Tetrahedron Vol. 37, No 16, pp. 2697 to 2724, 1981
Printed in Great Britain.

0040-4020/81/162697-28$05.00/0
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 112

OXYGEN INSERTION REACTIONS OF BRIDGED BICYCLIC KETONES

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(*Received in the U.S.A.* 18 *December* 1980)

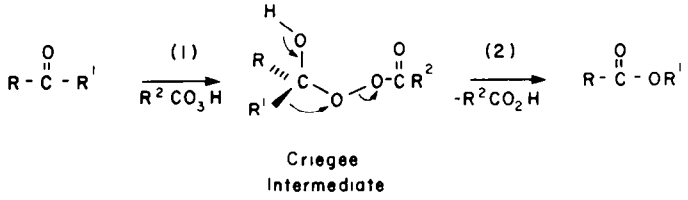
CONTENTS

INTRODUCTION

Oxygen insertion reactions can convert bridged bicyclic ketones to bridged bicyclic lactones of utility as intermediates in stereoselective syntheses of alkaloids, steroids, carbohydrates, prostaglandins, and terpenoid natural products. This review[1,2] of methods for effecting such oxygen insertions is based upon reports of the Baeyer–Villiger rearrangement with organic peroxides or basic hydrogen peroxide. Modifications of this reaction using ceric(IV) or lead(IV) salts as oxidants, or alternative stepwise reactions leading from ketones to lactones or a functional equivalent, are included as applicable. The discussion presumes the generally accepted mechanism for the Baeyer–Villiger reaction of ketones with organic peracids of Scheme 1.[2g] Addition of peracid to ketone carbonyl (step 1) creates a tetrahedral "Criegee" intermediate. Subsequently (step 2), the Criegee intermediate rearranges to ester or lactone products. The formation of the Criegee intermediate is generally not, except where noted in the discussion, the rate limiting process. More often the Criegee intermediate rearranges to lactones in a rate limiting synchronous fashion, although cleavage processes have been noted.

Of major interest for this review are the roles of oxidants, solvents, and catalysts in dictating the regiochemistry of oxygen insertions; of especial interest is the tension between bridgehead and

methylene migrations. Chemoselective methods for separating regioisomeric lactones will be noted in several instances.



Scheme 1. A general mechanism for the Baeyer–Villiger reaction.

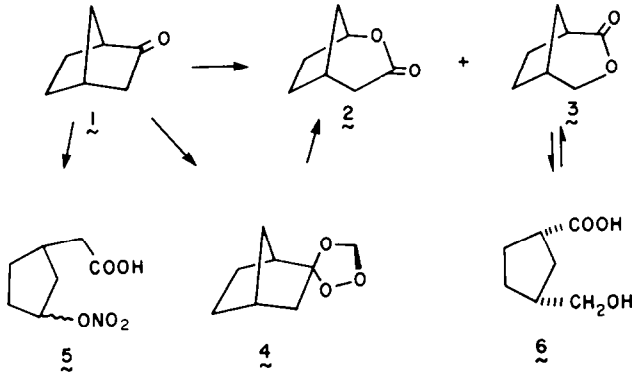
Although several Baeyer–Villiger-like oxidations using reagents other than organic peroxides are noted as appropriate, the reader is referred to other sources[1] for oxygen insertions resulting from Schmidt[3] or Beckmann rearrangements,[4] or by oxidations of alcohols.[5]†

I. BICYCLO[2.2.1]HEPTANONES

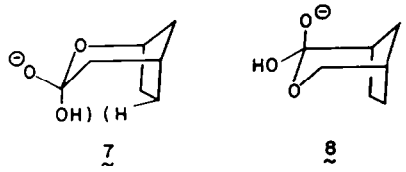
I.A. 2-*Oxo-isomers*

1. *Parent system and substituted derivatives*

I.A.1.a. *Major bridgehead migration.* Insertion of oxygen into norbornan-2-one **1** with 28% peracetic acid/sulfuric acid catalyst,[6] PAA/sodium acetate buffer,[6] TFPAA/disodium hydrogen phosphate buffer or unbuffered,[7] leads to isolation in 88–100% yield of only bridgehead migrated lactone **2**. In a complementary method to the Baeyer–Villiger reaction vinyl acetate/ozone leads from **1** to lactone **2** in 20% yield via an intermediate ozonide **4** formed from formaldehyde oxide,[8] $CH_2{=}O^+{-}O^-$. Ceric ammonium nitrate[9] converts ketone **1** to a 3:2 *trans*:*cis* ratio of bridgehead cleavage products **5** in 50% yield.



Some methylene migrated lactone **3** can be obtained if the Baeyer–Villiger oxidation of **1** is carried out using 15% hydrogen peroxide/sodium hydroxide. Thus Deslongchamps[10] isolated, after a workup which converted hydroxyacids to lactones, 65% yield of a 54:46 ratio of separable lactones **2** and **3**. The methylene migrated lactone **3** hydrolyzes preferentially with sodium hydroxide/pyridine/25°/70 min to afford the corresponding hydroxyacid **6**, which recloses to lactone **3** upon heating with an acid catalyst



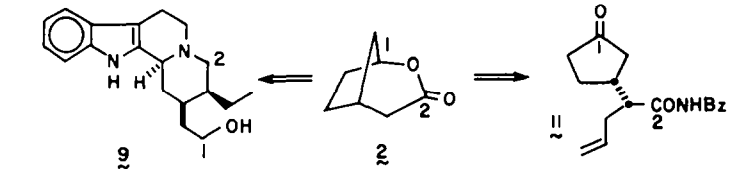
while azeotroping the water.[10] The preference for hydrolysis of the 3-oxabicyclo[3.2.1]octan-2-one isomer **3** over the 2-oxabicyclo[3.2.1]octan-3-one isomer **2** in both acid and base has been attributed to a

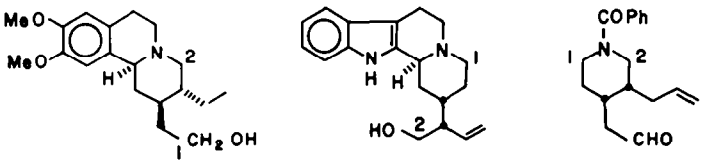
†Abbreviations used throughout this review will be MCPBA, meta-chloroperbenzoic acid; PAA, peracetic acid; TFPAA, trifluoroperacetic acid; THP, tetrahydropyranyl; Bz, benzyl; CAN/CAS, ceric ammonium nitrate/ceric ammonium sulfate; TsOH, toluenesulfonic acid.

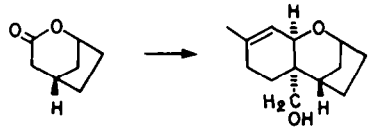
more severe congestion for the tetrahedral intermediate 7 in hydrolysis of the former compared to intermediate 8 for hydrolysis of 3.[12] Preferential hydrolysis of one of a pair of regioisomeric lactones has been reported in other instances as summarized in Table 7, Section III C. We[11] have also found that a 95:5 mixture of lactones 2 and 3 can be obtained by MCPBA oxidation of ketone 1.

Examples of major bridgehead migration of substituted norbornan-2-ones are listed in Table 1. Of special interest from a synthetic perspective is the use, mainly by Takano *et al.*, of a regioisomeric insertion of oxygen at the bridgehead of norbornan-2-one 1 as the basis of numerous stereoselective syntheses. Examples include the syntheses from norbornan-2-one 1 of corynatheidol 9;[13] an emetine alkaloid 10;[14] meroquinene aldehyde 12,[15] a key intermediate in a cinchona alkaloid synthesis; antirhine 13;[16] and the synthesis by Roush *et al.*[17] of trichothecene ring system 14. Deslongchamp[18] has converted ketone 15 to lactone 16 as part of a synthetic approach to triquinacene 17.

The substituted norbornanones 18, 19 have been utilized[19] to synthesize the Corey prostaglandin aldehyde 21, a useful intermediate. The ketone 20 has been used in an approach to prostaglandin D_2 methyl ester.[20] Similarly, the norbornan-2-ones 22 have been converted to prostaglandin D_2 methyl ester[21] and prostaglandin $F_{2\alpha}$.[22]







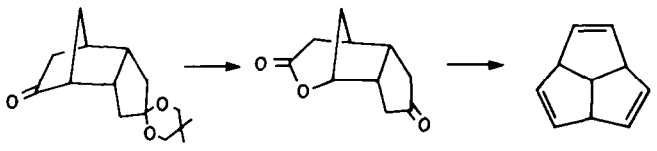
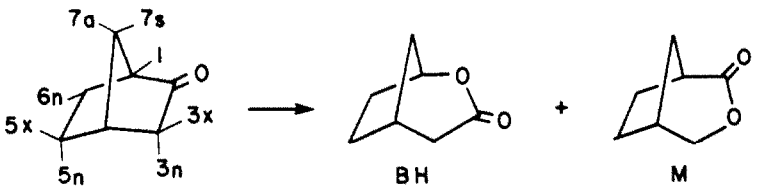
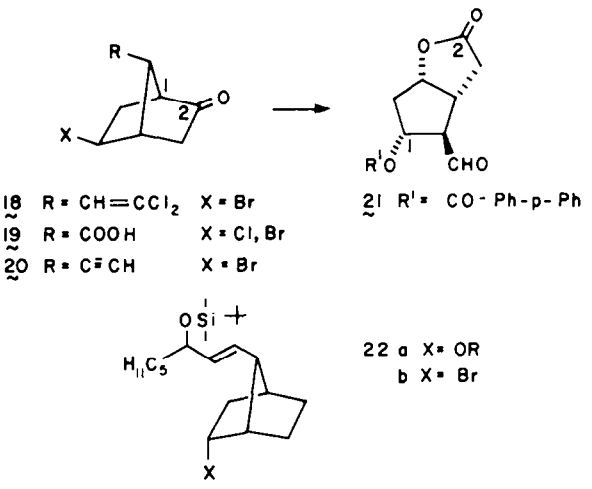


Table 1. Major bridgehead (BH) oxygen insertion reactions of bicyclo[2.2.1]heptan-2-ones



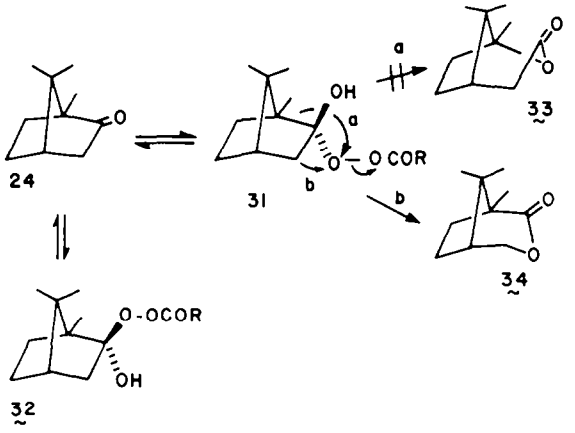
Ketone	Substituents	Conditions	(% BH)	Lactone Yield (%)	Ref.
1	-	28% PAA/NaOAc	100	88	6
		CF_3CO_3H/NaH_2PO_4	100	100	7
		Vinylacetate/O_3/heat	100	20	8
		CAN/CH_3CN	100	(50% 5)	9
		15% HOOH/OH^-/7 days	54	65	10
		MCPBA/CH_2Cl_2	95	78	11
15	5n,6n-$CH_2C(OCH_2CMe_2CH_2O)CH_2$-	Vinylacetate/O_3/heat	100	8[a]	8
		MCPBA/CH_2Cl_2	73	-	18
18	5x-Br, 7a-CH=CCl_2	MCPBA	100	89	23a
			-	-	23b
19a	5x-Br, 7a-COOH	PAA	78	Cleanly	24
19b	5x-Cl, 7a-COOH	MCPBA/NaHCO	100	Cleanly	25
20a	5x-Br, 7a-C-CH	MCPBA/ TsOH	100	79	19b,c; 26
			-	-	23b
20b	5x-Br, 7a-H		-	-	23b
22a	5n-$OSiMe_2tBu$ 7a-CH=CHCH($OSiMe_2tBu$)C_5H_{11}	PAA/buffer	71	70	20
			all but trace	65	21
		HOAc/HOOH/NaOAc	100	65	27
22b	5n-Br 7a-CH=CHCH($OSiMe_2tBu$)C_5H_{11}	MCPBA	100	65	22
22c	5n-OCH_2Ph 7a-CH=CHCH($OSiMe_2tBu$)C_5H_{11}	PAA/10 days	98	-	12
		PAA/earlier	70	-	12
23	1-Me	40% PAA/buffer/30 days	100	42	28
24	1, 7s, 7a-tri-Me	40% PAA/NaOAc	75	-	28
		-	100	82	29a
		40% PAA/40:60 H_2SO_4:HOAc	0	30	29a
		Vinylacetate/O_3/heat	100	63	8
		Anodic oxidation	100[b]	-	29c
25	3x-Me	p-Nitroperbenzoic acid	50	70	30
26	3x-Cl, 5n-OMe, 7a-CN	Fails to react with various peracids	-	-	27
27	5n-OAc, 7a-OMe	MCPBA/$NaHCO_3$	70	-	27
		HCOOH/30% HOOH	100	81	27
28	5n-OMe, 7a-n-Bu	HOAc/30% HOOH/NaOAc	80	73	27
29	5n-OCH_2Ph, 7a-OMe	Phthalic acid/90% HOOH	73	83	27
		Maleic acid/30% HOOH	67	85	27
		90% aq HOAc/30% HOOH/NaOAc	100	70	27
		MCPBA/$NaHCO_3$	55	81	27
		HCO_3H/NaOAc	92	72	27
		HCO_2H/30% HOOH	85	78	27
30	7a, 7s-H, n-C_5H_{11}	6% PAA	100	75	31

(a) Isolated as an olefinic acid cleavage product; (b) Isolated as a rearranged lactone. See also, ref. 29b.



1.A.1.b. *Major nonbridgehead migration.* Baeyer and Villiger[32] in 1899 reported the isolation of the campholide 34 formed by methylene migration upon oxidation of camphor 24 with Caro's acid, persulfuric acid. Doering and Speers[33] in 1950 ascribed the reversal of the expected alkyl migratory aptitude preference, tetriary > primary, to the tertiary site in camphor 24 being part of a bridgehead.

In 1956 Murray *et al.*[34] attributed the preference for methylene migration in camphor 24 to a conformational factor shown in Scheme 2. Assuming alkyl migration occurs by decomposition of a tetrahedral Criegee intermediate 31 formed by peracid addition to the *endo* face of camphor 24, migration of the tertiary carbon by path a to give 33 involves a boat form transition state, while migration of methylene carbon by path b to give 34 involves a more favorable chair form.

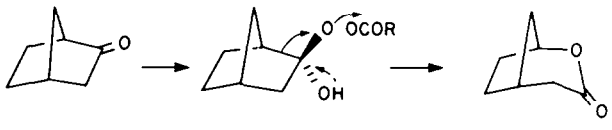


Scheme 2. The boat/chair model for the Baeyer–Villiger rearrangement of camphor 24.

Sauers[28,29] in 1959–61 restudied the peracid oxidation of camphor 24 using peracetic acid and found the reaction course depends upon the acidity of the reaction medium. With 6:15:6 40% PAA/acetic acid/sulfuric acid at 25° a 30% yield of α-campholide 34, formed by methylene carbon migration, was obtained. In weakly acidic medium, PAA/sodium acetate, 82% of the bridgehead migrated lactone 33 was initially reported,[29] although in 1961 a more careful analysis[28] showed this to be a 75:25 ratio of lactones 33 and 34. Apparently, under the strongly acidic conditions, lactone 34 ring opened to form hydroxy acid which was not isolated; this has not been shown experimentally, however.

Sauers[29] considered that protonation of the carboxylic acid leaving group lowers the activation energy for Baeyer–Villiger rearrangement allowing alternate reactions to compete more successfully. With protonation of the Criegee intermediate,[31] electronic stabilization by the migrating group becomes less important in facilitating migration. Sauers considered the above explanations of Doering[33] and Murray *et al.*[34] to be "no longer applicable ... (for the formation of α-campholide 34) ... although they may contribute to the various forces involved".[29]

In 1960 Meinwald[6] studied the reaction of norcamphor 1 with peracetic acid and observed solely the electronically favored bridgehead migration product 2 shown in Scheme 3. (See IA, Table 1) Meinwald

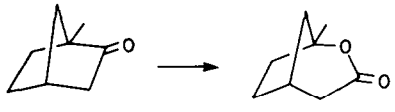


1 35 2

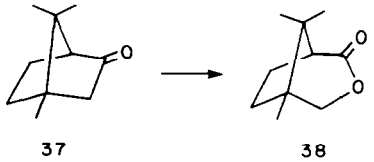
Scheme 3. The chair model for Baeyer–Villiger oxidation of norcamphor 1.

saw a puzzle. If increased acidity compresses the activation energies in camphor 24 so that lactones derived from both bridgehead and methylene migration are formed, why did norcamphor 1 give rise only to lactone 2? As shown in Scheme 2 the *endo/exo* Criegee intermediates 31 and 32 exist in equilibrium. The simplest rationalization, Meinwald felt, was that camphor 24 gave the electronically unfavored lactone 34 via a sterically favored chair pathway b, as suggested by Murray *et al.*[34] *only* from the sterically favored Criegee intermediate 31 formed by *endo* attack of peracid. The less favored *exo* attack of peracid on camphor 24 to give 32 was not leading to the observed lactones 33 and 34. In contrast, as shown in Scheme 3, the intermediate 35, formed by sterically favored *exo* attack on norcamphor 1 did lead to the product lactone 2. Rearrangement of the tetrahedral intermediate 35 via a chair conformation affords bridgehead migrated lactone 2. Meinwald's[6] conclusion was that the migrating group in these reactions depends on both electronic and steric factors with there being a "subtle balance between equilibrium concentrations of the possible Criegee intermediates and competitive rates for the rearrangement of each intermediate in either of two directions".

Sauers[28] in 1961 next studied the Baeyer–Villiger reaction of 1-methylnorcamphor 23. Although the 1-methyl group has a large rate retarding effect via its influence upon the concentration of the Criegee intermediate, only electronically favored bridgehead migration to lactone 36 was observed. Epicamphor 37, which retains the 7,7-dimethyl bridge substituents of camphor 24, gave only methylene migrated lactone 38, as expected for migration via a chair conformation of a Criegee intermediate formed by *endo* face attack on epicamphor 37 (Compare Scheme 2). The 75:25 ratio of lactones 33 and 34 from oxidation of camphor 24, Sauers next suggested, results from boat conformation steric effects favoring methylene carbon migration competing successfully with electronic effects favoring bridgehead migration in controlling reaction outcome. In this paper[28] Sauers countered a criticism of the boat/chair transition state model made by Edward[101] in 1960. In a study of A-norsteroidal ketones Edward had found an electronically favored lactone to be formed by an apparently sterically less favored boat transition state. Sauers cautioned against extension of the boat/chair steric arguments (of Scheme 2) to a non-rigid system. Nevertheless, Sauers also accommodated Edward's results by assuming an initial A-ring inversion followed by product formation via a chair transition state.

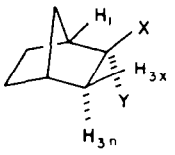


23 36



37 38

In 1964 Sauers[35] suggested an additional torsional strain factor that, with electronic effects and boat/chair steric interactions in the transition states for the Baeyer–Villiger reaction, would influence the bridgehead vs methylene carbon migration ratio. Sauers looked at a series of ring expansions of norbornyl type systems in which alkyl migrates toward incipient positive carbon or nitrogen centers; these were reaction of norcamphor 1 with hydrazoic acid or diazomethane; deamination of *exo*-norbornylmethylamine 39, solvolysis of *exo* norbornylmethyl tosylate 40, and decomposition of norbornyl azide 41. In all cases, methylene carbon migration is favored over bridgehead carbon migration; only the Baeyer–Villiger reaction of norcamphor 1 leads preferentially to bridgehead carbon migration.

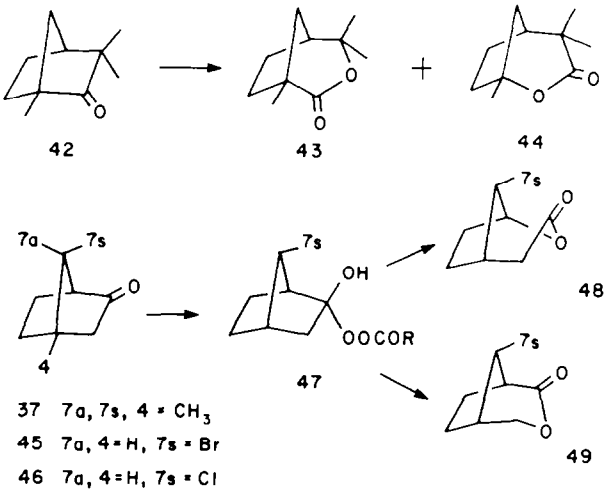


1 X, Y = O
35 X = OOCOR, Y = OH
39 X = CH_2NH_2, Y = H
40 X = CH_2 OTos, Y = H
41 X = N_3, Y = H

In searching for a force which would work in opposition to both electronic and chair conformation transition states favoring bridgehead migration of norbornanone 1, Sauers first rejected influences based upon the conformation of the leaving residue, which can attain *trans* coplanarity with either migrating group (See however, III.B). Noyori *et al.*[37] in 1980 challenged the earlier proposal of Sauers[35] that conformation of the leaving residue, because it can attain *trans* coplanarity with either migrating group, should not influence reaction regiochemistry. The theory of Noyori has not been applied to norbornanone Baeyer–Villiger oxidations (Tables 1 and 2), but the ideas are discussed infra (See III.B) for oxidations of a series of 8-oxabicyclo[3.2.1]nonan-3-ones. The crucial factor favoring methylene migration was suggested to be relief of torsional strain caused by eclipsing of the C-2 substituents and the hydrogens on C-3, estimated at 2–3 kcal/mol. Nonbonded interactions between the substituents on C-2 and the C-1 hydrogen are less severe since the dihedral angle relationships are 44° (H-1 and the C-2 *exo* substituent) and 79° (H-1 and the C-2 *endo* substituent). Migration of the C-2–C-3 bond proceeds with greater relief of eclipsing strain than does migration of the C-1–C-2 bond.

Applied to the Baeyer–Villiger reaction of bridged bicyclic ketones, torsional strain relief from 35 should always favor migration of the C-2–C-3 bond. This is true regardless of the *exo* or *endo* configuration of the hydroxyperester functions!

As a test of the torsional strain argument, Sauers[28] cited the results of fenchone 42 oxidation (40% peracetic acid) giving in 35% yield a 60:40 mixture of lactones 43 and 44. For fenchone 42 electronic effects are similar for the competing tertiary migrating groups. Assuming rearrangement of a Criegee intermediate formed by peracid attack on the *exo* face of 42, competition is between a chair transition state favoring bridgehead carbon migrated lactone 44 and of torsional strain relief favoring methylene migrated lactone 43. The opposing factors are nearly equal, slightly favoring methylene carbon migration.



37 7a, 7s, 4 = CH_3
45 7a, 4 = H, 7s = Br
46 7a, 4 = H, 7s = Cl

The regiochemistry of oxygen insertion for a series of 7-*syn* substituted norbornan-2-ones 37, 45 and 46 can be analyzed in a similar way according to Sauers.[35] Assuming that 7-*syn* substitution results in Baeyer–Villiger rearrangement via Criegee intermediates 47 formed by peracid attack on the *endo* face of the ketone, bridgehead migration, while electronically favored, will require boat-form transition states leading to 48, and will result in less relief of torsional strain than will methylene migration leading to 49. As boat-form interactions lessen in 48 more bridgehead migration might be expected. The increase in bridgehead migration product 48; 7s = Me (0%), Br (29%), Cl (47%), parallels a decrease in the bulk of the 7-*syn* substituent.

It should be noted that if, in fact, lactones 48 and 49 exist at any point along the reaction coordinate in chair/boat conformations rather than in half-chair conformations with planar *s-trans* lactone

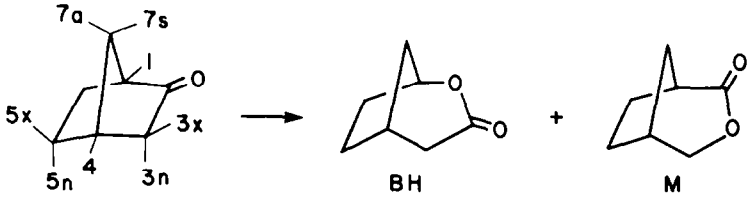
rotamers,[36] then the boat-form interaction of 48 consists of torsional strain plus whatever steric interaction exist between the 7s-substituent and carbonyl π-electrons. It is not, however, apparent how a change in 7s-substituent should affect the steric component of the interaction, since it is not clear if such an interaction is repulsive in nature.

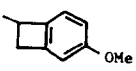
In addition, for an exothermic process, the transition state for rearrangement of 47 should more resemble the Criegee intermediate than the product lactones 48 and 49. Thus, analysis of lactone boat/chair/half-chair conformational energies may be inappropriate as transition state models. What is clear is that questions concerning the stereochemistry of the Criegee reaction intermediate 47 and the nature and source of presumed transition state steric and torsional interaction make such proposed explanations for the regiochemistry of Baeyer–Villiger oxidations of norbornan-2-ones incomplete and replete with uncertainty.

Roberts and Newton[27] in 1978 reported examples of preferred methylene migration in norbornan-2-ones *lacking* 7-*syn* substituents characteristic of previous examples (See Table 2). With MCPBA/CH_2Cl_2 7-*anti*-cyano-5-*endo*-methoxynorbornan-2-one 50 afforded *only* methylene migrated lactone 52, while the 7-*anti*-cyano-5-*endo*-bromonorbornan-2-one 51 afforded an 80:20 mixture of lactones 53 and 54, favoring methylene carbon migration. The electron withdrawing ability of the *anti*-cyano substituent at C-7 appears to be decreasing the ability of the neighboring C-1 bridgehead carbon to migrate; although it is not clear what role, if any, the 5-*endo* substituents in 50 and 51 play in these results. It should be noted in Table 1 (Section I.A.1.a) that 7-*anti*-COOH (19a), MeO- (27, 29), n-butyl (28) and even H (1) substituents also can result in some methylene migrated lactone with peracetic acid, although bridgehead migrated lactone is preferred in these cases.

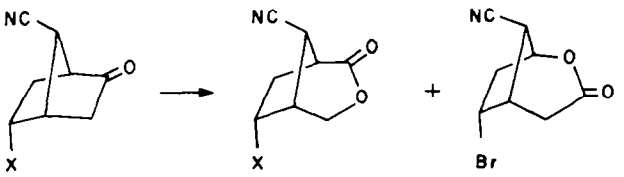
In the same paper Roberts and Newton[27] suggested that an *endo* substituent at C-5 capable of hydrogen bonding to a transannular pseudo-axial hydroxyl group at C-2 of a chair-like transition state 55 will facilitate bridgehead migration. The data of Table 1 (Section I.A.1.a) do not in general support this suggestion. For example: norbornanone 1, C-5 *endo*-H–C-7 *anti*-H, gives 85% *bridgehead* migrated lactone 2, while ketone 28, C-5 *endo*-methoxy–C-7 *anti*-n-butyl, gives only 80%, 5% *less* than 1, of bridgehead migration with meta-chloroperbenzoic acid. Even discounting a possible electron donating effect for the 7-*anti*-n-butyl group in 28, which should favor bridgehead migration, the C-5 *endo* methoxy group relative to H may slightly favor methylene carbon migration. Similar regiochemical comparisons from Table 1 of ketones having 5-*endo* oxygen containing functional groups do not appear to show a

Table 2. Major nonbridgehead (M) oxygen insertions of bicyclo[2.2.1]heptan-2-ones



Ketone	Substituents	Conditions	(% M)	Lactone Yield (%)	Ref.
1	-	$ClSiMe_2t$-Bu/O_3/$NaBH_4$	100[a]	50	38
24	1, 7a, 7s-tri-Me	H_2SO_5	100	-	32
		40% PAA in 40:60 H_2SO_4/HOAc	100	-	29a
37	4, 7a, 7s-tri-Me	40% PAA/NaOAc	100	94	28
42	1, 3x, 3n-tri-Me	40% PAA/buffer	60	35	28
45	7s-Br	40% PAA/NaOAc	71	73	35
46	7s-Cl	40% PAA/NaOAc	53	77	35
50	5n-OMe, 7a-CN	MCPBA/$NaHCO_3$/CH_2Cl_2	100	65	27
51	5n-Br, 7a-CN	MCPBA/$NaHCO_3$/CH_2Cl_2	84	60	27
56	5x-Br, 7s-Me, 7a-COOMe	Peracids	100	96	39
57	7a, 7s-di-Me	H_2SO_5	100	42	40
58	7s-Me, 7a- CH_2CH_2- 	Peracids	No Reaction	0	41

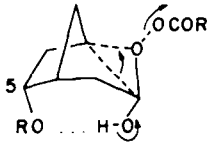
(a) Isolated as the hydroxyacid.



50 X = OCH_3
51 X = Br

52 X = OCH_3
53 X = Br

54



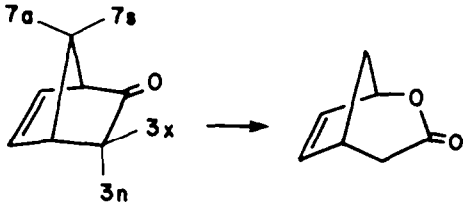
55

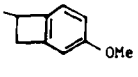
general pattern of facilitating bridgehead carbon migration. (Note the discussion of hydrogen bonding effects in Section III.B.). Roberts and Newton[27] also noted an interesting effect of peracid on the regioselectivity of oxygen insertion of 5-*endo*-benzyloxy-7-*anti*-methoxynorbornan-2-one 29, shown earlier in Table 1 (Section I.A.1.a). As Sauers[29] had found in 1959 that acid catalysis results in an increased competition from methylene carbon migration in camphor 24, so it appears that in those cases in which a relatively safe comparison can be made; that is, the comparisons maleic/phthalic and formic/acetic acids, the Baeyer–Villiger reaction becomes less selective for bridgehead carbon migration as the acidity of the parent acid is increased.

I.A.2. *Dehydroderivatives*

Baeyer–Villiger oxidations of bicyclo[2.2.1]hept-5-en-2-one[42] 59 and derivatives using various oxi-

Table 3. Bridgehead C-1 oxygen insertions of bicyclo[2.2.1]hept-5-en-2-ones

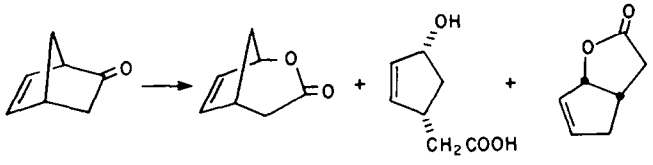


Ketone	Substituents	Conditions	Lactone Yield (%)	Ref.
59	-	40% PAA/NaOAc	56[a]	42
63a	7a-CH_2OBz	MCPBA/$NaHCO_3$	-	43a
63b	7a-$CH_2OCH_2CCl_3$	HOOH/NaOH or peracid	95+	43b
63c	7a-CH=CHCOMe	MCPBA	62	55
63d	7a-CH=CHCOn-C_5H_{11}	MCPBA	-	55
65	7a-CH_2OMe	MCPBA/$NaHCO_3$	95	44, 45
66	7s-Me, 7a-CH_2OTHP	50% HOOH/NaOH	80+	46, 47a-c
67	7s-Me, 7a-$CH=CH_2$	HOOH/NaOH	85	56
68	7s-CH_2OTHP, 7a-CH=CHCH(OTHP)C_5H_{11}	HOOH/NaOH	85	48
69	7s-F, 7a-CH=CHCH(OH)C_5H_{11}	HOOH/NaOH	75	49
70	3n, 7s-di-Me, 7a-$(CH_2)_3OTHP$	HOOH/NaOH	79	50
73	3n-Me, 7a-CH_2OBz, 7s-Me	HOOH/NaOH	85+	51
74	7s-Me, 7a- CH_2CH_2 	HOOH/NaOH	84	41
76	3n, 7s-di-Me, 7a-CH(OTHP)Me	HOOH/NaOH	74	52
78	3n, 7s-di-Me, 7a-CH_2OTHP	HOOH/NaOH	86	53
80	7s-Me, 7a-H	HOOH/NaOH	High	19d
83	7a, 7s-di-Me	MCPBA/CH_2Cl_2/$NaHCO_3$	-	54

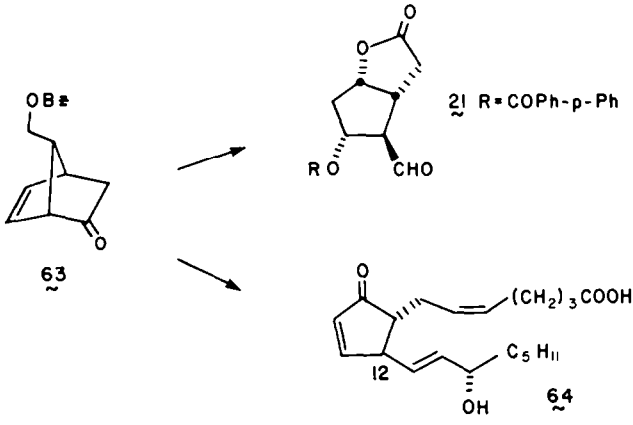
(a) Isolated as an allylically rearranged lactone 62.

dants occurs cleanly with migration of the allylic bridgehead position. Products observed are derivatives of the oxygen inserted lactone 60, the ring-opened hydroxyacid 61, or a rearranged lactone 62. Examples are shown in Table 3. Substituents at the 7-*syn* position do not alter the preference for migration of the allylic bridgehead as in the saturated bicyclic ring system (see I.A.1.b). Basic hydrogen peroxide can be used as an oxidant because of the strain inherent in the parent ketones.

The research groups mainly of Corey, Grieco, Roberts and Newton, have used the oxygen insertion reaction of norbornenones extensively in the synthesis of prostaglandins and prostaglandin analogs.



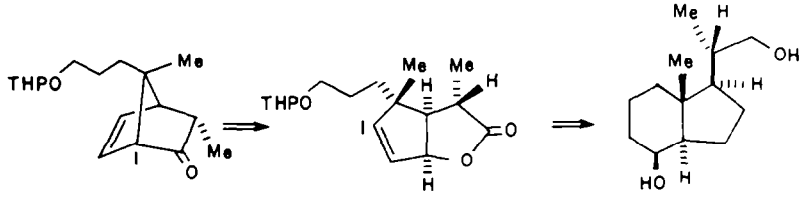
59 60 61 62



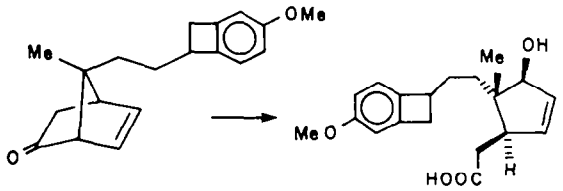
63 64

Examples include conversion of 63 to the Corey aldehyde 21, to PGC_2 and to PGA_2 64.[43] Other utility in the prostaglandin area includes conversion of ketone 65 to a prostaglandin intermediate[44] and to $PGF_{2\alpha}$ and PGE_2;[45] as well as formation of 12-methylprostaglandin analogs[46,47] from ketones 66 and 67, 12-hydroxymethylprostaglandins[48] from 68, and 12-fluoroprostaglandins[49] from 69 (see Table 3).

The stereochemical control engendered by using stereospecifically substituted norbornenones followed by regioselective Baeyer–Villiger reactions has also been used by Trost[50] in a stereochemically controlled route to the Inhoffen–Lythgoe diol 72 from 70 *via* lactone 71, thus effecting a formal total synthesis of vitamin D_3 and metabolites. Grieco[51] has similarly devised a stereocontrolled approach to sterol side-chain construction from ketone 73 (Table 3), and has used ketone 74 to prepare hydroxyacid 75, an intermediate in a total synthesis of *dl*-estrone.[41]

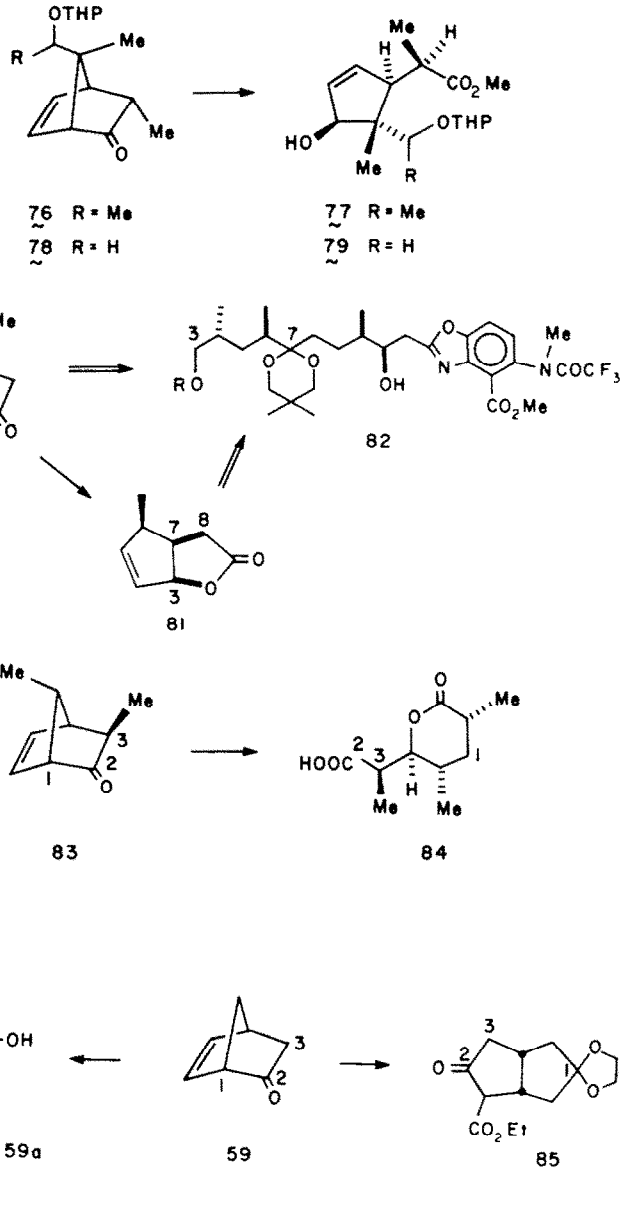


70 71 72



74 75

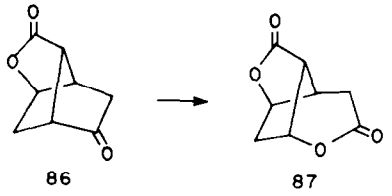
In a continuation of this general synthetic methodology of stereocontrolled synthesis Grieco[52] has utilized ketone 76 to prepare pseudoguaianolide synthon 77; ketone 78 to prepare the hydroazulenone synthon 79 for helenanolide synthesis;[53] ketone 80 to synthesize lactone 81, an intermediate in an elaboration of the C-3 to C-12 fragment of calcimycin A 82;[19a] and ketone 83 to synthesize the Prelog–Djerassi lactone 84, utilized in a synthesis of methynolide.[54] Barco *et al.*[42b] have recently reported a new route from ketone 59 to a 9(0)-methanoprostacyclin synthon 85 used in PGI_2 analog synthesis, and Crabbé *et al.*[42c] have converted ketone 59 to Brefeldin-A 59a.



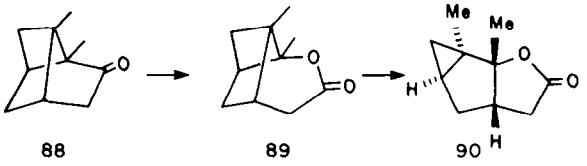
I.A.3. Bridged tricyclics and polycyclics

Baeyer–Villiger oxidation of the bridged lactone 86 with MCPBA/$NaHCO_3$/CH_2Cl_2 reportedly[25] proceeds with only bridgehead migration to give dilactone 87 in 75% yield. Formation of the lactone bridge in 86 does not change the preference for bridgehead insertion of oxygen observed during oxidation of other 5-*exo*-X-7-*anti*-carboxylic acid bicyclo[2.2.1]heptan-2-ones[24,25] (see Table 1, structures 19a, b). The 6,7-methylene bridged carvone camphor 88 with perbenzoic acid also affords in 78% yield[57a] a bridgehead migrated lactone 89, which rearranges in acid to lactone 90. The 3,5-methylene bridged ketone 91a with 90% hydrogen peroxide/boron trifluoride inserts oxygen only adjacent to the methyl

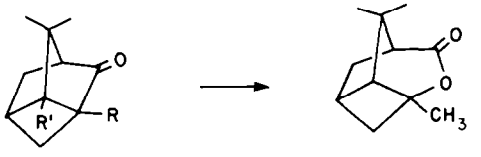
substituted bridgehead to give 92, while the related ketone 91b, under the same reaction conditions, affords a mixture of regioisomeric lactones in unspecified ratio.[57b] Conversion of ketones 91a and 91b to lactonic product is partial in both instances.



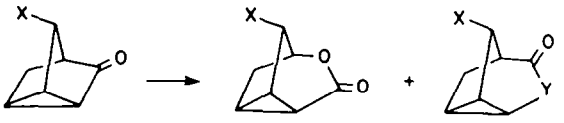
86 87



88 89 90



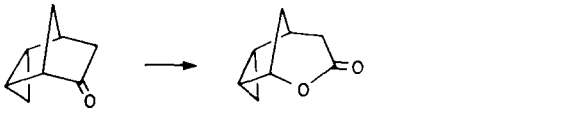
91a R = CH_3, R' = H
b R = H, R' = CH_3 92



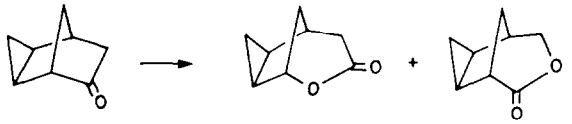
93a X = H
93b X = COOH
94a X = H
94b X = COOH
95 X = COOH
96 X = H Y = NH

Baeyer–Villiger oxidation of the nortricyclanones 93 (see also, 7-oxo-isomers, I B) presents the issue of relative bridgehead migratory preference. For 93a X = H, peracetic acid oxidation affords in unspecified yield[58] only lactone 94a from migration of the bridgehead away from cyclopropyl. (Compare IB, in which regiospecific cyclobutyl migration is observed.) For 93b, X = COOH, a small contribution from cyclopropyl migration is found; peracetic acid converts ketone 93b in unspecified yield[24] to a 7:1 mixture of lactones 94b and 95. It is of interest that nortricyclanone 93a, upon Beckmann rearrangement of its oxime, reportedly affords only cyclopropyl migrated lactam 96.[59]

The fused cyclopropyl ketones 97 and 99 are part of an interesting puzzle discussed in Section II.A. The *syn*-fused cyclopropyl ketone 97 rearranges with bridgehead regiospecificity in 80% yield with MCPBA to give lactone 98. The *anti*-fused cyclopropyl ketone 99 under the same conditions affords an 8:2 mixture of lactones 100 and 101 with bridgehead migration again preferred.[60]



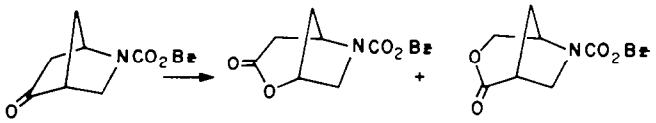
97 98



99 100 101

I.A.4. Aza-analogs

Oxidation of azabicyclic ketone 102 with peracetic acid proceeds regioselectively as shown by ^1H NMR analysis of the reaction mixture to give bridgehead migrated lactone 103 in 65% yield; a 30% recovery of lactone 103 after column chromatography on silica gel results from lactone hydrolysis on the column. With MCPBA/CH_2Cl_2 a 2:1 ratio of lactones 103 and 104 was isolated in 50% combined yield.[11] (Compare II A 2).

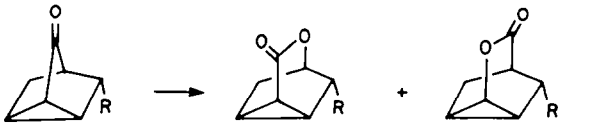


102 103 104

I.B. 7-Oxoisomers

The tricyclic ketones 93a and 93b present the problem of regioselectivity of oxygen insertion. Peracetic acid (probably 40%) selectively inserted oxygen at the bridgehead away from cyclopropyl carbon in ketone 93a to give lactone 94a unspecified yield.[61] (Compare IV.B, a preferred cyclopropyl migration.[73a]) The carboxylic acid derivative 93b (see I.A.3) afforded a 7:1 mixture of lactones 94b and 95 with peracetic acid in unspecified yield.[24] The carboxylic acid functionality decreases the tendency of the β-bridgehead to migrate by a remote inductive effect (Compare III.B, II.A.2, I.A.1.a, I.A.1.b).

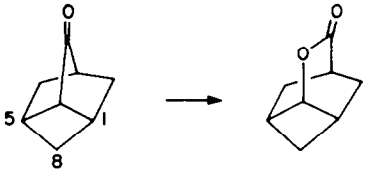
The homologous cyclobutyl ketone 105, on the other hand, with sodium hydrogen phosphate buffered trifluoroperacetic acid afforded regioselectively (98%+) the lactone 106 formed by cyclobutyl migration.[58,63] (see Refs. 57, I.A.3 and Ref. 67a, III.C) Participation by the 1,8 bonds of 105 in the migration transition state has been proposed.



93a R=H
93b R=CO_2H

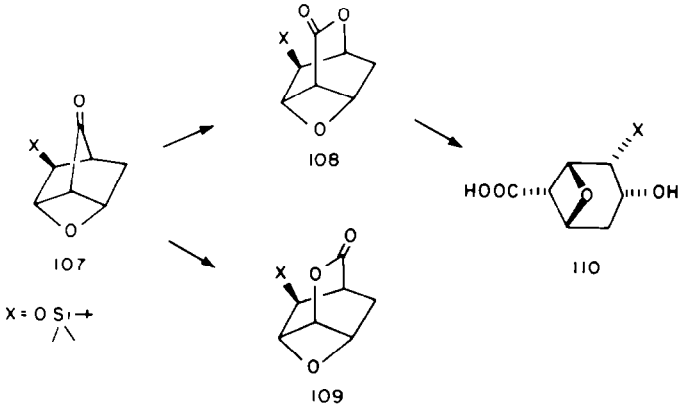
94a R=H
94b R=COOH

95 R=COOH



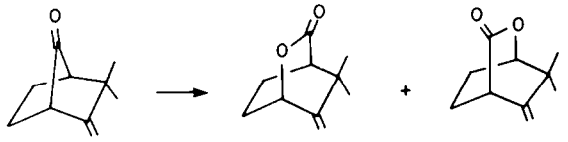
105 106

The oxygen bridged analog 107 has been used in a synthetic route to 6-oxabicyclo[3.1.1]heptane 110, an intermediate in the preparation of thromboxane A_2 analogs. Baeyer–Villiger oxidation of 107 with MCPBA/sodium carbonate/CH_2Cl_2 afforded 83% yield of lactone 108 and 9% of lactone 109. Migration of the oxetane ring is postulated to be retarded by the electron deficient character of the ring;[64] a role for the substituent X in determining reaction regiochemistry has not been addressed.



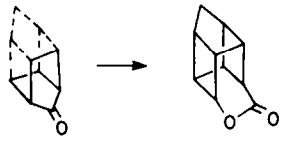
107 108 109 110

A novel and selective Baeyer–Villiger reaction of camphen-7-one 111 has been effected under mildly acidic conditions in dioxane contaminated with its hydroperoxides.[65] Lactones 112a and 112b were obtained in a 4:1 ratio (yield not reported) with ^1H NMR indicating oxygen insertion mainly at the allylic bridgehead. No double bond epoxidation was observed. Peracetic acid converted ketone 111 to a 4:1 mixture of olefin epoxide and Baeyer–Villiger products. (Experimental details were not provided.)



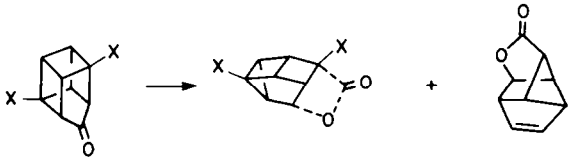
111 112a 112b

The cage molecule 113 can be considered formally a bicyclo[2.2.1]heptan-7-one derivative. Insertion of oxygen adjacent to the carbonyl of 1,4-bishomocubanone 113 to give lactone 114 has been effected with 30% hydrogen peroxide/acetic acid[66] in 80–85% yield, ceric ammonium sulfate/aq acetonitrile[67] in 80% yield, and MCPBA/benzene/TsOH in 86% yield.[67] During preparation of this manuscript Mehta[62]



113 114

has reported CAN/acetonitrile oxidation of homocubanone 238a to tetracyclo[4.2.0.0.^{2,4}0^{3,8}]octane 249a (16%) and the tetracyclic lactone 250 (6%). The dibromohomocubanone 248b likewise afforded 249b (15%).



248a X = H ⟶ 249a
b X = Br ⟶ 249b
250

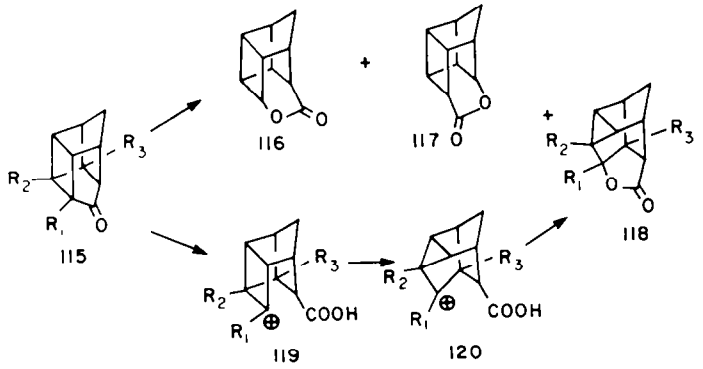
Table 4. Oxygen insertions of 1,3-*bis*-homocubanones

Ketone	R_1	R_2	R_3	Oxidant	Yield (%)	Ratio 116	117	118	Ref.
115a	H	H	H	MCPBA/$CHCl_3$	60	50	1.1	13	68a,b
				MCPBA/PhH	90	50	10	-	67a
				CAS or CAN	78	-	100	-	67a
				CAN	-	-	-	100	68a
				$Pb(OAc)_4$	55	-	-	100	68a
				PAA	86	50	50	-	66
115b	H	H	CO_2Bz-p-NO_2	MCPBA	70	54	-	16	68a
115c	Me	H	CO_2Bz-p-NO_2	MCPBA	87	76	-	11	68a
115d	H	Me	CO_2Bz-p-NO_2	MCPBA	86	58	-	28	68a
115e	Me	Me	CO_2Bz-p-NO_2	MCPBA	82	70	-	13	68a

CAS: ceric ammonium sulfate/aq acetonitrile; CAN: ceric ammonium nitrate/aq acetonitrile; PAA: peracetic acid; MCPBA: meta-chloroperbenzoic acid/benzene/toluenesulfonic acid,[67a] or chloroform solvent.[68a]

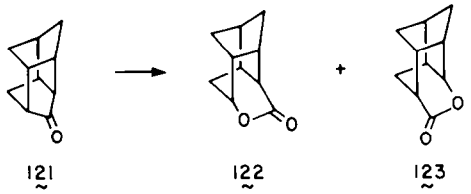
The issue of regioselectivity arises with Baeyer–Villiger oxidations of 1,3-bis-homocubanones 115, as shown in Table 4. Ketone 115a was reported by Mehta[67] to oxidize with MCPBA to a 5:1 mixture of lactones 116 and 117, with the major product arising from migration of the cyclobutyl bridgehead. (see I.A.3, III.C, cyclobutyl preferred migrations) By contrast ceric ammonium sulfate was reported by

Mehta[67] to give only the lactone 117 derived by migration of the cyclopentyl bridgehead. The complementary regiochemistry *appeared* to be significant. Mehta[66] reported peracetic acid to be nonregioselective, converting ketone 115a to a 50:50 mixture of lactones 116 and 117. This latter result is surprising, for peracetic acid is generally *more* regioselective than MCPBA (Compare I.A.1.a, ketone 29 and II.A.2). Indeed, the discussions and conclusions of Mehta[66,67] were challenged by Yonemitsu *et al.*



Using various oxidation conditions with ketones 115 Yonemitsu *et al.*[68] obtained only traces of cyclopentyl migrated lactones 117. The major products in all cases were identified with the aid of ^{1}H-NMR, starting with deuterium labeled ketone 115a, as the lactones 116, derived by cyclobutyl migration, and the rearranged lactones 118. Lactone 118a was identified by independent synthesis. Lactones 118 are formed via an unusual cleavage of a tetrahedral Criegee intermediate (see the Introduction). Evidence for a carbocation mechanism in the MCPBA oxidation of 115 was provided by observation of solvent, kinetic, and methyl substituent effects using ketones 115b–e. As solvent polarity increases, the percentage of rearrangement products was found to increase as expected for a cationic mechanism involving 119 and 120. In looking at the ratios of lactones 116:118 from 115 in Table 4, it is seen that a methyl group at R-1 in 115c increases the ratio 116:118 favoring unrearranged lactone 116. However, a methyl group at R-2 in 115d decreases the ratio 116:118, favoring rearranged lactone 118. This behavior is as expected if cations 119 and 120 are involved. As a point of interest, rate studies indicated addition of peracid to the ketone carbonyl of 115a to be the rate determining step.[68a]

The importance of the cyclobutyl group in the cleavage process to give 119 was shown by oxidation of ketone 121, which lacks the single carbon-carbon bond of 1,3-*bis*-homocubanone 115a. Ketone 121 with MCPBA[68a] afforded in 87% yield a 3:2 mixture of the unrearranged lactones 122 and 123. As with 1,3-*bis*-homocubanone 115a, the major lactone arises by migration of the bridgehead away from the cyclopentyl face.

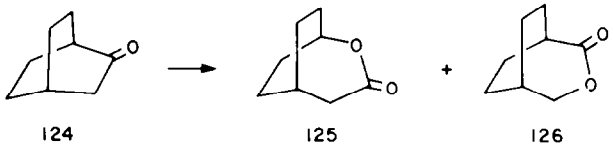


II. BICYCLO[2.2.2]OCTANONES

II.A. 2-Oxo-isomers

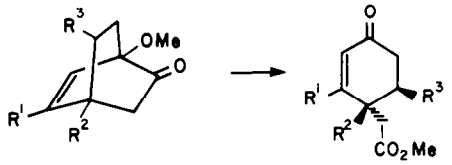
II.A.1. Parent system and dehydroderivatives

Meinwald and Frauenglass[6] observed solely bridghead migration upon oxidation of bicyclo[2.2.2]octanone 124 with sodium acetate buffered 28% PAA to lactone 125 in 85% yield. We[11] have found MCPBA/CH_2Cl_2 oxidation of ketone 124 gives a 75:25 ratio of bridgehead migrated lactone 125 to methylene migrated lactone 126.



The dehydroderivative, bicyclo[2.2.2]octen-5-one 127a, affords with 28% PAA an 80% yield of a rearranged lactone 128a, derived from the product of bridgehead migration.[6] Recently Holmes[104] has reported PAA/sodium acetate oxidation of 1-methoxybicyclo[2.2.2]oct-5-enes 127b–f and conversion to the allylically rearranged 4,4-disubstituted cyclohexenones 128b–f (52–85% yields), useful intermediates in natural product synthesis.

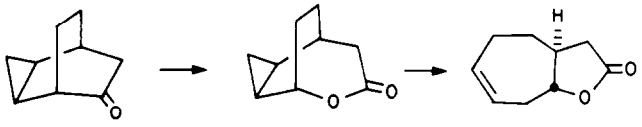
127a 128a



127 b $R^1 = R^3 = H$ $R^2 = Me$
c $R^1 = Me$ $R^2 = R^3 = H$
d $R^1 = R^2 = Me$ $R^3 = H$
e $R^1 = R^2 = R^3 = Me$
f $R^1 = R^2 = R^3 = H$

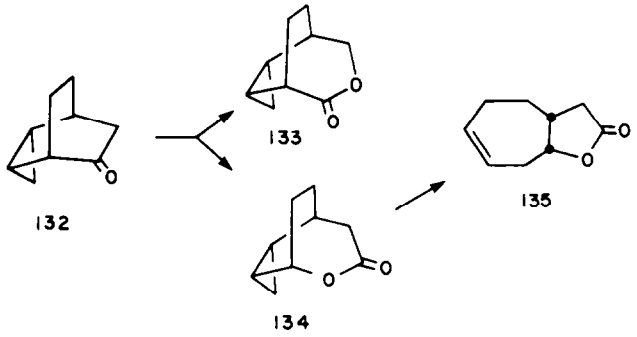
128 b–f

The cyclopropyl-fused ketones 129 and 132 (see I.A.3) show interesting behavior upon sodium bicarbonate buffered MCPBA oxidation in methylene chloride.[60] The *anti*-fused cyclopropyl ketone 129 after 2 days reaction time affords solely bridgehead migrated lactone 130 in 62% yield. This lactone rearranges in aqueous perchloric acid to the *trans*-fused butyrolactone 131.



129 130 131

By contrast, the *syn*-fused cyclopropylketone 132 after 5 days reaction time affords in essentially quantitative yield a 9:1 ratio of lactones 133 and 134, with methylene migration preferred. The bridgehead migrated lactone 134 rearranges in acid to a *cis*-fused butyrolactone 135. A rationale for the reversal in regioselectivity of oxygen insertion with change in stereochemistry of the cyclopropyl group has not been offered.[60] The preference for methylene migration in the oxidation of ketone 132 contrasts with favored bridgehead migration for 129 and for the bicyclo[2.2.1]analogs 97 and 99 (see I.A.3).

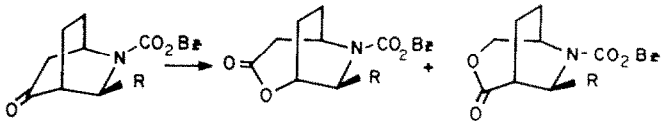


132 133 134 135

II.A.2. Aza-analogs

We[147] have found oxidation of N-carbobenzoxy-2-azabicyclo[2.2.2]octan-5-one 136 with PAA affords the bridgehead migrated lactone 139 in 81% yield. With MCPBA/CH_2Cl_2 a 67:33 mixture of lactones 139 and 141 is isolated in 66% yield. Baxter and Holmes[69] in 1977 reported the 3-*exo* derivatives 137 and 138 gave exclusively the methylene migrated lactones 142 (40%) and 143 (45%) with MCPBA/CH_2Cl_2/sodium

bicarbonate. Later studies by us[11] and Baxter and Holmes[103] indicate ketone 137 with MCPBA actually affords lactones 140 and 142 in a 60:40 ratio. The He(I) photoelectron spectrum of N-carboethoxy 2-azabicyclo[2.2.2]octan-5-one 136 indicates a significant interaction between the nitrogen lone-pair and the carbonyl oxygen at C-5;[70] however, the main factor leading to preferred methylene migration for 138, R = COOMe, appears to be the electronegativity of the methoxycarbonyl substituent at C-3, which decreases the tendency of the bridgehead C-4 to migrate.



136 R = H
137 R = CH_2OCOPh
138 R = COOMe

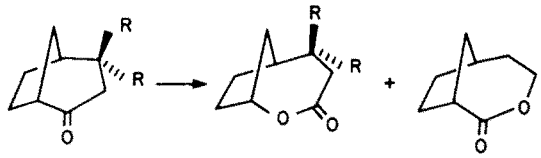
139 R = H
140 R = CH_2OCOPh

141 R = H
142 R = CH_2OCOPh
143 R = COOMe

III. BICYCLO[3.2.1]OCTANONES

III.A. 2-Oxo-isomers

Peracetic acid oxidation of 4,4-dimethylbicyclo[3.2.1]octan-2-one 144 afforded bridgehead migrated lactone 145 and its corresponding hydroxyacid in 76% combined yield.[71] We[11] have found peracetic acid oxidation of the parent bicyclo[3.2.1]octan-2-one 146 to be similarly regioselective for lactone 147; however, MCPBA oxidation of 146 afforded an 88:12 ratio of lactones 147 and 148.



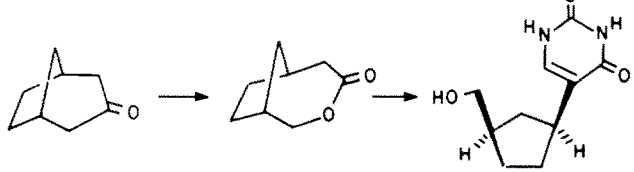
144 R = Me
146 R = H

145 R = Me
147 R = H

148

III.B. 3-Oxo-isomers

Bicyclo[3.2.1]octan-3-one 149 has been converted to lactone 150 with sodium bicarbonate buffered MCPBA in ethanol free chloroform after one week[72] in 61% yield or with MCPBA/CH_2Cl_2/56 hr/25° in 81% yield.[73] Lactone 150 was converted to 5-(*cis*-3-hydroxymethylcyclopentyl)uracil 151, a carbocyclic analog of 2', 3'-dideoxypseudouridine.[72]

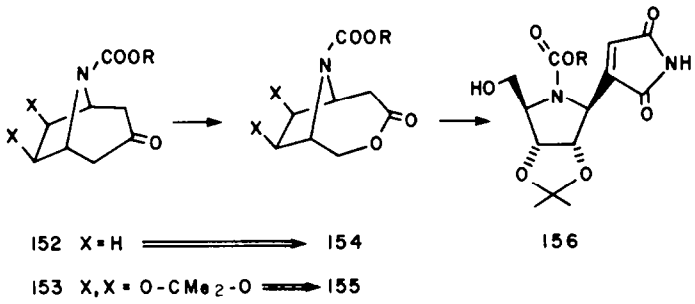


149 150 151

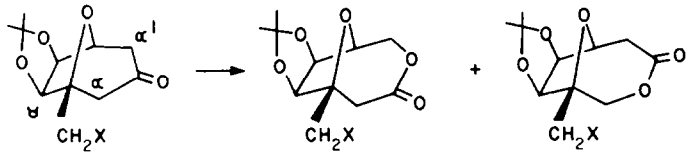
Table 5. γ-Substituent electronic effects on regioselectivity in the Baeyer–Villiger oxidation of ketones 157 and 160 with trifluoroperacetic acid[37a]

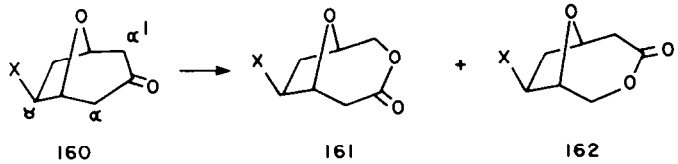
Ketone	X	^{13}C=O Shift	Lactone Ratio 158:159	Ketone	^{13}C=O Shift	Lactone Ratio 161:162
157a	H	205.59	47:53	160a	206.67	-
157b	n-Bu	-	50:50	-	-	-
157c	OCH_2Ph	205.41	52:48	160c	205.66	70:30
157d	OCOMe	204.19	65:35	160d	204.78	54:46
157e	OCOPh	204.49	72:38	160e	204.86	65:35
157f	$OCOCF_3$	203.34	77:23	-	-	-
157g	OSO_2CF_3	202.74	86:14	-	-	-

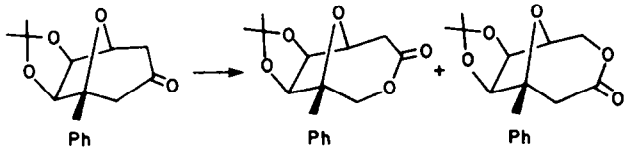
Forcing conditions, MCPBA/tetrachloroethane/48 hr reflux, were used to oxidize N-carbomethoxy 8-azabicyclo[3.2.1]octan-3-ones 152[11] and 153[74] to lactones 154 (75% yield based upon 30% conversion) and 155 (60% yield). Lactone 155 has been converted to 156, a nitrogen analog of showdomycin, a C-nucleoside antibiotic. The ribofuranosyl ring oxygen of showdomycin is replaced by an N-carbomethoxy group in 156.



Noyori *et al.*[37] have managed to isolate the roles played by electronic[37a] and steric[37b] effects in determining the regiochemistry of oxygen insertion during trifluoroperacetic acid (TFPAA) in methylene chloride oxidations of γ-substituted 8-oxabicyclo[3.2.1]octan-3-ones 157 and 160 in 80–100% yields. Electronic effects are shown in Table 5. An increase in electron withdrawing ability of the group X at the γ-position of 157 or 160 results in a decreased tendency of the α-carbon to migrate to an electron deficient center from a tetrahedral Criegee intermediate. Some indication of decreased electron density at the α-carbon has been provided by the *upfield* shifts of ^{13}C NMR signals for the carbonyl carbon as the electron withdrawing ability of the group X increases. The more distant α′ carbon is presumably unaffected, or at least less affected by the nature of the X-group.[37a] When the group CH_2X of 157 is replaced by phenyl in 163, TFPAA oxidation gives 93% yield of an 88:12 mixture of lactones 164 and 165 favoring α over α′ methylene carbon migration.[37a,75] The preference for α migration has been attributed by Noyori[75] to the cation supporting ability of phenyl, although how a phenyl group, predicted on inductive grounds to be electron withdrawing,[76] stabilizes a remote migrating electron deficient center has not been explained.

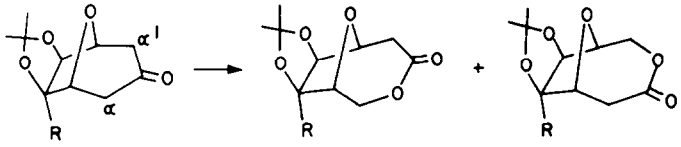






Steric effects[37b] on the regioselectivity of oxygen insertion of substituted 8-oxa-bicyclo[3.2.1]octan-3-ones 166 are shown in Table 6. Oxidations were performed with TFPAA in methylene chloride for 36 hr and 75–85% yields of lactones 167 and 168 based upon ketone converted to lactone were recovered. The

low percentage conversions in the Baeyer–Villiger oxidations of 166 are a result of the low equilibrium concentrations of tetrahedral Criegee intermediates. With regard to the regiochemical results, an indication of the similar electron density at the α and α' positions in all cases studied in Table 6 is provided by the similar $^{13}C{=}O$ NMR chemical shifts for the carbonyl carbon atoms. Thus ruling out a substituent electronegativity rationale for the observed regiochemical results, the decreased tendency for the α substituent to migrate was related by Noyori to the stereoelectronic requirements for alkyl group



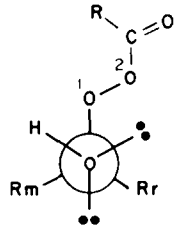
166 167 168

Table 6. γ-Substituent steric effects on regioselectivity in the Baeyer–Villiger oxidation of ketones 166 with trifluoroperacetic acid[37b]

Ketone	R	Conversion (%)	$^{13}C{=}O$ Shift	Lactone Ratio 167:168
166a	H	-	204.32	-
166b	Me	62	-	33:67
166c	n-Pent	48	205.07	25:75
166d	t-Bu	0	-	-
166e	Ph	19	204.54	39:61
166f	CH_2OCH_2Ph	32	204.56	23:77
166g	CH_2OCOPh	28	204.20	40:60

migration. This theory is outlined using the generalized Criegee tetrahedral intermediate 169.

In order for a group R_m of 169 to migrate to ^1O with ejection of carboxylic acid two prerequisites must be met. Firstly, the groups R_m–C–^1O–^2O should have R_m and ^2O in an antiperiplanar geometry. Secondly, and a previously unrecognized factor suggested by Noyori, one of the hydroxyl nonbonding electron pairs must also be antiperiplanar to R_m as in the conformation shown.

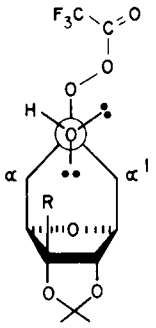


169

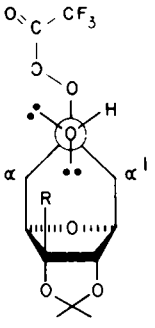
By application of these concepts to the 6-*endo*-substituted ketones of Table 6, it can be predicted that lactone formation will occur primarily from the reactive conformers 170 and 171. Alternative reactive conformers with the hydroxyl proton toward the group R were considered by Noyori[37b] to suffer from steric repulsion between R and the hydroxyl hydrogen. Possible hydrogen bonding effects between the hydroxyl proton and oxygen atoms of R groups were ruled out because alkyl groups and ether or ester containing groups R of Table 6 show the same directing effect. In addition Noyori suggested that hydrogen bonded conformers do not satisfy the stereoelectronic requirements for migration.

Of the two reactive conformers 170 and 171, reaction via the R/hydroxyl H *anti* conformation and α' migration is to be preferred over reaction via the R/hydroxyl H *syn* conformation with α migration. Noyori[37b] does not indicate why reaction of the R/hydroxyl H *syn* conformation 170 is disfavored, but presumably the hydroxyl proton may interact repulsively with the group R.

Noyori *et al.*[77] have utilized 8-oxabicyclo[3.2.1]oct-6-en-3-ones 172, readily available from furan and suitable bromoketones, to provide stereochemical control in the synthesis of furan rings. Ketones 173, formed by stereoselective functionalization of ketones 172, were oxidized with TFPAA/methylene

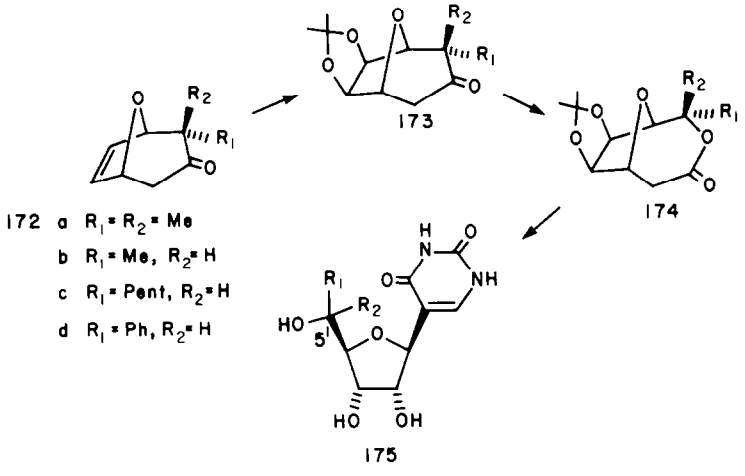


170 R/H Syn



171 R/H Anti

chloride regioselectively to lactones 174 in greater than 80% yields. Lactones 174 have been elaborated to pseudouridines 175 modified at the C-5′ position.[78] In a like manner ketone 176 has been converted to showdomycin[79] 177; pseudouridine[79] 178 and its 2-thio-, 6-aza- and similar analogs;[75,79] pyrazole homo-C-nucleoside[80] 179, homoshowdomycin[81] 180; and homopyrazomycin[81] 181. The 4′-phenylated pyrimidine C-nucleosides 182 was prepared from ketone 163,[82] and ketones 183 and 184 provided the first stereocontrolled entry to 1′, 4′-dialkylated pyrimidine C-nucleosides[83] 185 and 186 (see also Ref. 37*c* for a preparation of C-nucleosides from ketone 166).

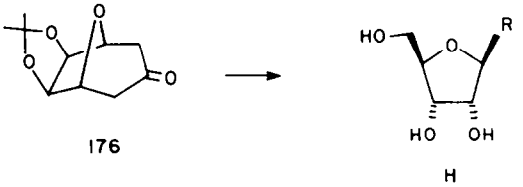


172 a $R_1 = R_2 = Me$
b $R_1 = Me$, $R_2 = H$
c $R_1 = Pent$, $R_2 = H$
d $R_1 = Ph$, $R_2 = H$

173

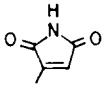
174

175

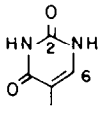


176

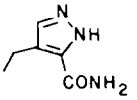
177 R =



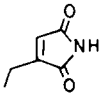
178 R =



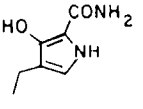
179 R =

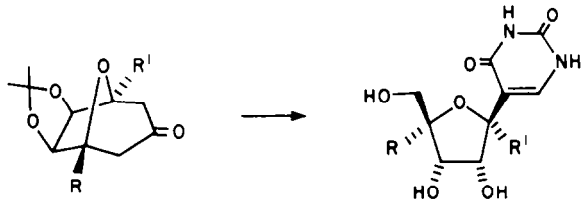


180 R =



181 R =



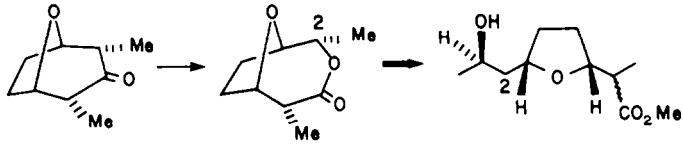


163 R = Ph, R' = H ⟶ 182

183 R = R' = Me ⟶ 185

184 R = R' = n C_5H_{11} ⟶ 186

White *et al.*[84] have utilized lactone 188, prepared by oxidation of ketone 187 with TFPAA/sodium hydrogen phosphate/CH_2Cl_2 in 94% yield, to construct methyl nonactate and methyl-8-epinonactate 189. The macrotetralide antibiotic nonactin consists of nonactic acid subunits linked in alternating enantiomeric sequences.

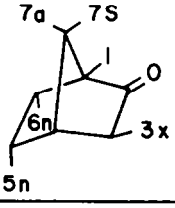


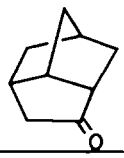
187 188 189

III.C. 6-Oxo-isomers

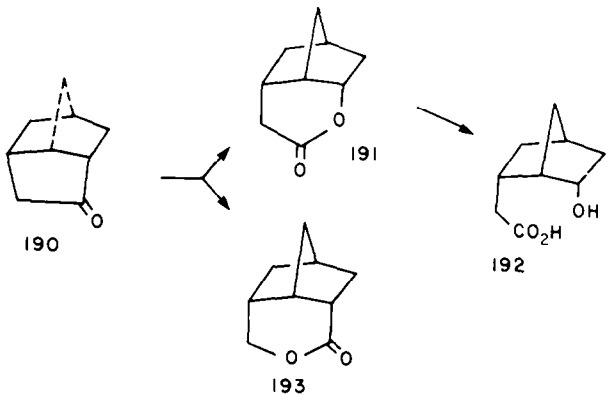
The cage molecules 190, 197 and 199, can be considered formally as bicyclo-[3.2.1]octan-6-one derivatives. (see also I.A.3, compound 105) Brendan-4-one has been oxidized to a 1:1.2 mixture of hydroxyacid 192 and lactone 193 with TFPAA/disodium hydrogen phosphate/CH_2Cl_2.[85] The bridgehead migrated lactone 191 hydrolyzed preferentially under the reaction conditions to 192, enabling it to be easily separated from the methylene migrated lactone 193. This hydrolytic behavior contrasts sharply with the preferential basic hydrolysis of the methylene migrated lactones derived from bicyclo[2.2.1]heptan-2-ones, as shown in Table 7 (see I.A.1.a).

Table 7. Lactone regioisomers which have been separated by preferential hydrolysis

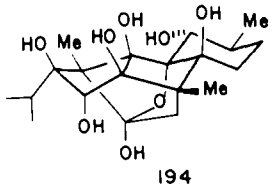


Ketone	Substitution	Conditions	Reactive Regioisomer	Ref.
1	-	NaOH/pyridine/25°	M	9, 10
15	5n, 6n- $CH_2C(OCH_2CMe_2CH_2O)CH_2$	dil. NaOH/DME	M	18a, b
22a	5n-$OSiMe_2$t-Bu 7a-CH=CHCH($OSiMe_2$t-Bu)C_5H_{11}	2N NaOH	M	20
22c	5n-OCH_2Ph 7a-CH=CHCH($OSiMe_2$t-Bu)C_5H_{11}	PAA/10 days	M	12
24	1, 7a, 7s-tri-Me	H_2SO_5	M	24, 32
25	3x-Me	dil. NaOH/cold	M	30
190		TFPAA/Na_2HPO_4	BH	85

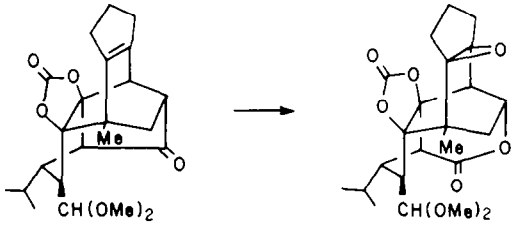
M = Lactone formed by migration of methylene carbon; BH = Lactone formed by migration of bridgehead carbon; PAA = Peracetic acid; TFPAA = Trifluoroperacetic acid



As part of an impressive total synthesis of the diterpene ryanodol 194 by Deslongchamps and numerous coworkers,[86] Baeyer-Villiger oxidation of intermediate ketone 195 with sodium acetate buffered 40% PAA afforded 85% of a desired epoxylactone 196 formed by migration of one of the two bridgehead carbons. An isomeric lactone of unidentified structure was obtained in 15% yield.

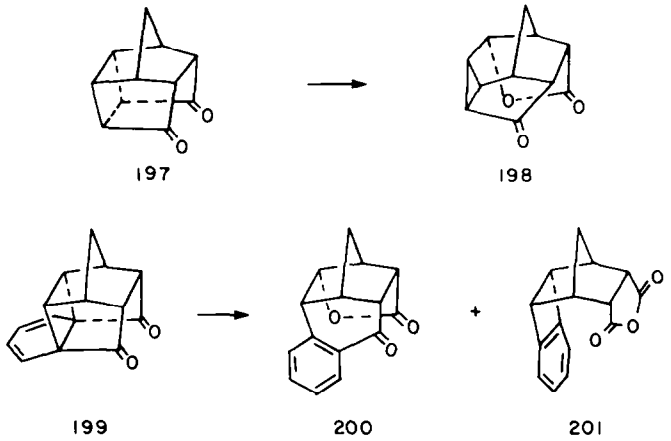


194



195 196

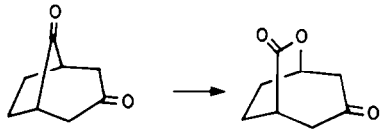
Polycyclic diketone 197 was oxidized with MCPBA (two equivalents) to an unidentified dilactone in 93% yield.[67a] With one equivalent of MCPBA the same dilactone was obtained in 43% yield.[67a] A monolactone obtained in 82% yield from diketone 197 using CAN/aq acetonitrile[67a] was later shown by Mehta[67c] and by Hirao *et al.*[68] with the aid of ^{13}C NMR spectroscopy indicating cyclopropyl carbon, to be 198. Diketone 199, on the other hand, afforded a rearranged lactone 200 in 40% yield and the anhydride 201 in 30% yield with CAN as oxidant. Structures were assigned by spectroscopic techniques.[67b,d]



197 198 199 200 201

III.D. 8-Oxo-isomers

Oxidation of bicyclo[3.2.1]octan-3,8-dione 202 with MCPBA afforded in 86% yield the single monolactone 203 resulting from migration of a bridgehead carbon.[73] Steric hindrance toward addition of peracid to the C-3 carbonyl inhibits formation of the reactive Criegee intermediate required for Baeyer–Villiger oxidation at C-3 (see Introduction and III.B).

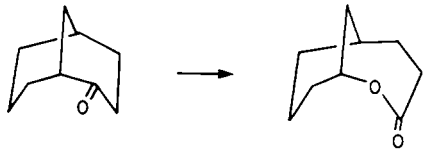


202 203

IV. BICYCLO[3.3.1]NONANONES

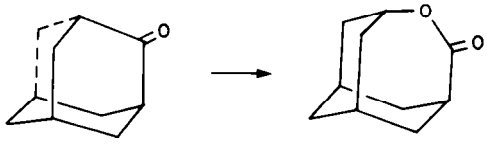
IV.A. 2-Oxo-isomers

Bicyclo[3.3.1]nonan-2-one 204 has been reported to insert oxygen only at the bridgehead position with MCPBA to afford lactone 205 in 83% yield.[73] The ease of oxidation of ketone 204 contrasts sharply with the failure of the related 3-keto isomer 208 to react under the same conditions (see IV.B).



204 205

Adamantanone 206, which can be considered a methylene bridged bicyclo[3.3.1]-nonan-2-one, has been converted to the lactone 207 in high yields by numerous oxidizing agents; for example, TFPAA[87] (90 + %), propionic acid/hydrogen peroxide[87] (90 + %), selenium dioxide/30% hydrogen peroxide[88] (96%), monoperphthalic acid[89] (no yield given), PAA[66,90] (90–95%), CAN/aq acetonitrile[9] (73%), bis(trimethylsilyl)-monoperoxysulfate[91] (88%), and MCPBA[9] (73%).

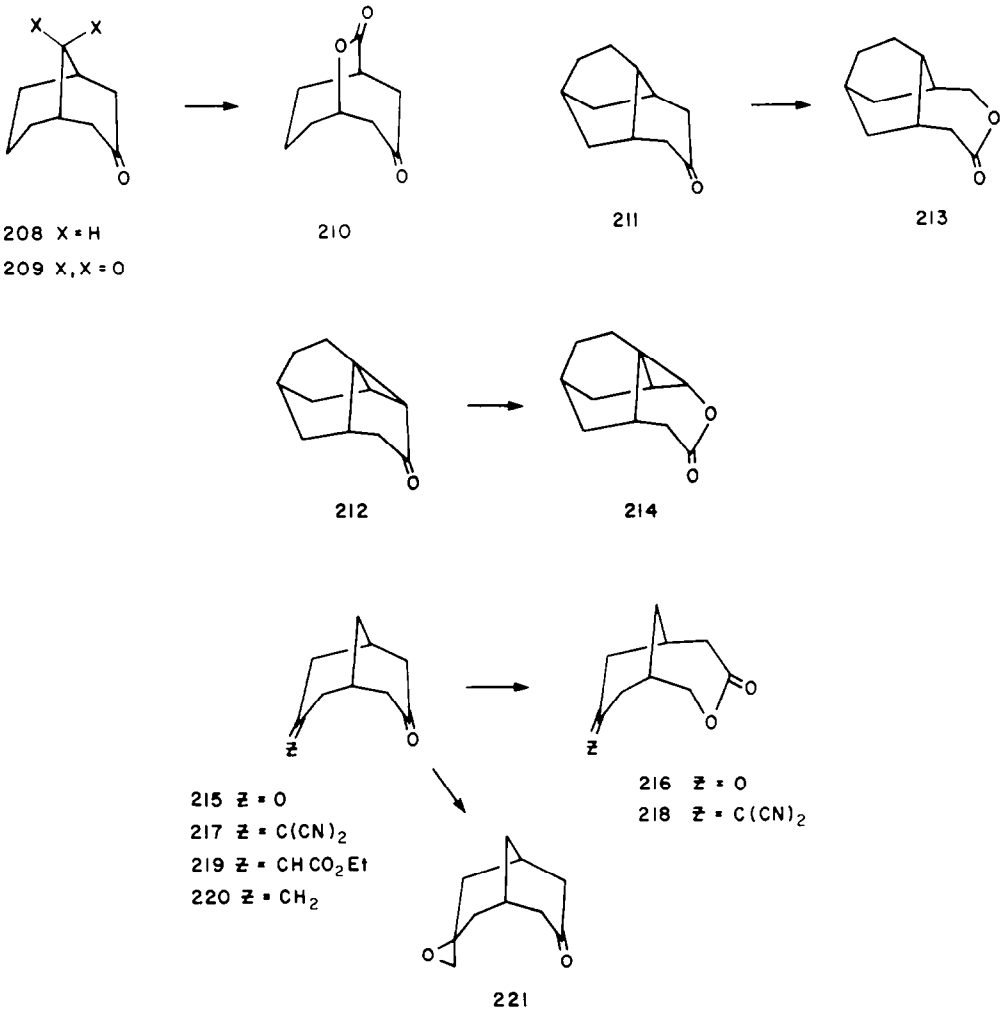


206 207

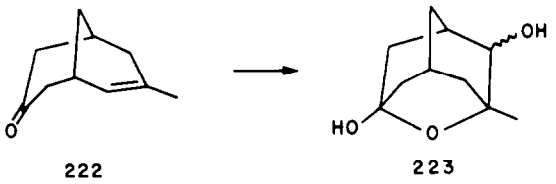
IV.B. 3-Oxo-isomers

IV.B.1. Carbocycles

Bicyclo[3.3.1]octan-3-one 208 has been reported to be unreactive toward MCPBA oxidation.[92] Similarly, diketone 209 reacts only at the 9-keto functionality to give ketolactone 210 in 89% yield with MCPBA.[73a] Failure of the 3-keto group to undergo Baeyer–Villiger oxidation is attributed to steric hindrance toward formation of the tetrahedral Criegee intermediate at the C-3 carbonyl. In line with this reasoning, when the 7-*endo*-methylene hydrogen is tied back as in ketones 211 and 212, MCPBA affords 86% and 88% yields of lactones 213 and 214.[73a] In the latter case 212 oxygen inserts stereoselectively at the cyclopropyl bridgehead position (compare I.A.3). Steric hindrance is also lessened in the 7-keto derivative 215, which reacts with MCPBA/TsOH/CH_2Cl_2 to give a monolactone 216 in 79% yield,[93] and in the 7-exodicyanomethylene derivative 217, which undergoes oxygen insertion to give lactone 218 with MCPBA/CH_2Cl_2 in 15% yield after 9 days reflux.[73b] Ketone 219 failed to react with MCPBA/CH_2Cl_2 after 8 hr reflux.[73b]



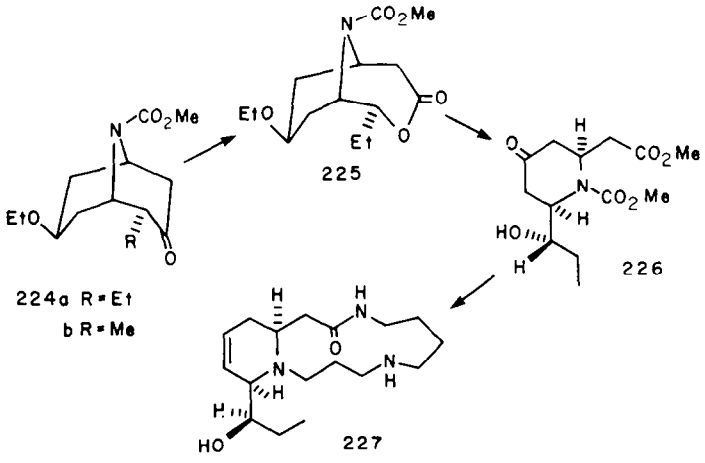
If there is an electrophilic olefinic bond at C-7, peracid reacts preferentially at the alkene. Thus, ketone 220 affords with MCPBA/CH_2Cl_2/TsOH the monoepoxide 221 in 75% yield,[93] while the endocyclic olefinic ketone 222 with monoperphthalic acid affords after epoxide formation, ring opening, and hemiacetal formation, the oxaadamantane 223.[94]

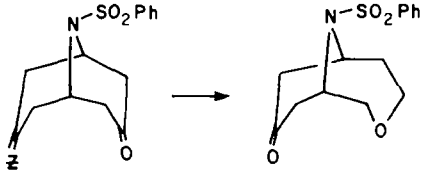


IV.B.2. Aza-analogs

In a synthetic approach[95] to the *cis*-2,6-disubstituted piperidine fragment palustramic acid 226, a component of palustrine 227, 9-azabicyclo[3.3.1]octan-3-one 224a was regioselectively and with site selectivity oxidized with MCPBA/MC to afford lactone 225 in 93–94% yield. Methanolysis of lactone 225 afforded erythro-*cis*-ester 226 containing the correct relative configuration of the asymmetric centers of palustrine 227 except with respect to the hydroxyl configuration.

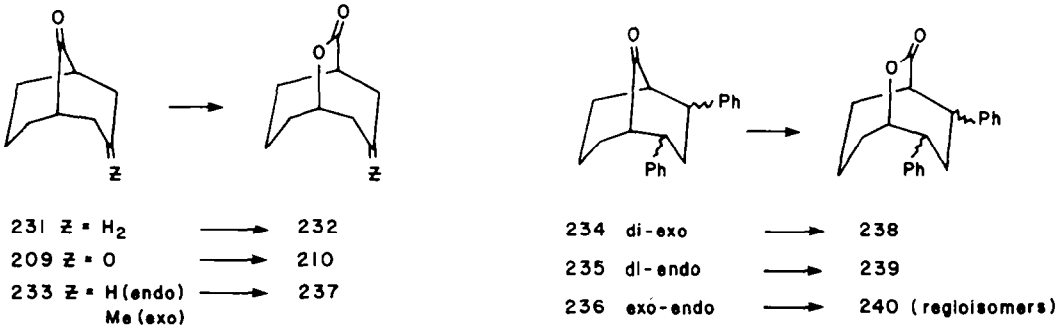
The methyl analog[95] 224b reacted similarly with MCPBA; however, the monoketone 228, ostensibly because of steric hindrance in the double chair conformation,[96,97] (see IV.A) was inactive toward peracid oxidation. The 9-N-benzenesulfonyl analog 229 afforded monolactone 230 with MCPBA/CH_2Cl_2 in 68% yield.[93,96]





IV.C. 9-Oxo-isomers

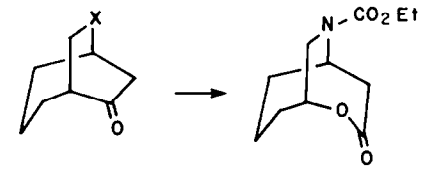
Baeyer–Villiger oxidation of bicyclo[3.3.1]nonan-9-one 231 is not blocked by steric hindrance to formation of the tetrahedral Criegee intermediate, which hindered oxidation of the 3-oxo-isomers. Because of ready access to a double chair conformation, bicyclo[3.3.1]nonan-9-one 231 can form the Criegee intermediate without undue steric difficulty and affords lactone 232 in 82% yield with 40% PAA/sodium acetate.[98] (Compare IV.B) A carbonyl functionality at C-3 is less reactive than that at C-9 and MCPBA oxidation of diketone 209 affords monolactone 210 in 89% yield.[73a] The bicyclo[3.3.1]non-9-one derivatives 233–236 have been oxidized by the following acids with yields of lactones 237–240 in parentheses: 233–237 with monoperphthalic acid[99] (85%), 234–238 with 40% PAA (100%),[100] 235–239 with 30% aq hydrogen peroxide/40% aq selenic acid[100] (90%), 236–240 with 40% PAA[100] (75% as a 62:38 mixture of regioisomers of unassigned structure).



V. BICYCLO[3.2.2]NONANONES

V.A. 6(8)-Oxo-isomers

Although Baeyer–Villiger oxidation of bicyclo[3.2.2]nonan-6-one 241 has not been reported, N-carbethoxy-6-azabicyclo[3.2.2]nonan-8-one 242 has been oxidized to bridgehead migrated lactone 243 with 40% PAA in 52% yield[11] (see II.A).



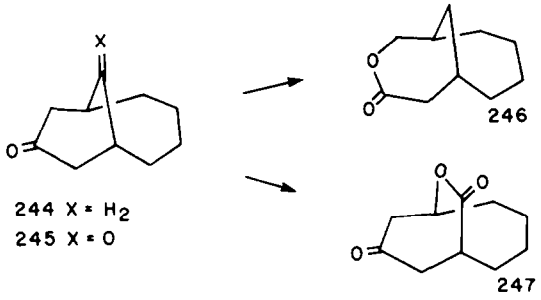
241 X = CH_2 243

242 X = NCO_2Et

VI. BICYCLO[4.3.1]DECANONES

VI.A. 8-Oxo-isomers

Bicyclo[4.3.1]decan-8-one 244 reacts slowly with MCPBA/CH_2Cl_2, but does afford lactone 246 in 78% yield after ten days.[73a] (see III.B, IV.B) The 8,10-dioxoderivative 245 undergoes oxygen insertion with positional selectivity with MCPBA/CH_2Cl_2 to afford solely lactone 247 in 85% yield.[73a]



244 X = H_2
245 X = O

246

247

VI.B. 10-Oxo-isomers

See VI.A, ketone 245.

CONCLUSION

Baeyer–Villiger rearrangements of bridged bicyclic ketones, in which migratory aptitide competition pits bridgehead against methylene carbon migration, generally occur with preferential bridgehead migration. However, the observed regioselectivity of Baeyer–Villiger oxygen insertions is dependent upon a subtle interplay between electronic and steric/torsional strain factors. Exceptions to the bridgehead migration preference have been noted, primarily when strongly electron withdrawing groups were attached to the carbon alpha to the migrating bond (orbital interactions may be important here) or, in the case of bicyclo[2.2.1]heptan-2-ones, when there were present 7-*syn* substituents which sterically hinder peracid attack from the *exo* direction.

An antiperiplanar stereoelectronic requirement for orbital alignment of hydroxyl oxygen lone pair electrons, the migrating bond, and the O–O bond broken during loss of the leaving group during rearrangement of a tetrahedral intermediate has been invoked, in combination with steric effects, to explain a series of regioselective oxygen insertions (III.B).

Where comparisons have been made, oxidations with peracetic acid result in greater regioselectivity than those of the stronger MCPBA (I.A.1.a, II.A.2). Steric hindrance to addition of peracid to carbonyl slows down oxidations of bicyclo[3.x.1]alkan-3-ones (x = 2, 3) by lowering the equilibrium concentration of the reactive Criegee intermediate. Elevation of reaction temperature, addition of radical scavengers, acid catalysis, and use of trifluoroperacetic acid has resulted in acceptable oxidation rates and product yields in several instances with sluggish substrates. Use of ceric ammonium nitrate and ceric ammonium sulfate as alternative oxidants to peracid reagents for oxygen insertion reactions needs to be explored further. When oxygen insertion adjacent to methylene is desired, conversion of the carbonyl group to an enol ether (enolization away from the bridgehead) and ozonolysis affords upon reductive workup a hydroxyacid equivalent of the Baeyer–Villiger methylene carbon migration product (I.A.1.a, Table 1).

Bridged bicyclic ketones offer the joint possibilities of stereochemical control both during their synthesis and in their functionalization reactions. Accordingly, it is expected that Baeyer–Villiger oxidations of bridged bicyclic ketones to afford lactones will see increasing utility as a methodology for effecting stereocontrolled syntheses.

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