hz, 6-CH), 3.10 (1H, m, 5-CH), 2.50-2.45 (2H, m, 3-CH_2), 2.29-2.14 (4H, m, 4-CHeq, 7-CHeq and 8-CH_2), 1.65-1.56 (1H, m, 4-CHax), 1.47-1.38 (1H, m, 7-CHax), 1.14 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (9-CO), 209.3 (2-CO), 73.2 (6-CH), 61.8 (1-C), 52.5 (5-CH), 38.8 (3-CH_2), 35.6 (8-CH_2), 27.8 (7-CH_2), 16.3 (4-CH_2), 15.0 (CH_3).

***exo*-5-Methyl-6,9-dioxobicyclo[3.3.1]nonan-2-yl 3,5-dinitrobenzoate**. To a solution of 6-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (**6**) (170 mg, 0.93 mmol) in dry

dichloromethane were added triethylamine (2.79 mmol, 282 mg, 400 μL) and 3,5-dinitrobenzoyl chloride (1.02 mmol, 235 mg) at 25 °C. The mixture was then stirred at 25 °C for 16 h. Water (20 mL) was then added, and the mixture extracted with dichloromethane (4 x 20 mL). The combined organic layers were washed with water (3 x 10 mL), dried over $MgSO_4$, filtered and evaporated. Flash column chromatography (silica gel, 8:2 dichloromethane: ethyl acetate) of the residue gave ***exo-5*-methyl-6,9-dioxobicyclo[3.3.1]nonan-2-yl 3,5-dinitrobenzoate** (30 mg, 8%) IR (film): 2936, 1731, 1704, 1629, 1545, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, t, *J* = 2.1 Hz, 4-aryl), 9.05 (2H, d, *J* = 2.1 Hz, 2,6-aryl), 5.62 (1H, m, 2-CH), 3.21 (1H, m, 1-CH), 2.69 (1H, ddd, *J* = 16.5, 7.5, 4.5 Hz, 7-CHeq), 2.47 (1H, dt, *J* = 16.5, 9.5 Hz, 7-CHax), 2.39-2.27 (2H, m, 3-CHeq and 8-CHeq), 2.15-2.02 (3H, m, 3-CHax and 4-CH_2), 1.86 (1H, m, 8-CHax), 1.26 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8 (9-CO), 209.4 (6-CO), 161.6 (*C*OOAr), 148.9 (3,5-aryl), 133.6 (1-aryl), 129.5 (2-aryl), 122.9 (4-aryl), 81.1 (2-CH), 63.2 (5-C), 48.4 (1-CH), 38.1 (7-CH_2),* 37.7 (4-CH_2),* 24.4 (3-CH_2), 18.9 (8-CH_2), 16.8 (5-C*C*H_3); *m/z* (EI^+, %) 395 (20), 394 (M^+, 100), 364 (17); HRMS $[M+H]^+$ $C_{17}H_{17}N_2O_8$ calcd. 377.0979, found 377.0981.

6-Hydroxy-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (**7**). To a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione (200 mg, 1.1 mmol) in dry acetonitrile (12 mL) were added acrolein (92 mg, 111 μL, 1.65 mmol) and DABCO (0.22 mmol, 24 mg) at 25 °C. The solution was then heated at 95 °C for 48 h. After allowing to cool, water (20 mL) was added, and the mixture extracted with dichloromethane (4 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give **7** (200 mg, 80%) as a 90:10 mixture of ***exo*-7**: ***endo*-7**. IR (film): 3416, 2917, 1701, 1450 cm^{-1}; ***exo*-7**: ^1H NMR (600 MHz, $CDCl_3$) δ 5.05 (1H, tsept., *J* = 5.0, 1.0 Hz, 1-CCH_2CH=), 4.34 (1H, m, 6-CH), 2.92 (1H, dm, *J* = 6.8 Hz, 5-CH), 2.57 (1H, m, 3-CHeq), 2.40-2.30 (2H, m, 1-CCH_2), 2.25-2.05 (5H, m, 3-C*Hax*, 4-CH_2, 8-CH_2), 1.80 (1H, m, 7-CHeq), 1.70 (1H, m, 7-CHax), 1.61 (3H, s, =C(CH_3)CH_3), 1.59 (3H, s, =C(CH_3)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (9-CO), 212.3 (2-CO), 134.7 (1-CCH_2CH=*C*), 118.7 (1-CCH_2*C*H=), 77.2 (6-CH), 66.5 (1-C), 52.5 (5-CH), 40.4 (3-CH_2), 36.3 (8-CH_2), 31.0 (1-*C*CH_2), 26.1 (7-CH_2), 25.8 (1-C-*cis*-*C*H_3), 18.8 (4-CH_2), 17.9 1-C-*trans*-*C*H_3); ***endo*-7**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (1H, m, 1-CCH_2CH=), 4.06 (1H, dt, *J* = 11.5, 4.9 Hz, 6-CH), 3.11 (1H, m, 5-CH), 2.55 (1H, m, 3-CHeq), 2.40-2.30 (2H, m, 1-CCH_2), 2.26-2.15 (3H, m, 3-CHax, 4-CH_2), 2.11-2.05 (2H, m, 8-CH_2), 1.80 (1H, m, 7-CHeq), 1.70 (1H, m, 7-CHax), 1.58 (6H, m, =C(CH_3)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.3 (9-CO), 210.3 (2-CO), 135.0 (1-CCH_2CH=*C*), 118.6 (1-CCH_2*C*H=), 73.7 (6-CH), 65.2 (1-C), 52.8 (5-CH), 40.6 (3-CH_2), 34.2 (8-CH_2), 30.6 (1-*C*CH_2), 27.2 (7-CH_2), 26.1 (1-C-*cis*-*C*H_3), 18.8 (4-CH_2), 14.6 (1-C-*trans*-*C*H_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{14}H_{21}O_3$ calcd. 237.1485, found 237.1481.

6-*exo*-Hydroxy-1,4,4-trimethylbicyclo[3.3.1]nonane-2,9-dione (**8**). To a stirred solution of 2,5,5-trimethyl-1,3-cyclohexanedione (1.0 g, 6.5 mmol) in dry acetonitrile (25 mL) were added acrolein (0.65 mL, 9.72 mmol) and DABCO (145 mg, 1.3 mmol) at 25 °C. The mixture was heated at 95 °C for 4 h. After allowing to cool, the residue was dissolved in dry DMF (20 mL) and the mixture heated at 135 °C for 24 h. After allowing to cool, the solvent was evaporated and the residue was washed with chloroform (2 x 5 mL) to give ketol **8** (0.90 g, 66% over 2 steps, single diastereoisomer) as an oil: IR (film): 3455, 2958, 1728, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (1H, m, 6-CH), 2.72 (1H, d, *J* = 18.0 Hz, 3-CHeq), 2.49 (1H, m, 5-CH), 2.45 (1H, dd, *J* = 18.0 Hz, 3-CHax), 2.26-2.09 (2H, m, 7-CHeq and 8-CHeq), 2.00-1.82 (2H, m, 7-CHeq and 8-CHeq), 1.22 (3H, s, 4-C(C*H*$_3$)CH_3), 1.17 (3H, s, 1-CC*H*$_3$), 0.91 (3H, s, 4-C(CH_3)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5 (9-CO) 209.2 (2-CO), 73.4 (6-CH), 65.3 (5-CH), 64.3 (1-C), 52.6 (3-CH_2), 37.5 (8-CH_2), 31.6 (4-C), 31.1 (4-*C*CH_3eq), 28.1 (7-CH_2), 27.4 (4-C*C*H_3ax), 16.2 (1-C*C*H_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{19}O_3$ calcd. 211.1329, found 211.1338.

6-Hydroxy-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (**9**). To a solution of 2,4,4-trimethylcyclohexane-1,3-dione (200 mg, 1.28 mmol) in dry acetonitrile (12 mL) were added acrolein (106 mg, 128 μL, 1.98 mmol) and DABCO (144 mg, 1.28 mmol) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (20 mL) was added. The mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic layers washed three times with water, dried over $MgSO_4$, filtered and evaporated to give ketol **9** (264 mg, 98%), as a 65:35 mixture of ***exo*-9**: **endo-9**, IR (film): 3417, 2936, 1729, 1697, 1469 cm^{-1}. Column chromatography (silica gel, 4:6 ethyl acetate: dichloromethane) afforded ***exo*-9**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (1H, dq, *J* = 4.5, 2.4 Hz, 6-CH), 2.95 (1H, m, 5-CH), 2.20 (1H, m, 8-CHeq), 2.12-2.00 (2H, m, 4-CHeq and 8-CHax), 1.70-1.65 (2H, m, 7-CH_2), 1.48 (1H, dm, *J* = 14.4 Hz, 4-CHax), 1.19 (3H, s, 1-CCH_3),* 1.15 (3H, s, 3-C(C*H*$_3$)CH_3),* 0.97 (3H, s, 3-C(CH_3)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2 (2-CO), 213.7 (9-CO), 78.1 (6-CH), 60.4 (1-C), 51.9 (5-CH), 45.8 (3-C), 39.4 (8-CH_2), 35.5 (4-CH_2), 26.1 (3-C*C*H_3eq), 25.6 (7-CH_2), 24.6 (3-C*C*H_3ax), 18.7 (1-C*C*H_3) and ***endo*-9**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (1H, dt, *J* = 11.0, 4.5 Hz, 6-CH), 3.15 (1H, m, 5-CH), 2.17 (1H, dm, 8-CHeq), 2.05 (1H, dd = *J* 14.7, 2.0 Hz, 4-CHeq), 1.80–1.70 (2H, m, 4-CHax and 7-CHeq), 1.41–1.26 (2H, m, 7-CHax and 8-CHax), 1.22 (3H, 1-CCH_3),* 1.20 (3H, 3-C(*C*H_3)CH_3),* 0.97 (3H, s, 3-C(CH_3)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1 (2-CO), 211.9 (9-CO), 74.3 (6-CH), 58.9 (1-C), 52.5 (5-CH), 45.7 (3-C), 37.0 (8-CH_2), 30.9 (4-CH_2), 27.1 (7-CH_2), 26.0 (3-C*C*H_3eq), 24.1 (3-C*C*H_3ax), 18.3 (1-C*C*H_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{19}O_3$ calcd. 211.1329, found 211.1333.

6-Hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione (**10**). To a solution of 2-methyl-1,3-cyclohexanedione (100 mg, 0.79 mmol) in acetonitrile (6 mL) were added methacrolein

(84 mg, 98 μL, 1.19 mmol) and DABCO (18 mg, 0.16 mmol) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (5 mL) was added and the mixture extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give ketol **10** (150 mg, 96%) as an 80:20 mixture of ***endo*-10**: ***exo*-10**: IR (film): 3455, 2936, 1728, 1697 cm^{-1}. Column chromatography (silica gel, 40:60 ethyl acetate:dichloromethane) gave ***endo*-10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (1H, dd, *J* = 10.5, 4.8 Hz, 6-CH), 3.08 (1H, ddd, *J* = 8.9, 4.8, 2.1 Hz, 5-CH), 2.64 (1H, m, 3-CHeq), 2.37 (1H, m, 3-CHax), 2.24 (1H, m, 4-CHeq), 2.12-2.00 (2H, m, 7-CH and 8-CHeq), 1.92 (1H, m, 8-CHax), 1.77 (1H, m, 4-CHax), 1.13 (3H, s, 1-CCH_3), 1.02 (3H, d, *J* = 6.3 Hz, 7-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 212.0 (9-CO), 209.9 (2-CO), 78.4 (6-CH), 62.9 (1-C), 52.0 (5-CH), 44.4 (8-CH_2), 38.4 (3-CH_2), 32.7 (7-CH), 17.7 (4-CH_2), 16.2 (1-CCH_3),* 15.5 (7-CCH_3)*; ***exo*-10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (1H, m, 6-CH), 2.96 (1H, ddd, *J* = 10.2, 4.2, 2 Hz, 5-CH), 2.62 (1H, ddd, *J* = 16.2, 7.4, 3.4 Hz, 3-CHeq), 2.34 (1H, m, 3-CHax), 2.20 (1H, m, 4-CHeq), 2.10 (1H, m, 7-CH), 2.01 (1H, m, 8-CHeq), 1.82 (1H, dd, *J* = 12.9, 4.5 Hz, 8-CHax), 1.70 (1H, m, 4-CHax), 1.14 (3H, s, 1-CCH_3), 1.00 (3H, d, *J* = 6.6 Hz, 7-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5 (9-CO), 211.8 (2-CO), 80.4 (6-CH), 62.5 (1-C), 52.1 (5-CH), 44.5 (8-CH_2), 38.4 (3-CH_2), 29.9 (7-CH), 18.6 (4-CH_2), 16.8 (1-CH*C*H$_3$), 16.7 (7-C*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{17}O_3$ calcd. 197.1172, found 197.1170.

6-Hydroxy-7-methyl-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (**11**). To a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione (100 mg, 0.55 mmol.) in dry acetonitrile (6 mL) were added methacrolein (57.8 mg, 68 μL, 0.82 mmol) and DABCO (0.55 mmol, 62 mg) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give ketol **11** (118 mg, 86%) as a 70:30 mixture of ***exo*-11**: ***endo*-11**; IR (film): 3416, 2918, 1700, 1456 cm^{-1}; ***exo*-11**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.05 (1H, m, 1-CCH_2C*H*=), 3.98 (1H, m, 6-CH), 2.92 (1H, m, 5-CH), 2.62-2.51 (1H, m, 3-CH eq), 2.39-2.27 (3H, m, 1-C-CH_2 and 3-CHax), 2.24-2.13 (m, 2H, 4-CH_2), 1.98 (1H, m, 7-CH), 1.97-1.74 (2H, m, 8-CH_2), 1.61 (3H, s, 1-C-*cis*-CH_3), 1.58 (3H, s, 1-C-*trans*-CH_3), 0.97 (3H, d, *J* = 7.0 Hz, 7-CHC*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) 212.4 (9-CO), 210.3 (2-CO), 134.8 (1-CCH_2CH=*C*), 118.6 (1-CCH_2*C*H=), 80.6 (6-CH), 65.8 (1-C), 52.2 (5-CH), 43.3 (8-CH_2), 40.5 (3-CH_2), 31.0 (1-C-*C*H$_2$), 29.4 (7-CH), 26.0 (1-C-*cis*-*C*H$_3$), 18.5 (4-CH_2), 17.9 (1-C-*trans*-*C*H$_3$), 16.6 (7-CH*C*H$_3$); ***endo*-11:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.05 (1H, m, 1-CCH_2C*H*=), 3.55 (1H, dd, *J* = 7.0, 4.8 Hz, 6-CH), 3.07 (1H, ddd, *J* = 6.52, 3.2, 1.4 Hz, 5-CH), 2.62–2.51 (2H, m, 3-CH_2), 2.39-2.27 (2H, m, 1-CCH_2), 2.13–2.06 (2H, m, 4-CH_2), 1.98 (1H, m, 7-CH), 1.87-1.74 (2H, m, 8-CH_2), 1.65 (3H, s, 1-C-*cis*-*C*H$_3$), 1.60 (3H, s, 1-C-*trans*-*C*H$_3$), 1.00 (3H, d, *J* = 7.0 Hz, 7-CHC*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.7 (9-CO), 212.5 (2-CO), 135.0 (1-CCH_2CH=*C*), 118.5 (1-CCH_2*C*H=), 78.8 (6-CH), 66.1 (1-C), 52.2 (5-CH), 43.0 (8-CH_2), 40.3 (3-CH_2), 32.1 (7-CH),

30.6 (1-C*C*H_2), 26.0 (1-C-*cis*-*C*H_3), 17.6 (1-C-*trans*-*C*H_3), 16.6 (7-CH*C*H_3), 15.1 (4-CH_2); HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{23}O_3$ calcd. 251.1642, found 251.1639.

6-Hydroxy-8-methyl-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (**12**). To a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione (100 mg, 0.55 mmol) in dry acetonitrile (6 mL) were added crotonaldehyde (57 mg, 68 μL, 0.82 mmol) and DABCO (62 mg, 0.55 mmol) at 25 °C. The solution was heated at 95 °C for 60 h. After allowing to cool, water (10 mL) was added, and the mixture was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Column chromatography (silica gel, 2:8 ethyl acetate:dichloromethane) of the residue gave ketol **12** (61 mg, 44%) as 60:40 mixture of ***exo*-12**: ***endo*-12**; IR (film): 3432, 2971, 2992, 1728, 1697 cm^{-1}. Repeated column chromatography of a small fraction enabled the *exo*-isomer to be isolated, and hence NMR data for the *endo*-isomer to be deduced: ***exo*-12**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (1H, tsept., *J* = 7.1, 1.4 Hz, 1-CCH_2C*H*=), 4.27 (1H, dt, *J* = 3.0, 2.5 Hz, 6-CH), 2.87 (1H, dm, *J* = 8.7 Hz, 5-CH), 2.60-2.33 (5H, m, 1-CCH_2 , 8-CH and, 3-CH_2), 2.15-2.03 (2H, m, 4-CH_2), 1.89-1.74 (2H, m, 7-CH_2), 1.64 (6H, s, 1-C-*cis*-CH_3 and 1-C-*trans*-CH_3), 0.99 (3H, d, *J* = 6.8 Hz, 8-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6 (9-CO), 209.5 (2-CO), 134.2 (1-CCH_2CH=*C*), 119.4 (1-CCH_2*CH*=), 75.5 (6-CH), 71.7 (1-C), 52.6 (5-CH), 39.6 (3-CH_2), 38.3 (8-CH), 36.3 (7-CH_2), 27.1 (1-C*C*H_2), 26.1 (1-C-*cis*-*C*H_3), 19.7 (4-CH_2), 18.0 (1-C-*trans*-*C*H_3), 15.8 (8-CH*C*H_3); ***endo*-12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, m, 1-CCH_2C*H*=), 4.10 (1H, dt, *J* = 11.1, 5.4 Hz, 6-CH), 2.99 (1H, app. t, *J* = 6.0 Hz, 5-CH), 2.58-2.43 (5H, m, 1-CCH_2, 8-CH and 3-CH_2), 2.15-2.03 (2H, m, 4-CH_2), 1.83-1.71 (2H, m, 7-CH_2), 1.64 (6H, s, 1-C-*cis*-CH_3 and 1-C-*trans*-CH_3), 0.96 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 212.6 (9-CO), 211.6 (2-CO), 135.0 (1-CCH_2CH=*C*), 118.5 (1-CCH_2*CH*=), 71.3 (6-CH), 70.2 (1-C), 52.4 (5-CH), 40.2 (3-CH_2), 37.5 (8-CH), 37.4 (7-CH_2), 29.8 (1-C*C*H_2), 26.0 (1-C-*cis*-*C*H_3), 18.0 (4-CH_2), 17.8 (1-C-*trans*-*C*H_3), 15.7 (8-CH*C*H_3). Traces of a third diastereoisomer were detected by ^{13}C NMR spectroscopy. HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{23}O_3$ calcd. 251.1642, found 251.1640.

2-Hydroxy-5-methylbicyclo[3.2.1]octane-6,8-dione (**13**). To a solution of 2-methyl-1,3-cyclopentanedione (100 mg, 0.89 mmol) in dry DMF (4 mL) was added acrolein (72 mg, 90 μL, 1.3 mmol) at 25 °C. The solution was heated at reflux at 130 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture was extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (3 x 15 mL), dried over $MgSO_4$, filtered and evaporated to give ketol **13** (90 mg, 60%) as an 80:20 mixture of ***exo*-13**: ***endo*-13**: IR (film): 3450, 2933, 1765, 1723, 1453 cm^{-1}; ***exo*-13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (1H, m, 2-CH), 3.03 (1H, app. t, *J* = 5.4 Hz, 1-CH), 2.70-2.52 (2H, m, 7-CH_2), 2.25 (1H, m, 4-CHeq), 1.95-1.87 (2H, m, 3-CH_2), 1.81-1.77 (1H, m, 4-CHax), 1.07 (3H, s, 5-

CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5 (8-CO), 211.1 (6-CO), 77.5 (2-CH), 59.3 (5-*C*CH_3), 52.7 (1-CH), 42.1 (7-CH_2), 40.1 (4-CH_2), 26.6 (3-CH_2), 12.2 (5-C*C*H_3); ***endo*-13**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (1H, m, 2-CH), 3.08 (1H, dd, *J* = 7.5, 3.3 Hz, 1-CH), 2.50-2.43 (2H, m, 7-CH_2), 2.25 (1H, m, 4-CHeq), 1.95-1.75 (3H, m, 3-CH_2 and 4-CHax), 1.06 (3H, s, 5-CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (8-CO), 211.6 (6-CO), 73.6 (2-CH), 58.3 (5-*C*CH_3), 54.4 (1-CH), 38.7 (7-CH_2), 35.9 (4-CH_2), 27.1 (3-CH_2), 11.6 (5-C*C*H_3). HRMS (ESI-TOF) $[M+H]^+$ $C_9H_{13}O_3$ calcd. 169.0859, found 169.0861.

2-Hydroxy-3,5-dimethylbicyclo[3.2.1]octane-6,8-dione (**14**). To a solution of 2-methyl-1,3-cyclopentanedione (100 mg, 0.89 mmol) in dry acetonitrile (6 mL) were added methacrolein (1.3 mmol, 93 mg, 73 μL) and DABCO (0.18 mmol, 20 mg) at 25 °C. The solution was heated at reflux at 130 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (3 x 15 mL), dried over $MgSO_4$, filtered and evaporated to give ketol **14** (80 mg, 50%) as a 70:30 mixture of ***endo*-14**: ***exo*-14**; IR (film): 3499, 2933, 1767, 1724, 1455 cm^{-1}; ***endo*-14**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (1H, dd, *J* = 9.6, 3.2 Hz, 2-CH), 3.03 (1H, dd, *J* = 7.5, 3.3 Hz, 1-CH), 2.96 (1H, d, *J* = 19.4 Hz, 7-CHax), 2.48 (1H, dd, *J* = 19.4, 7.5 Hz, 7-CHeq), 1.92-1.67 (3H, m, 3-CH and 4-CH_2), 1.02 (3H, s, 5-CCH_3), 1.01 (3H, d, *J* = 6.6 Hz, 3-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4 (8-CO), 211.6 (6-CO), 78.9 (2-CH), 59.4 (5-*C*CH_3), 53.7 (1-CH), 44.5 (7-CH_2), 39.1 (4-CH_2), 32.9 (3-*C*HCH_3), 17.3 (3-CH*C*H_3), 11.6 (5-C*C*H_3) (400 MHz, $CDCl_3$); ***exo*-14**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (1H, ddd, *J* = 5.1, 3.4, 2.3 Hz, 2-CH**),** 3.01 (1H, m, 1-CH), 2.60-2.58 (2H, m, 7-CH_2), 2.08 (1H, m, 3-CHeq), 1.92-1.67 (2H, m, 3-CH and 4-CHax), 1.03 (3H, s, 5-CC*H*$_3$), 0.97 (3H, d, *J* = 6.7 Hz, 3-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1 (8-CO), 211.4 (6-CO), 79.6 (2-CH), 58.8 (5-*C*CH_3), 52.5 (1-CH), 46.7 (7-CH_2), 41.8 (4-CH_2), 30.2 (3-*C*HCH_3), 15.4 (3-CH*C*H_3), 12.0 (5-C*C*H_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{15}O_3$ calcd. 183.1016, found 183.1014.

2-Hydroxy-4,5-dimethylbicyclo[3.2.1]octane-6,8-dione (**15**). To a solution of 2-methyl-1,3-cyclopentanedione (100 mg, 0.89 mmol) in dry acetonitrile (6 mL) were added crotonaldehyde (1.3 mmol, 93 mg, 73 μL) and DABCO (101 mg, 0.90 mmol) at 25 °C. The resulting solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (3 x 15 mL), dried over $MgSO_4$, filtered and evaporated to give ketol **15** (109 mg, 61%) as a 37:50 mixture of mixture of ***endo*-15**: ***exo*-15**; IR (film): 3441, 2936, 1763, 1719, 1455, 1041 cm^{-1}; ***endo*-15**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (1H, ddd, *J* = 11.1, 5.9, 3.4 Hz, 2-CH), 3.04 (1H, dd, *J* = 7.0, 3.4 Hz, 1-CH), 2.88 (1H, d, *J* = 19.5 Hz, 7-CHax), 2.56 (1H, dd, *J* = 19.5, 7.0 Hz, 7-CHeq), 2.05 (1H, dt, *J* = 14.4, 5.5 Hz, 3-CHeq), 1.65 (1H, m, 4-CH), 1.27 (1H, m, 3-CHax), 0.98 (3H, d, *J* = 5.0 Hz, 4-CHC*H*$_3$), 0.88

(3H, s, 5-CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4 (8-CO), 209.9 (6-CO), 71.8 (2-CH), 61.3 (5-*C*CH_3), 53.8 (1-CH), 39.7 (4-CH), 38.6 (7-CH_2), 36.3 (3-CH_2), 15.0 (4-CH*C*H_3), 9.79 (5-C*C*H_3); ***exo*-15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (1H, ddd, *J* = 5.1, 4.1, 1.6 Hz, 2-CH), 2.98 (1H, m, 1-CH), 2.55-2.45 (2H, m, 7-CH_2), 2.36 (1H, m, 4-CH), 1.82 (1H, ddt, *J* = 15.8, 5.6, 1.3 Hz, 3-CHeq), 1.55 (1H, ddd, *J* = 15.8, 13.1, 3.9 Hz, 3-CHax), 0.99 (3H, d, *J* = 5.0 Hz, 4-CHC*H*$_3$), 0.90 (3H, s, 5-CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5 (8-CO), 214.3 (6-CO), 75.8 (2-CH), 62.4 (5-*C*CH_3), 52.1 (1-CH), 44.0 (4-CH) 42.0 (7-CH_2), 35.6 (3-CH_2), 15.1 (4-CH*C*H_3), 10.0 (5-C*C*H_3). The ^{1}H NMR spectrum showed the presence of third diastereoisomer (13%). HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{15}O_3$ calcd. 183.1016, found 183.1012.

2-Hydroxy-5-methyl-4-phenylbicyclo[3.2.1]octane-6,8-dione (**16**). To a solution of 2-methyl-1,3-cyclopentanedione (100 mg, 0.89 mmol) in dry acetonitrile (6 mL) were added cinnamaldehyde (176 mg, 168 μL, 1.3 mmol) and DABCO (99 mg, 0.89 mmol) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (3 x 15 mL), dried over $MgSO_4$, filtered and evaporated. Column chromatography (silica gel, 20:80 ethyl acetate:dichloromethane) gave ketol **16** (20 mg, 10%) as a 60:40 mixture of mixture of ***endo*-16**: ***exo*-16**; IR (film): 3488, 2988, 1763, 1721, 1455, 1046 cm^{-1}; ***endo*-16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (3H, m, *m*- and *p*-H), 7.03 (2H, *J* = 7.8, 2.4 Hz, *o*-H), 4.38 (1H, ddd, *J* = 10.4, 5.9, 3.5 Hz, 2-CH), 3.19 (1H, dd, *J* = 7.5, 3.5 Hz, 1-CH), 3.16 (1H, *J* = 19.0 Hz, 7-CHax), 2.65 (1H, *J* = 14.0, 4.8 Hz, 4-CH), 2.60 (1H, *J* = 19.0, 7.5 Hz, 7-CHeq), 2.29-2.23 (1H, m, 3-CHeq), 2.05 (1H, m, 3-CHax), 0.77 (3H, s, 5-CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5 (6-CO), 210.3 (8-CO), 137.6 (*ipso*-phenyl), 128.7 (phenyl), 128.6 (phenyl), 128.1 (phenyl), 71.7 (2-CH), 61.7 (5-*C*CH_3), 54.3 (1-CH), 50.6 (4-CH), 38.8 (7-CH_2), 35.3 (3-CH_2), 10.7 (5-C*C*H_3); ***exo*-16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (3H, m, *m*- and *p*-H), 7.07 (2H, *J* = 7.8, 2.4 Hz, *o*-H), 4.63 (1H, ddd, *J* = 5.2, 3.5, 1.7 Hz, 2-CH), 3.41 (1H, dd, *J* = 13.7, 4.8 Hz, 4-CH), 3.13 (1H, dd, *J* = 8.0, 4.5 Hz, 1-CH), 2.68-2.56 (2H, m, 7-CH_2), 2.26 (1H, m, 3-CHeq), 2.04 (1H, m, 3-CHax), 0.79 (3H, s, 5-CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (8-CO), 212.5 (6-CO), 138.0 (*ipso*-phenyl), 128.7 (phenyl), 128.6 (phenyl), 128.1 (phenyl), 75.1 (2-CH), 62.7 (5-*C*CH_3), 54.1 (1-CH), 52.6 (4-CH), 42.0 (7-CH_2), 34.8 (3-CH_2), 11.0 (5-C*C*H_3); HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{17}O_3$ calcd. 245.1172, found 245.1172.

6-Hydroxy-1-methyl-8-phenylbicyclo[3.3.1]nonane-2,9-dione (**17**). To a solution of 2-methyl-1,3-cyclohexanedione (100 mg, 0.79 mmol) in CH_3CN (6 mL) at 25 °C were added cinnamaldehyde (155 mg, 1.1 mmol, 150 μL) and DABCO (89 mg, 0.79 mmol). The solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the

mixture extracted with dichloromethane (4 x 10 mL). The combined organic layers were washed with water (3 x 15 mL), dried over $MgSO_4$, filtered and evaporated. Column chromatography (silica gel, 1:9 ethyl acetate:dichloromethane) gave **17** (22 mg, 10%) as a yellow oil, a 70:30 mixture of ***endo*-17**: ***exo*-17**; IR (film): 3443, 2927, 1725, 1691, 1496, 1041. ***endo*-17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (3H, m, 3,4,5-phenyl), 7.03-6.97 (2H, m, 2,6-phenyl), 4.34 (1H, dt, *J* = 11.0, 5.5 Hz, 6-CH), 3.09 (1H, app. t, *J* = 5.5 Hz, 5-CH), 2.75 (1H, m, 3-CHeq), 2.81-2.70 (2H, m, 3-CHax and 8-CH), 2.58 (1H, m, 4-CHeq), 2.44-2.25 (2H, m, 7-CH_2), 1.82 (1H, m, 4-CHax), 0.95 (3H, s, 1-CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5 (9-CH), 208.0 (2-CH), 138.2 (*ipso*-phenyl), 128.7 (phenyl), 128.6 (phenyl), 128.5 (phenyl), 71.2 (6-CH), 68.9 (1-C), 52.8 (5-CH), 51.2 (8-CH), 40.2 (3-CH_2), 37.0 (7-CH_2), 17.2 (4-CH_2), 15.0 (1-C*C*H_3); ***exo*-17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (3H, m, 3,4,5-phenyl), 7.03-6.97 (2H, m, 2,6-phenyl), 4.52 (1H, dd, *J* = 2.5, 2.2 Hz, 6-CH), 3.45 (1H, dd, *J* = 13.9, 4.7 Hz, 5-CH), 2.96 (1H, m, 3-CHeq), 2.81-2.70 (2H, m, 3-CHax and 8-CH), 2.65-2.62 (1H, m, 4-CHeq), 2.44-2.45 (2H, m, 7-CH_2), 2.11 (1H, m, 4-CHax), 1.00 (3H, s, 1-CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2 (9-CH), 207.8 (2-CH), 138.5 (*ipso*-phenyl), 128.7 (phenyl), 128.6 (phenyl), 128.5 (phenyl), 75.0 (6-CH), 70.4 (1-C), 53.0 (5-CH), 52.2 (8-CH), 39.0 (3-CH_2), 36.0 (7-CH_2), 20.7 (4-CH_2), 15.1 (1-C*C*H_3). HRMS (ESI-TOF): *m/z* $[M+H]^+$ $C_{16}H_{18}O_3$ calcd 259.1329, found 259.1328.

6-Hydroxy-1,3,3,7-tetramethylbicyclo[3.3.1]nonane-2,9-dione (**18**). To a solution of 2,4,4-trimethylcyclohexane-1,3-dione (0.20 g, 1.28 mmol) in dry acetonitrile (10 mL) were added methacrolein (134 mg, 0.16 mL, 1.92 mmol) and DABCO (143 mg, 1.28 mmol) at 25 °C. The solution was heated at 95 °C for 16 h. After this time the reaction was allowed to cool to 25 °C then evaporated. Water (15 mL) was then added and the mixture extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with water (2 x 15 mL) then with and brine, dried over $MgSO_4$, filtered and evaporated to give ketol **18** (186 mg, 65%) as a colourless oil (mixture of diastereoisomers approx. 43:41:14:2 and confirmed by oxidation to **20**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 and 3.78 (1H, m), 3.50 (1H, dd, *J* = 10.5, 4.5 Hz), 3.15-2.63 (2H, m), 2.40-0.90 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.4, 216.1, 215.2, 213.8, 213.40, 212.1, 211.7, 207.5, 83.9, 83.1, 81.2, 79.3, 77.4, 59.9, 59.8, 59.3, 53.0, 51.9, 51.7, 46.2, 45.8, 45.72, 45.4, 45.3, 44.1, 43.4, 37.1, 35.3, 33.4, 31.9, 31.5, 31.4, 29.4, 27.4, 26.3, 26.1, 26.1, 25.8, 25.5, 25.3, 24.6, 24.1, 19.2, 18.6, 18.5, 18.3, 17.2, 16.5; *m/z* (EI^+, %) 225 (3), 224 (M^+, 17), 196 (6), 138 (52), 123 (100); HRMS M^+ $C_{13}H_{20}O_3$ calcd. 224.1407, found 224.1408.

6-Hydroxy-1,3,3,8-tetramethylbicyclo[3.3.1]nonane-2,9-dione (**19**). To a solution of 2,4,4-trimethylcyclohexane-1,3-dione (100 mg, 0.64 mmol) in dry acetonitrile (6 mL) were added crotonaldehyde (0.96 mmol, 67 mg, 80 μL) and DABCO (0.64 mmol, 72 mg) at 25 °C. The resulting solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was

added and the mixture extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (3 x 10 mL), dried over $MgSO_4$, filtered and evaporated to give **19** (71 mg, 49%) as a pale yellow oil, (mixture of diastereoisomers approx. 41:28:26:5 and confirmed by oxidation to **21**); IR (film): 3405, 2972, 2937, 1726, 1694, 1496, 1061, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 and 4.00 (1H, m), 3.20 and 2.90 (1H, m), 2.70-1.20 (5H, m), 1.25-0.80 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 216.8, 214.9, 214.0, 213.6, 212.5, 211.5, 80.9, 76.3, 72.6, 70.6, 63.8, 63.6, 62.5, 61.9, 52.4, 52.2, 51.7, 51.2, 46.0, 45.7, 45.6, 45.4, 45.3, 42.6, 41.1, 39.8, 36.2, 36.1, 36.0, 34.6, 34.2, 31.9, 30.9, 30.7, 27.3, 27.1, 26.6, 26.5, 24.7, 24.6, 24.3, 24.1, 17.1, 17.0 (2 lines), 16.9, 16.4, 15.7, 15.6, 14.6; *m/z* (EI^+, %) 225 (8), 224 (M^+, 58), 196 (14), 178 (22), 138 (88), 123 (100); HRMS M^+ $C_{13}H_{20}O_3$ calcd. 224.1407, found 224.1408.

1,3,3,7-*exo*-Tetramethylbicyclo[3.3.1]nonane-2,6,9-trione (**20**). To a solution of 6-hydroxy-1,3,3,7-tetramethylbicyclo[3.3.1]nonane-2,9-dione (**18**, 200 mg, 0.90 mmol) in dry dichloromethane (10 mL) was added pyridinium chlorochromate (230 mg, 1.08 mmol) and the resulting dark solution was stirred at 25 °C for 16 h. After allowing to cool, the solution was filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate, the mixture filtered through a pad of silica, and the filtrate evaporated to give an 85:15 mixture of epimers. On standing for 2 weeks, the mixture afforded trione **20** (191 mg, 94%) as pale green needles, m.p. 94-95 °C; IR (film): 2262, 1716, 1699, 1270, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 3.69 (1H, dd, *J* = 10.8, 1.7 Hz, 5-CH), 2.51 (1H, app. septet, *J* = 10.8 Hz, 7-CH), 2.31 (1H, dd, *J* = 14.5, 10.8 Hz, 4-CHeq), 2.32-2.22 (2H, m, 8-CH_2), 1.75 (1H, d (br), *J* = 14.5 Hz, 4-CHax), 1.25 (3H, s, 3-CCH_3eq), 1.13 (3H, s, 1-CC*H*$_3$), 1.00 (3H, s, 3-CCH_3ax), 0.98 (3H, d, *J* = 6.3 Hz 7-CHC*H*$_3$); ^{13}C NMR (100 MHz, CD_3CN) δ 215.6 (2-CO), 206.7 (9-CO), 205.4 (6-*C*O), 64.8 (5-CH), 60.6 (1-C), 45.6 (3-C), 41.7 (8-CH_2), 38.9 (7-*C*HCH_3), 36.4 (4-CH_2), 26.3 (2-C*C*H$_3$*eq*), 24.3 (2-C*C*H$_3$*ax*), 18.7 (1-C*C*H$_3$), 13.7 (7-CH*C*H$_3$); *m/z* (EI^+, %) 223 (9), 222 (M^+, 66), 194 (36), 138 (100), 123 (97); HRMS M^+ $C_{13}H_{18}O_3$ calcd. 222.1251, found 222.1251.

1,3,3,8-Tetramethylbicyclo[3.3.1]nonane-2,6,9-trione (**21**). To a solution of 6-hydroxy-1,3,3,8-tetramethylbicyclo[3.3.1]nonane-2,9-dione (**19**, 50 mg, 0.2 mmol) in dry dichloromethane (3 mL) was added pyridinium chlorochromate (0.26 mmol, 57 mg) and the mixture was stirred at 25 °C for 16 h. The mixture was then filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate, filtered through a pad of silica and the filtrate evaporated. The residue was purified by flash column chromatography (silica gel, 1:9 ethyl acetate:dichloromethane) to give trione **21** (15 mg, 30%) as a 70:30 mixture of **8**-***endo*-21**: **8**-***exo*-21**. IR (film): 2975, 1741, 1716, 1698, 1455 cm^{-1}; **8**-***endo*-21**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (1H, dt, *J* = 10.7, 1.5 Hz, 5-CH), 2.57 (1H, dd, *J*

= 15.5, 6.3 Hz, 7-CHeq), 2.47 (1H, m, 8-CH), 2.35-2.21 (2H, m, 7-CHax and 4-CHeq), 1.68 (1H, m, 4-CHax), 1.31 (3H, s, 3-CCH_3eq), 1.18 (3H, s, 1-CCH_3), 1.08 (3H, s, 3-CCH_3ax), 0.82 (3H, d, *J* = 7.2 Hz, 8-$CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2 (2-CO), 205.0 (9-CO), 204.2 (6-CO), 64.4 (5-CH), 63.0 (1-C), 45.2 (3-C), 42.6 (7-CH_2), 37.4 (8-CH), 36.9 (4-CH_2), 27.0 (3-C*C*H_3eq), 24.8 (3-C*C*H_3ax), 16.6 (1-C*C*H_3), 15.3 (8-CH*C*H_3); **8-*exo*-21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (1H, dt, *J* = 10.8, 1.8 Hz, 5-CH), 2.41 (1H, dd, *J* = 4.7, 1.8 Hz, 7-CHeq), 2.32-2.05 (3H, m, 7-CHeq, 4-CHeq and 8-CH), 1.75 (1H, m, 4-CHax), 1.36 (3H, s, 3-CCH_3eq), 1.22 (3H, d, *J* = 6.7 Hz, 8-CHC*H*$_3$), 1.17 (3H, s, 1-CCH_3), 1.02 (3H, s, 3-CCH_3ax); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6 (2-CO), 205.5 (9-CO), 203.8 (6-CO), 63.1 (5-CH), 62.0 (1-C), 45.1 (3-C), 43.8 (7-CH_2), 37.2 (4-CH_2), 35.8 (8-CH), 27.4 (3-C*C*H_3eq), 24.7 (3-C*C*H_3ax), 17.3 (1-C*C*H_3), 15.1 (8-CH*C*H_3); *m/z* (EI^+, %) 223 (7), 222 (M^+, 49), 194 (19), 179 (62); HRMS M^+ $C_{13}H_{18}O_3$ calcd. 222.1251, found 222.1251.

1,3,3-Trimethylbicyclo[3.3.1]nonane-2,6,9-trione (**22**). To a solution of 6-hydroxy-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (**9**) (75 mg, 0.36 mmol) in dry dichloromethane (3 mL) was added pyridinium chlorochromate (92 mg, 0.43 mmol) and the dark solution was stirred at 25 °C for 16 h. The mixture was then filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate, the solution filtered through a pad of silica and the filtrate was evaporated to give trione **22** (50 mg, 67%) as a white solid, m.p. 99-104 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 3.65 (1H, d, *J* = 10.8 Hz, 5-CH), 2.45 (1H, m, 7-CHeq), 2.37-2.25 (2H, m, 4-CHeq and 7-CHax), 2.21 (1H, app. dd, *J* = 13.3, 7.6 Hz, 8-CHeq), 1.72 (1H, m, 4-CHax), 1.47 (1H, td, *J* = 13.3, 5.3 Hz, 8-CHax), 1.26 (3H, s, 3-CCH_3eq), 1.13 (3H, s, 1-CCH_3), 1.01 (3H, s, 3-CCH_3ax); ^{13}C NMR (100 MHz, CD_3CN) δ 215.5 (2-CO), 206.0 (9-CO),* 205.8 (6-CO),* 65.1 (5-CH), 59.8 (1-CCH_3), 45.7 (3-C), 36.3 (7-CH_2), 35.3 (4-CH_2), 33.1 (8-CH_2)**,** 26.2 (3-C*C*H_3), 24.4 (3-C*C*H_3), 18.9 (1-C*C*H_3); *m/z* (EI^+, %) 209 (8), 208 (M^+, 62), 180 (53), 138 (68), 123 (100), 110 (52); HRMS M^+ $C_{12}H_{16}O_3$ calcd. 208.1094, found 208.1094.

1-Methylbicyclo[3.3.1]nonane-2,6,9-trione (**23**). To a solution of 6-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (**6**) (40 mg, 0.22 mmol) in dry dichloromethane was added pyridinium chlorochromate (56 mg, 0.26 mmol) in one portion at 25 °C and stirred for 16 h. The mixture was then filtered through a pad of Celite® and evaporated. The residue was dissolved in ethyl acetate, the solution passed through a pad of silica and the filtrate evaporated to give trione **23** (30 mg, 76%) as a pale green powder, m.p. 97-99 °C. IR (film): 1711, 1453, 1246, 1036, 1029 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 3.45 (1H, t, *J* = 5.0 Hz, 5-CH), 2.70-2.55 (4H, m, 7-CH_2 and 8-CH_2), 2.53 (1H, m, 3-COCHeq), 2.12-2.03 (2H, m, 4-CH_2), 1.75 (1H, m, 3-CHax), 1.22 (3H, s, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ 209.9 (9-CO), 208.0 (2-CO), 204.6 (6-CO), 64.5 (5-CH), 63.9 (1-C), 37.9 (3-CH_2), 37.5 (7-CH_2), 32.1

(8-CH_2), 23.4 (4-CH_2), 16.5 (CH_3); HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{13}O_3$ calcd. 181.0859, found 181.0857.

1,7-*exo*-Dimethylbicyclo[3.3.1]nonane-2,6,9-trione (**24**). To a solution of 6-hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione (**10**) (50 mg, 0.25 mmol) in dry dichloromethane was added pyridinium chlorochromate (66 mg, 0.30 mmol) in one portion at 25 °C, and the mixture was stirred for 16 h. The mixture was then filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate and the solution passed through a pad of silica. The filtrate was evaporated to give trione **24** (37 mg, 77%) as a light green oil; IR (film): 2983, 2988, 1740, 1709, 1457, 1038 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 3.54 (1H, dd, *J* = 7.2, 2.6 Hz, *5*-CH), 2.75-2.52 (3H, m, 7-CH and 3-CH_2), 2.25-2.15 (3H, m, 8-CH_2 and 4-C*H*H), 2.04 (1H, m, 4-CH*H*), 1.20 (3H, s, 1-CCH_3), 1.04 (3H, d, *J* = 6.3 Hz, 7-CHC*H*$_3$); ^{13}C NMR (100 MHz, CD_3CN) δ 210.7 (9-CO), 208.1 (2-CO), 204.2 (6-CO), 64.8 (5-CH), 64.6 (1-C), 41.6 (7-CH), 41.1 (8-CH_2), 37.6 (3-CH_2), 22.5 (4-CH_2), 16.5 (1-C*C*H_3), 14.5 (7-CH*C*H_3); *m/z* (EI^+, %) 194 (M^+, 34), 166 (19), 152 (20), 140 (30), 69 (100); HRMS M^+ $C_{11}H_{14}O_3$ calcd. 194.0937, found 194.0938.

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