Synthesis and Synthetic Utility of Halolactones

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1 Introduction

The conversion of β,γ- or γ,δ-unsaturated acids into iodolactones was first reported and developed by Bougault.[1-4] His favoured procedure was to dissolve the unsaturated acids in aqueous sodium bicarbonate, and treat the resultant solution with a solution of iodine in aqueous potassium iodide; the iodolactone would separate from the reaction medium. Illustrative reactions of iodolactonization are the conversion of γ,δ-pentenoic acid (1)[5,6] into the γ-iodolactone (2), and of cyclohex-1-en-1-ylacetic acid (3) into the γ-iodolactone (4).[5,7,8] The bromolactonization of unsaturated acids can be accomplished similarly and originates from the work of Fittig,[9,10] Stobbe,[11,12] and others.[13] There are

$CH_2{=}CHCH_2CH_2CO_2H$

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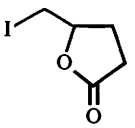

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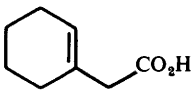

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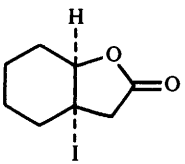

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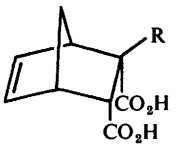
[1] M. J. Bougault, *Compt. rend.*, 1904, **139**, 864.
[2] M. J. Bougault, *Ann. Chim. Phys.*, 1908, **14**, 145.
[3] M. J. Bougault, *Ann. Chim. Phys.*, 1908, **15**, 296.
[4] M. J. Bougault, *Ann. Chim. Phys.*, 1911, **22**, 125.
[5] E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, 1954, **76**, 2315.
[6] M. de M. Campos and L. do Amaral, *Arch. Pharm.*, 1965, **298**, 92.
[7] J. Klein, *J. Amer. Chem. Soc.*, 1959, **81**, 3611.
[8] R. P. Linstead and C. J. May, *J. Chem. Soc.*, 1927, 2565.
[9] R. Fittig, *Annalen*, 1884, **226**, 366.
[10] R. Fittig and E. Hjelt, *Annalen*, 1883, **216**, 52; R. Fittig, *Annalen*, 1898, **304**, 222, 211; R. Fittig, *Annalen*, 1904, **331**, 142.
[11] H. Stobbe, *Annalen*, 1899, **308**, 77, 82.
[12] H. Stobbe, *Annalen*, 1902, **321**, 119.
[13] W. H. Perkin, jun. and A. E. Smith, *J. Chem. Soc.*, 1904, **85**, 155.

relatively few examples of the conversion of unsaturated acids into chlorolactones.[14–16]

2 Reagents and Reaction Conditions

The standard procedure in most common use for iodolactonization is still that of Bougault reported above. However, as an alternative to aqueous media, a variety of organic solvents (particularly chloroform[6,11,14,17–19] and carbon tetrachloride[1,14,20]) have been successfully used in specific cases. Reactions have also been carried out in two phase solvent systems (*e.g.* methylene chloride–water,[21] carbon tetrachloride–water[21,22]), solvent mixtures (*e.g.* aqueous tetrahydrofuran[23] and aqueous methanol[16]) as well as in the absence of any solvent.[17] Although aqueous media are usually preferred for iodolactonizations, organic solvents are customarily employed for chloro- and bromolactonization. In solvents of low dielectric constant, halolactonization often does not occur satisfactorily due to competition with the formation of dihalo acids[24] resulting from the addition of halogen to the double bond of the unsaturated acid. In aqueous media an excess of base is usually undesirable and may need to be neutralized prior to the addition of halogen.[25–27] Bougault[3] showed that an increasing excess of sodium carbonate led to a diminution in the yields of iodolactones, often to virtually nothing, and encouraged the formation of alternative products. In a study of the bromolactonization of the norbornene dicarboxylic acids (5; R = Me), where two different product lactones (6 and 7) were possible, Ranganathan[28] found that the structure of the particular lactone



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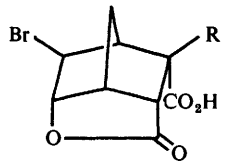

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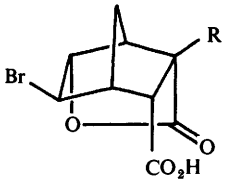

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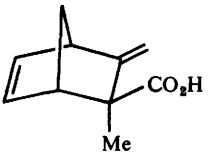
[14] G. Berti, *Gazzetta*, 1951, **81**, 305.
[15] G. Berti, *Tetrahedron*, 1958, **4**, 393.
[16] W. Reppe, O. Schlichling, K. Klager, and T. Toepel, *Annalen*, 1948, **560**, 1.
[17] R. T. Arnold, M. de M. Campos, and K. L. Lindsay, *J. Amer. Chem. Soc.*, 1953, **75**, 1044; M. de M. Campos, *J. Amer. Chem. Soc.*, 1954, **76**, 4480; M. de M. Campos, *An. Acad. Brazil Ci.*, 1955, **27**, 405.
[18] R. T. Arnold and K. L. Lindsay, *J. Amer. Chem. Soc.*, 1953, **75**, 1048.
[19] G. Berti, A. Marsili, P. Luigi, and M. Pacini, *Ann. Chim. (Rome)*, 1962, **62**, 1070.
[20] L. Alder and W. Günzl, *Chem. Ber.*, 1960, **93**, 809.
[21] W. E. Barnett and J. C. McKenna, *Tetrahedron Letters*, 1971, 2595.
[22] E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 1956, 4073.
[23] E. J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Letters*, 1977, 1625.
[24] See references 15, 42, and 43.
[25] E. Grovenstein, jun., D. V. Rao, and J. W. Taylor, *J. Amer. Chem. Soc.*, 1961, **83**, 1705.
[26] E. L. Cooper and E. W. Yankee, *J. Amer. Chem. Soc.*, 1974, **96**, 5876.
[27] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[28] S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Tetrahedron*, 1977, **33**, 807.

formed was dependent on the pH of the reaction medium. On reaction of (5) with bromine in aqueous solution at pH 3, the preferred course of reaction involved the more highly substituted carboxyl function to give (7; R = Me) as product; in contrast, the reaction with bromine in aqueous sodium bicarbonate at pH 8, proceeded with the least substituted carboxyl function to give (6; R = Me) as the product.

Reaction temperatures that have been used in halolactonization reactions vary considerably (0—80 °C) as do reaction times (several minutes to 48 h). Changes in reaction time may result in different isomeric lactones being formed.

Although most of the earlier experimental work suggested that β,γ-unsaturated acids gave β-halo-γ-lactones, more recent work, particularly by Barnett[29] has provided a number of examples of β-lactone formation. Bromolactonization of the acids (8) and (10) led respectively to the bromo-β-lactones (9) and (11; X = Br). In contrast the iodolactonization of (10) under standard conditions gave the iodo-γ-lactone (12). The different results were attributed to the differing



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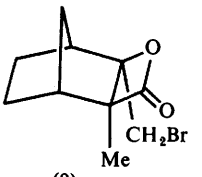

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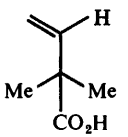

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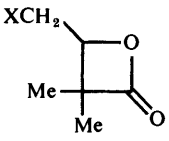

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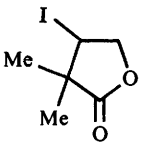


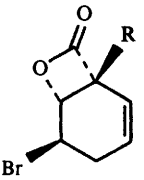
(12)

reaction procedures used for the bromo- and iodo-lactonization rather than to differences in the reactivity of the halogens. When iodolactonization of (10) was conducted under conditions comparable to those for bromolactonization (*i.e.* leaving out potassium iodide and adding an ethereal solution of iodine), iodo-β-lactone (11; X = I) was obtained. A careful examination of the reaction of (10) under standard iodo-lactonization conditions showed that after 15 min the iodo-β-lactone (11; X = I) was formed, but after 24 h in the reaction medium it had been completely converted into the iodo-γ-lactone (12). Thus (11) is the kinetically favoured and (12) the thermodynamically favoured product. Consistent with these observations Ganem[30] found that bromo-β-lactones (13)

[29] W. E. Barnett and W. H. Sohn, *Chem. Comm.*, 1972, 472; W. E. Barnett and W. H. Sohn, *Tetrahedron Letters*, 1972, 1777.

[30] G. W. Holbert, L. B. Weiss, and B. Ganem, *Tetrahedron Letters*, 1976, 4435.

when heated at 130 °C underwent concomitant 1,2-bromine migration and lactone ring expansion into the presumed thermodynamically more stable γ-isomer (**14**).



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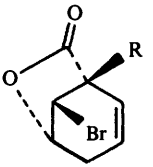


(14)

R = Me,CH_2OH

A convenient procedure for iodolactonization under neutral conditions was developed by Cambie[31] in which iodine is added to an unsaturated thallium (I) carboxylate in ether at 20 °C. The products are predominantly those of kinetic control.

Light may affect halolactonization reactions, and reported conditions for bromo- and in particular iodo-lactonization, often specify that the reaction should be performed in the dark. Product iodolactones are likely to be light-sensitive, and in certain cases may be photolysed to afford mixtures of products. This is particularly true for iodolactones in the norbornane series.[32]

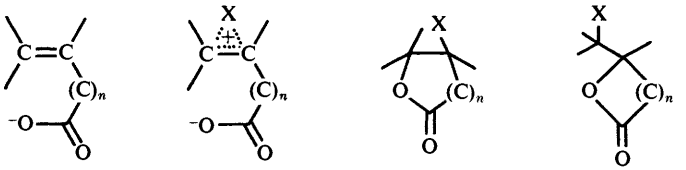
In the Cristol Firth modification of the Hunsdiecker reaction,[33] a carboxylic acid is converted into an organic halide on treatment with halogen and red mercuric oxide. This procedure has been successfully applied, particularly in norbornene[34,35] and steroid systems,[33] for the conversion of unsaturated acids into halolactones. A possible forerunner of this procedure was the demonstration by Bougault[1] that certain β,γ- and γ,δ-unsaturated acids could be converted into iodolactones when treated with iodine and yellow mercuric oxide in wet ether.[3] Successful halolactonizations have also been carried out using, as the halogen source, sodium hypobromite,[36,37] acetyl hypobromite,[17] cyanogen iodide,[18] iodine azide,[38] and *N*-bromosuccinimide.[39]

3 Mechanism and Stereochemistry

Bougault believed that iodine in aqueous sodium carbonate led to the formation

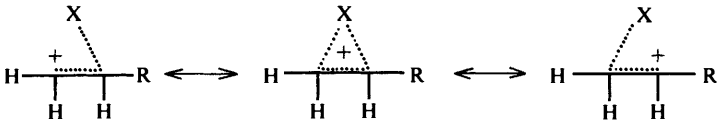
[31] R. C. Cambie, R. C. Hayward, J. L. Roberts, and P. L. Rutledge, *J. C. S. Perkin I*, 1974, 1864.
[32] P. J. Kropp, T. H. Jones, and G. S. Poindexter, *J. Amer. Chem. Soc.*, 1973, **95**, 5420.
[33] C. V. Wilson, *Org. Reactions*, 1957, **9**, 332; R. G. Johnson and R. K. Ingham, *Chem. Rev.*, 1956, **56**, 219.
[34] A. J. Solo and B. Singh, *J. Org. Chem.*, 1967, **32**, 567.
[35] D. I. Davies and P. Mason, *J. Chem. Soc.* (*C*), 1971, 288; D. I. Davies, P. Mason, and M. J. Parrott, *J. Chem. Soc.* (*C*), 1971, 3428.
[36] K. Alder, F. W. Chambers, and W. Trimborn, *Annalen*, 1950, **566**, 27.
[37] K. Alder and R. Ruhman, *Annalen*, 1950, **566**, 1.
[38] G. Mehta, P. K. Dutta, and P. N. Pandey, *Tetrahedron Letters*, 1975, 445.
[39] J. F. McQuillan, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 1964, 5526.

of nascent hypoiodous acid, which was then thought to add to the double bond of an unsaturated acid. The resultant iodo-hydrin was then believed to lactonize. Studies by Linstead and May,[8] and by Tarbell and Bartlett[40] disproved this halo-hydrin mechanism and led to the currently accepted mechanistic scheme of van Tamelen and Shamma.[5] Attack by positive halogen on the double bond of the unsaturated acid (15) affords an halonium ion (16) which then undergoes intramolecular displacement by the carboxylate anion to give one of the two possible halolactone products (17) and (18). The position of attack on the



(15) (16) (17) (18)

halonium ion in (16) by the carboxylate anion would appear to be controlled by electronic and stereochemical factors. For example γ,δ-unsaturated acids (15; $n = 2$), which could in principle afford either a γ-lactone (18; $n = 2$) or a δ-lactone (17; $n = 2$), have a preference for cyclization leading to the former. The low reactivity of vinylacetic acid $CH_2{=}CH{\cdot}CH_2CO_2H$ to halolactonization was taken by van Tamelen and Shamma[5] as support for an intermediate halonium ion (20) rather than an open carbonium ion (19) or (21). Of the two possible canonical forms (19) and (21), that (19) which could lead to the expected γ-

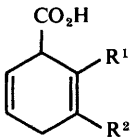


(19) (20) (21)

$R = CH_2CO_2^-$

lactone formation is a primary carbonium ion and would therefore contribute minimally to the hybrid—(generally successful cases involve a secondary carbonium ion either γ- or δ- to the carboxyl function), although Barnett and coworkers demonstrated that halo-β-lactones may be obtained from vinylacetic acid and its α-substituted analogues (*e.g.* 10→11)[21,29] in processes which could involve halonium ions β- to the carboxyl function. Barnett and Needham[41] have recently reported that the effect which methyl substituents have in directing the mode of bromolactonization of the 1,4-dihydrobenzoic acids (22) and (23) to give lactones (24, 25) and (26, 27) respectively demonstrates that the intermedi-

[40] D. S. Tarbell and P. D. Bartlett, *J. Amer. Chem. Soc.*, 1937, **59**, 407.
[41] W. E. Barnett and L. L. Needham, *J. Org. Chem.*, 1975, **40**, 2843.



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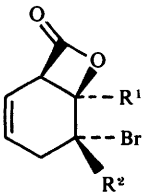

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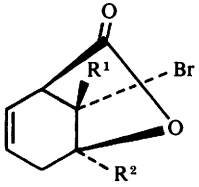

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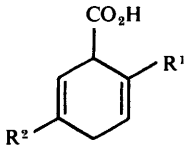

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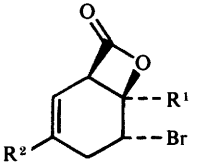

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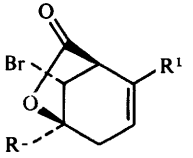


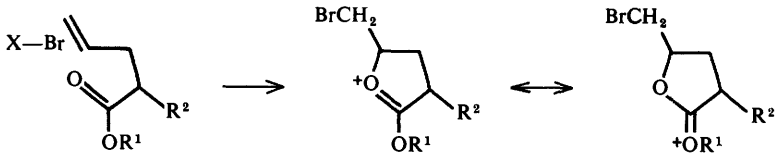
(27)

ate bromonium ions have greater degrees of carbonium ion character at the more substituted carbon atoms. Thus in the presence of γ-alkyl substituents [R^2 = Me in (22) and (23)], or with the β- substituent R^1 as $-$Me or $-$H, γ-lactone formation (26) and (27) predominates, whilst in the absence of γ-alkyl substituents [R^2 = H in (22) and (23)] and for dihydrobenzoic acid itself [R^1 = R^2 = H in (22) or (23)] β-lactone formation (24) and (25) occurs.

The presence of substituents on a saturated carbon atom α- to the carbonyl function appears to promote halolactonization. For example pent-3-enoic acid[42] and pent-4-enoic acid[43] react with bromine to give dibromides whereas 2,2-dimethylpent-3-enoic acid[15] and 2,2-dimethyl- and 2,2-diphenyl-pent-4-enoic acids[15] afford, under similar conditions, bromo-γ-lactones. The α-substituent(s) would appear to have a buttressing effect, which brings the cationic intermediate and carboxyl function into a sufficiently close proximity for them to enter into a transition state for lactonization, and prevent scavenging of the cation by halogen. This effect of α-substituents is particularly pronounced in the iodolactonization of vinylacetic acids.[29]

In non-polar organic solvents, in which little if any carboxylate anion is present, it is probable that oxonium species (29) are involved as proposed by Campos[17] for the bromolactonization of γ,δ-unsaturated acids (or their esters) (28) using bromine or acetyl hypobromite. This was elaborated by Amaral and Melo[44] for the iodolactonization of γ,δ-unsaturated acids using two mole proportions of iodine in chloroform solution. They proposed the initial fast formation of a complex (30) between the first mole of iodine and the double

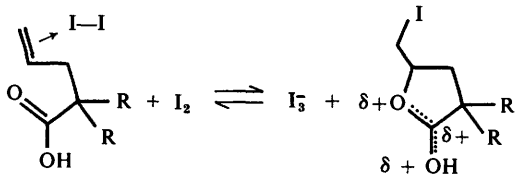
[42] R. Fittig and J. E. Mackenzie, *Annalen*, 1894, **283**, 47.
[43] R. Fittig and A. Messerschmidt, *Annalen*, 1881, **208**, 92.
[44] L. do Amaral and S. C. Melo, *J. Org. Chem.*, 1973, **38**, 800.



(28) (29)

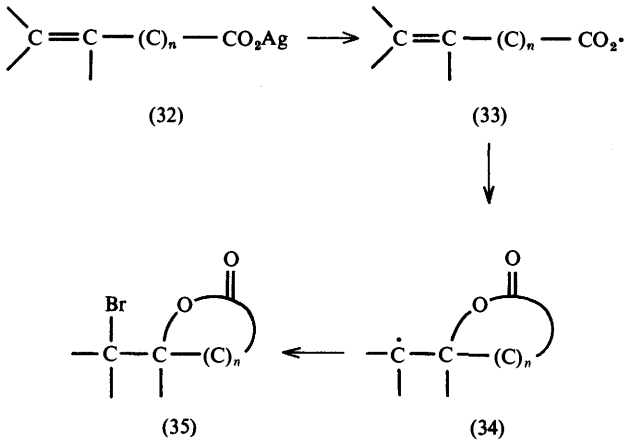
X= Br or OAc; R^1 and R^2= alkyl or H

bond, which cyclized to the oxonium species (31). The second mole of iodine was thought to help disperse the incipient negative charge involved in cyclization by forming a mole of tri-iodide ion. The yield of iodolactone is reduced to a maximum of only 50% if equimolar quantities of reactants are used.



(30) (31)

Halolactonization reactions carried out under the conditions of the Hunsdiecker[45] and Cristol Firth[34,35] reactions undoubtedly proceed through radical processes. Taking the Hunsdiecker reaction as an example, the carboxyl radical (33), obtained from the silver carboxylate (32) and bromine, adds to the double

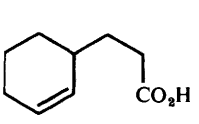


(32) (33) (35) (34)

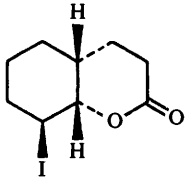
[45] P. Wilder, jun. and A. Winston, *J. Amer. Chem. Soc.*, 1955, **77**, 5598.

bond affording the new radical (34), which can abstract a bromine atom from a molecule of bromine to afford the bromolactone (35).

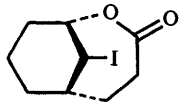
Halolactonization generally proceeds to preferentially afford *cis*-fused lactones, even though other modes of reaction do not appear to be prohibited on steric grounds.[46] For example cyclohexenylpropionic acid (36) affords a single *cis*-fused iodolactone (37) and none of either the alternative *cis*-fused lactone (38) or *trans*-fused lactone (39). The relatively slow rate of exchange of iodine, which



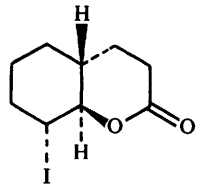
(36)



(37)



(38)



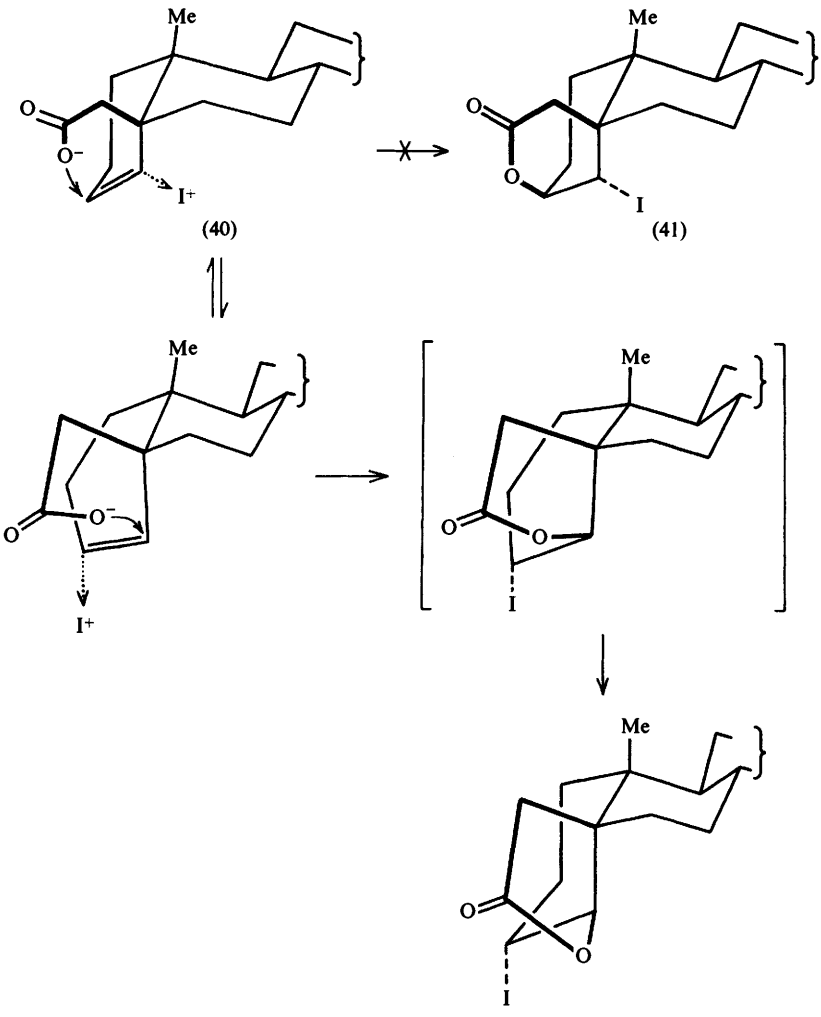
(39)

was observed in the exchange reaction between the iodolactone (4), derived from cyclohex-1-en-1-ylacetic acid (3) and radioactive sodium iodide, compared with the rate of iodolactonization of (3), was taken to indicate that the *cis*-fused lactone (4) was the thermodynamic and kinetic product and was not formed through isomerization of the unreported isomeric *trans*-lactone.[7]

Halolactonization conforms to the general *trans* diaxial pattern observed for other ionic additions to flexible cyclohexene systems.[47] An example, where *trans*-coplanar addition to the double bond occurs, is in the iodolactonization of Δ^3-5β-cholestenylacetic acid (40).[48] A pathway involving the quasi-chair conformation of ring A, which is observed ordinarily in additions to the double bond[49] could not have been involved in the formation of product lactone (42). If it had, formation of the alternative γ-iodo-δ-lactone (41) would have occurred instead. It was suggested[48] that, from an examination of molecular models, the severe steric hindrance to the formation of an axial α-side iodonium ion on ring A is considerably relieved if attack occurs at C-3 with ring A in a quasi-boat conformation. Such behaviour would lead, by *trans*-coplanar addition, to the formation of the observed δ-iodo-γ-lactone (42).

Returning to the iodonium ion intermediate (16) in iodolactonization, if the iodonium ion is not rapidly captured by the carboxylate ion centre then a faster rearrangement may occur. Such rearrangements occur most commonly with the carboxylic acid derivatives (43) of norbornene in which, in addition to the expected lactones (45) from intermediate (44), lactones of types (46) and

[46] H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, 1963, **28**, 3359.
[47] D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 1956, **10**, 44.
[48] A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, 1961, **83**, 198.
[49] G. H. Alt and D. H. R. Barton, *J. Chem Soc.*, 1954, 4284; D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem Soc.*, 1957, 2907.

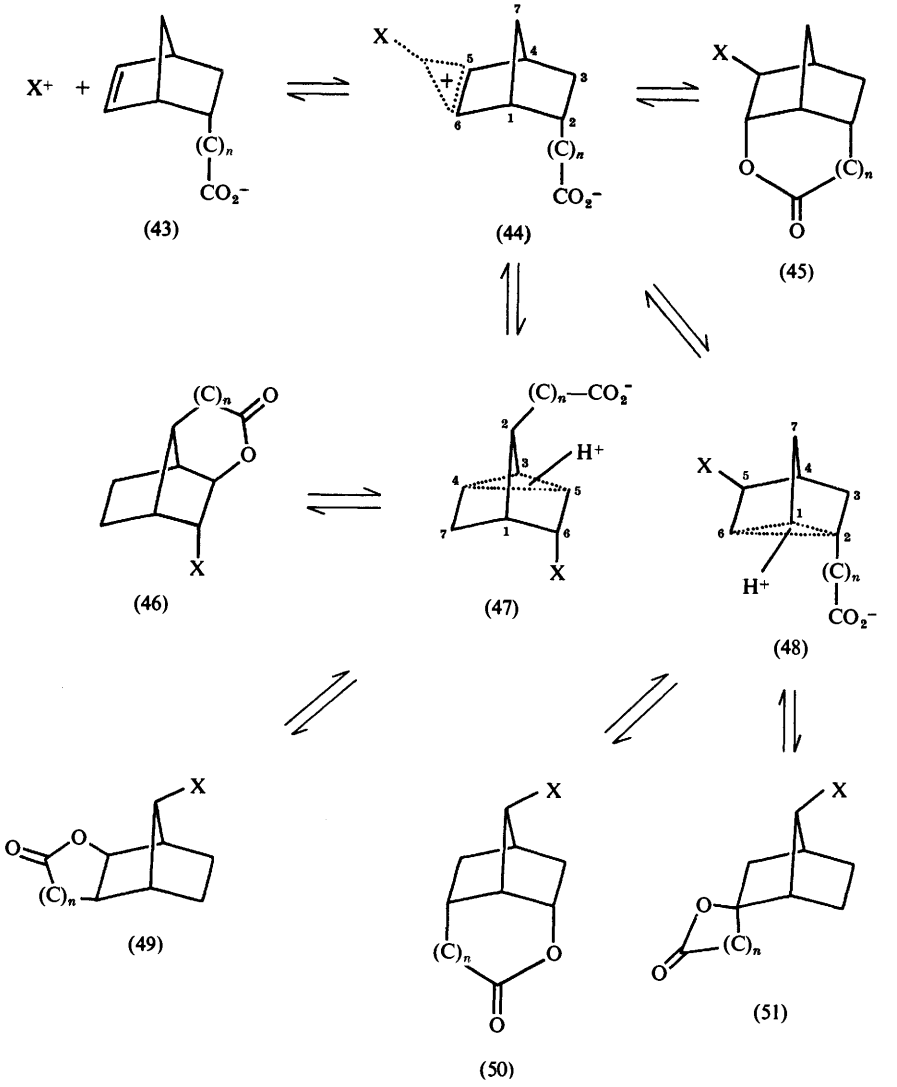


(49)—(51) have all been obtained as a consequence of the rearrangement of (37) to the norbornyl cations (47) and (48).[50–52]

[50] K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal, and H. G. Welsh, *J. Amer. Chem. Soc.*, 1967, **89**, 2401.

[51] C. D. Ver Nooy and C. S. Rondestvedt, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 3583; J. A. Berson and R. Swidler, *J. Amer. Chem. Soc.*, 1953, **75**, 1721; G. W. Oxer and D. Wege, *Tetrahedron Letters*, 1969, 3513; G. E. Risinger, L. L. Green, and E. E. Green, *Chem. and Ind.*, 1969, 298; D. N. Ford, W. Kitching, and P. R. Wells, *Austral. J. Chem.*, 1969, **22**, 1157; E. Crundwell, P. S. Farmer, and W. M. Kofi-Tsekpo, *Chem. and Ind.*, 1969, 1514; R. M. Moriarty, H. Gopal, H. G. Welsh, K. C. Ramey, and D. C. Lini, *Tetrahedron Letters*, 1966, 4555.

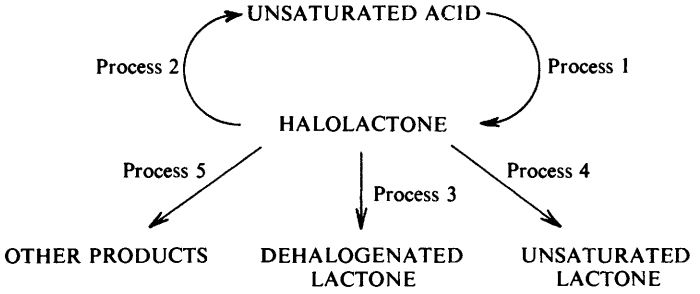
[52] J. A. Berson and D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, 1959, **81**, 4083.



4 Uses and Synthetic Applications of Halolactonization

Scheme 1 illustrates the uses of halolactonization and its application as a synthetic tool in organic chemistry.

Process 1 (halolactonization).—Halolactonization has, in certain cases, proved to be of value in determining the structure and stereochemistry of complex molecules. It has also proved useful as a means of separating mixtures of isomeric



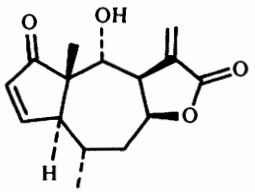
Scheme 1

unsaturated acids. Bougault[2] found that when a solution of iodine in aqueous potassium iodide was added to solutions of unsaturated acids in sodium bicarbonate, α,β-unsaturated acids were, in many cases, apparently unchanged, whereas β,γ-unsaturated acids reacted to give β-iodo-γ-lactones. Ponzio and Gastaldi,[53] however, suggested that α,β-unsaturated acids also react, but extremely slowly, under these conditions. Even so the difference in reactivity was sufficient for Bougault to suggest that iodolactonization could be used for the separation and analytical estimation of unsaturated acid isomers. However it was not totally successful and not really applicable for quantitative analysis. Later Linstead and May[8] re-examined the work of Bougault and his contemporaries and developed an improved iodometric procedure which they claimed was applicable to the quantitative estimation of mixtures of isomeric unsaturated acids.

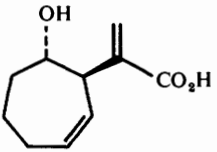
In the infra red the position of the lactone carbonyl absorption is a function of ring size, γ-lactones having a carbonyl absorption near 1770 cm^{-1} and δ-lactones near 1740 cm^{-1}. This has led to the use of iodolactonization, in conjunction with the infrared analysis of products, as a means for determining the position of unsaturation in unsaturated acids. In synthetic studies[54] directed towards the formation of the *trans*-hydroxy-*cis*-α-methylenebutyrolactone system found in natural anti-tumour agents [*e.g.* helenalin (52)], the hydroxy acids (53) and (55) were converted to their corresponding iodolactones (54) and (56).[47] In the n.m.r. spectra of (54) and (56) the coupling constants and chemical shifts of the methine protons were used to define the structures of (54) and (56), and to show that they had the *cis*-lactone stereochemistry as in (52).

t-Butyl cyanoketene reacts with norbornadiene to give two 1:1-adducts, which are separable by chromatography.[55] Evidence for the structure (57) of the major addition product was obtained by hydrolysis to afford the *exo*-acid (58a), which did not undergo iodolactonization. However methylation of this acid (58a), epimerization of the resultant ester (58b) with base, and hydrolysis gave the epimeric acid (58c), which readily gave the iodolactone (59). The 7-*exo*-

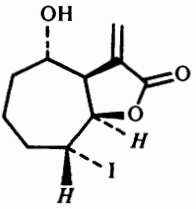
[53] G. Ponzio and C. Gastaldi, *Gazzetta*, 1912, **42**, 92.
[54] J. P. Marino and J. S. Farina, *J. Org. Chem.*, 1976, **41**, 3213.
[55] P. R. Brook and J. M. Harrison, *Chem. Comm.*, 1972, 997.



(52)



(53)



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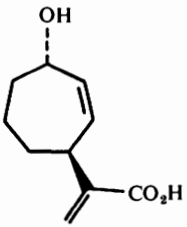

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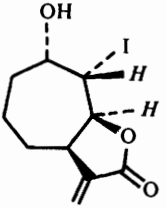
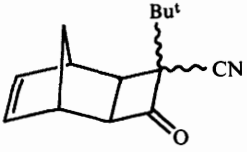
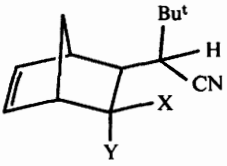


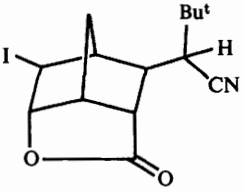
(56)



(57)



(58) a; X = CO_2H, Y = H
b; X = CO_2Me, Y = H
c; X = H, Y = CO_2H.

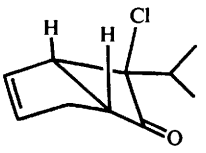


(59)

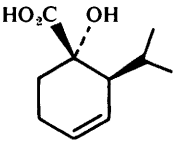
chloro adduct (60) of chloroisopropylketene and cyclopentadiene behaves anomalously with sodium hydroxide, and instead of undergoing the expected ring contraction is slowly converted into the three hydroxy acids (61)—(63).[56] The relative stereochemistry of the three acids at C-1 and C-2 was demonstrated by iodolactonization. Acid (61) rapidly afforded an iodolactone (64) whereas (62) and (63) gave only partial reaction after 24 h.

Tetrachloropropene (65) can be almost quantitatively transformed into a single monomeric trichloroallenyl-lithium.[57] The proof of structure involved carboxylation to afford (66) which gave the acid (67) in the Diels–Alder reaction with cyclopentadiene; (67) was then converted into the iodolactone (68). Halolactonization has been particularly useful in determining the structure and stereochemistry of many other Diels–Alder adducts of unsaturated acids with cyclopentadiene.[58] This is particularly applicable for the iodolactonization of

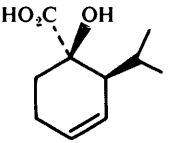
[56] P. R. Brook and J. M. Harrison, *J.C.S. Chem. Comm.*, 1974, 284.
[57] G. Köbrich and E. Wagner, *Angew. Chem. Internat. Edn.*, 1968, **7**, 470.
[58] S. Beckmann, *Bull. Soc. chim. France*, 1960, 1319.



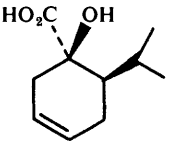
(60)



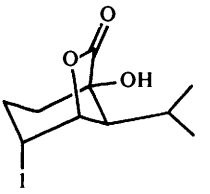
(61)



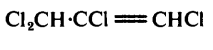
(62)



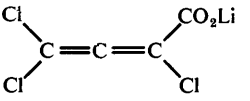
(63)



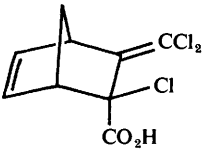
(64)



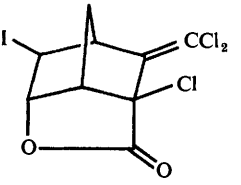
(65)



(66)



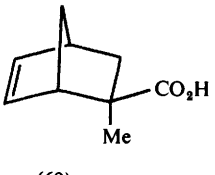
(67)



(68)

norbornene carboxylic acid derivatives. The application of the analogous acid catalysed lactonization to structure determination is fraught with difficulty due to the ease of rearrangement of intermediate norbornyl cations. For example the epimeric cyclopentadiene methacryclic acid adducts (69) and (70) on acid catalysed lactonization both give the same lactonic product (71).[59] Iodolactonization was however more discriminating, the *endo* isomer (70) affording iodolactone (72), and the *exo* isomer (69) being recovered unchanged. Bromolactonization was less useful since although the *endo* acid (70) was converted to the bromolactone analogue of (72) the *exo* acid (69) afforded a bromohydrin by addition of hypobromous acid to the double bond. The greater reactivity of norbornene *exo* carboxylic acids towards bromine compared with iodine, as evidenced by the above example, hindered attempts to determine, by bromolactonization, the

[59] J. S. Meek and W. B. Trapp, *J. Amer. Chem. Soc.*, 1957, **79**, 3909.



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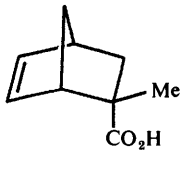

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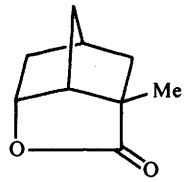

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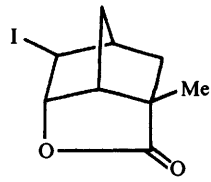
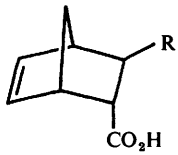
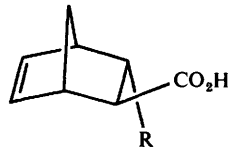


(72)

proportions of adducts (73a) and (74a) formed in the Diels–Alder addition of cinnamic acid derivatives to cylopentadiene.[60] Although the adduct (73a) with the *endo* carboxyl group gave a bromolactone, the isomeric adduct (74a) with



(73) a; R = Ar
b; R = Me

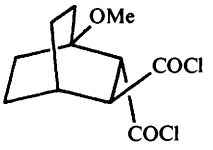


(74) a; R = Ar
b; R = Me

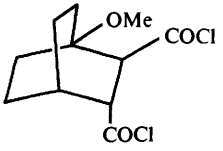
exo carboxyl did not remain unchanged and afforded mixtures of acidic bromination products; nortricyclene derivatives and bromolactones formed as a result of structural rearrangement. Iodolactonization of isomeric mixtures gave a quantitative conversion of (73a) to an iodolactone whereas the *exo* isomer (74a) proved to be inert thus enabling the proportions of (73a) and (74a) to be determined, as well as the separation and structure determination of (73a) and (74a). Despite the expeditious use of iodolactonization as the preferred method of isomer separation and isomer ratio determination of norbornene carboxylic acids, caution must be exercised in its use. In some detailed work on the thermal isomerization of optically pure methyl 2-*endo*-methylnorborn-5-en-2-*exo*-ylcarboxylate[61] it was necessary to separate mixtures of the epimeric acids (69) and (70). The *exo* isomer was observed not to be completely unreactive towards iodolactonization as had been anticipated, and gave a small amount of neutral material which hindered separation and led to anomalous optical rotations. In the case of the adducts of *trans*-crotonic acid with cyclopentadiene, the adduct (73b) with *endo* carboxyl readily affords an iodolactone, whereas the adduct (74b) with the *exo* carboxyl function gave an iodohydrin.[62] In spite of its drawbacks bromolactonization has nevertheless been successfully utilized in the determination of the structure of the benzene maleic anhydride photochemical adduct (for which eight structures were possible),[25] the stereochemistry of the

[60] C. S. Rondestvedt, jun. and C. D. Ver Nooy, *J. Amer. Chem. Soc.*, 1955, **77**, 4878.
[61] J. A. Berson and A. Remanick, *J. Amer. Chem. Soc.*, 1961, **83**, 4947.
[62] A. Beckmann and R. Mezger, *Chem. Ber.*, 1957, **90**, 1559.

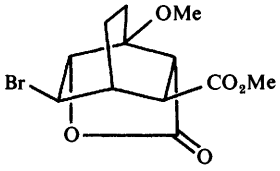
adducts of cyclopentadiene with *trans*-β-benzoylacrylic acids[63] and with phenylmaleic anhydride;[63] also the cycloheptatriene carboxylic acid adduct with maleic acid.[64] In a study of the regioselectivity of the Diels–Alder reaction, Fleming and co-workers[65] needed to determine the structures of the two adducts (75) and (76) that are formed in the reaction between 1-methoxycyclohexa-1,3-diene and fumaroyl chloride. This was accomplished by separating their derived dimethyl esters and then converting each to the bromolactones (77) and (78), which could be identified from their definitive spectra.



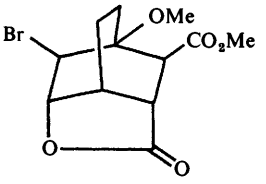
(75)



(76)

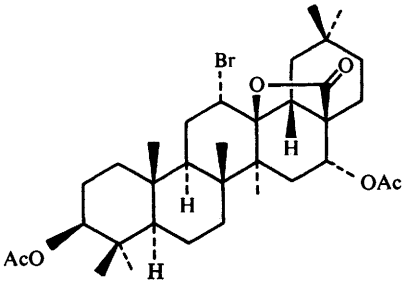


(77)



(78)

The *X*-ray structure[66] of the colourless monoclinic spheroidal crystals of the natural diacetylechinocystic acid bromolactone (79)[66,67] was recently deter-

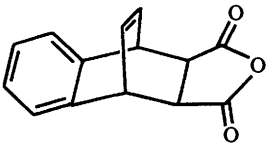


(79)

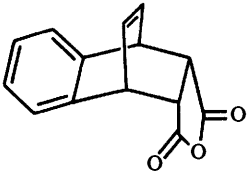
[63] F. Winternitz, M. Mousseron, and G. Rouzier, *Bull. Soc. chim. France*, 1955, 170.
[64] K. Alder, H. Jungen, and K. Rust, *Annalen*, 1957, **602**, 94.
[65] I. Fleming, J. P. Michael, L. E. Overman, and G. F. Taylor, *Tetrahedron Letters*, 1978, 1313.
[66] C. H. Carlisle, P. F. Lindley, A. Perales, R. B. Boar, J. F. McGhie, and D. H. R. Barton, *J.C.S. Chem. Comm.*, 1974, 284.
[67] W. R. White and C. R. Noller, *J. Amer. Chem. Soc.*, 1939, **61**, 938.

mined, and established unequivocally that the previously accepted structures for echinocystic acid and related compounds were correct. This illustrates the potential value of halolactones in structure determination by *X*-ray analysis.

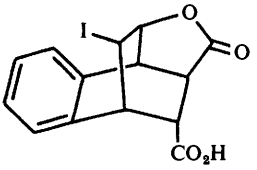
Process 2 (Regeneration of Unsaturated Acids from Halolactones).—Having separated a mixture of isomeric unsaturated acids by converting one to an iodolactone, the other being unreactive or at least incapable of forming a neutral product, it is then often necessary to convert the iodolactone back to an unsaturated acid. This procedure of unsaturated acid→iodolactone→unsaturated acid has proved invaluable in the preparation of isomerically pure materials for use in organic synthesis. The unsaturated acid is customarily regenerated using zinc in acetic acid,[60] although zinc–hydrochloric acid–acetic acid[7] and zinc in ethanol[68] have also been used. The Diels–Alder reaction between naphthalene and maleic anhydride affords two adducts, one of which is (80). Subjecting the second isomer to iodolactonization revealed that it was a 1:1-mixture of (80) and an isomeric adduct (81). Adduct (80) could be regenerated from the iodolactone (82) by reduction in acetic acid.[69] Other examples of the regeneration of



(80)



(81)



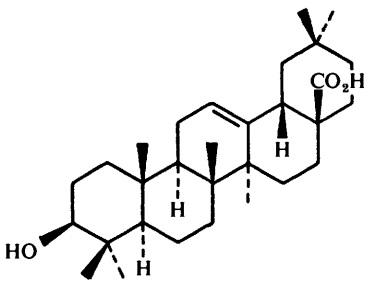
(82)

isomerically pure unsaturated acids from iodolactones include adducts of cyclopentadiene with acrylic,[20,70] vinylacetic,[71] α- and β-methyl or phenyl substituted acrylic[72] acids, β,β-dimethylacrylic acid,[73] and α,β-dimethylacryclic acid (tiglic acid).[74]

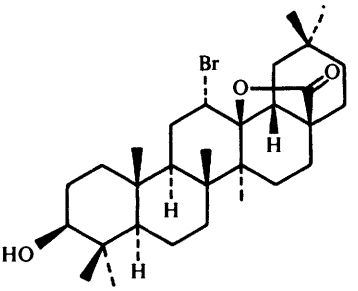
The formation of iodolactones can be useful in the separation of naturally-occurring unsaturated acids from other materials in plant extracts. For example oleanolic acid (83), a triterpene carboxylic acid constituent of mistletoe was purified by conversion to a bromolactone (84) from which it was subsequently regenerated on treatment with amalgamated zinc.[75]

Synthetic studies are often complicated by the production of isomeric species which are difficult to separate by normal physical or chemical methods. However in certain instances iodolactonization has proved to be of value. During the

[68] P. J. Garratt and J. F. White, *J. Org. Chem.*, 1977, **42**, 1733.
[69] K. Takeda, K. Kitahonoki, M. Sugiura, and Y. Takamo, *Chem. Ber.*, 1962, **95**, 2344.
[70] S. Beckman and H. Geiger, *Chem. Ber.*, 1961, **94**, 48.
[71] D. I. Davies and M. D. Dowle, *J.C.S. Perkin I*, 1978, 227.
[72] S. Beckmann, H. Geiger, and M. Schaber-Kiechle, *Chem. Ber.*, 1959, **92**, 2419.
[73] K. Alder and W. Roth, *Chem. Ber.*, 1957, **90**, 1830.
[74] S. Beckmann and H. Geiger, *Chem. Ber.*, 1959, **92**, 2411.
[75] A. Winterstein and W. Hammerle, *Z. Physiol. Chem.*, 1931, **199**, 56.

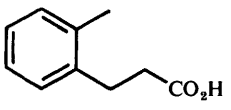


(83)

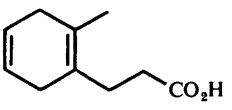


(84)

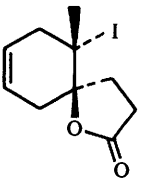
development of synthons for epoxyolefin cyclization,[76] the propionic acid (85) was subjected to Birch reduction. In addition to the required dihydro compound (86), varying proportions of the starting material (85) and a tetrahydro product were present in the product mixture. The dihydro compound (86) could be completely separated by converting it into the neutral iodospirolactone (87).



(85)

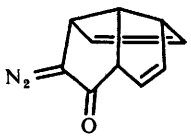


(86)

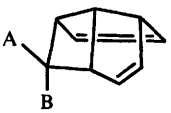


(87)

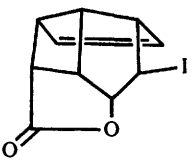
Unfortunately during the regeneration of (86) from (87) approximately 5% of (85) was also produced by aromatization of (86) under the reaction conditions. Photolysis of the α-diazoketone (88) gave a mixture of the epimeric carboxylic acids (89a) and (89b).[77] By subjecting the mixture to iodolactonization only (89a) formed an iodolactone (90), and this could be readily separated from the unreacted acid (89b). Reduction of the iodolactone (90) with zinc and



(88)



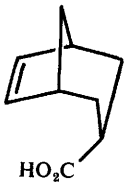
(89) a; A = H, B = CO_2H
b; A = CO_2H, B = H



(90)

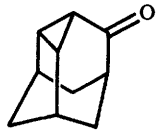
[76] D. Johnson, J. W. Smart, and J. K. Sutherland, *Chem. Comm.*, 1977, 497.
[77] L. A. Paquette, H. C. Berk, C. R. Degenhardt, and G. D. Ewing, *J. Amer. Chem. Soc.*, 1977, **99**, 4764.

acetic acid gave back the acid (89a). 3-*endo*-Carboxybicyclo[3,2,1]oct-6-ene (91) has been utilized in the synthesis of [3]-peristylene (triaxane) (92)[68] and 8,9-dehydroadamantan-2-one (93).[78] The acid (91) was prepared as a mixture, with its



(91)

(92)



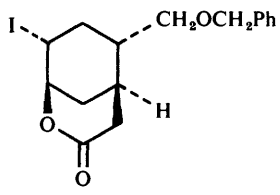
(93)

3-*exo* isomer, which could not be separated by preparative gas chromatography or preparative thin layer chromatography.[78] However the pure *endo* acid (91) could be obtained[68] by reduction (zinc–ethanol) of the iodolactone which had been separated from the unreacted *exo* isomer of acid (91). Similar operations (zinc–acetic acid) on mixtures of isomeric acids have been carried out during syntheses of teresantalol,[79] optically pure norbornene carboxylic acids[52] and [4,4,1]propell-3-enyl-*syn*- and *anti*-11-carboxylic acids.[80]

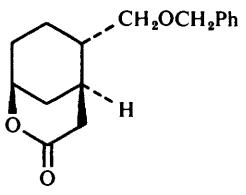
The ease with which unsaturated acids may be converted into halolactones, and the unsaturated acid subsequently regenerated from the halolactone, suggests that halolactonization has potential as a method for the protection of unsaturated acids.

Process 3 (Dehalogenation of Halolactones).—The reduction of halolactones to the corresponding dehalogenated lactone is a process of particular use in synthesis. In the first total synthesis of vitamin D_2 and an alternative synthesis of vitamin D_3, the iodolactone (94) was deiodinated to the lactone (95) as an essential stage of the synthesis.[81] Similarly deiodination of iodolactone (96), in a procedure involving hydrogen gas at 275 kN m^{-2}, a platinum catalyst and triethylamine–ethyl acetate as solvent, gave lactone (97) an important intermediate required for the synthesis of tricyclo[4,4,0,$0^{3,8}$]decane (twistane).[82] As part of structural proofs purified iodolactones derived from the Diels–Alder adducts of cyclopentadiene with acrylic acid[70] and tiglic acid[83] have been successfully dehalogenated to afford the corresponding deiodo lactones using hydrogen and Raney nickel in pyridine–methanol, and hydrogen and platinum oxide in ethyl acetate, respectively. Other iodolactones have been deiodinated hydrogenolytically *e.g.* those of bicyclo[2,2,2]oct-5-en-2-*endo*-ylcarboxylic acid (hydrogen and Raney nickel)[84] and cyclohex-1-en- and -2-enylacetic acids.[7]

[78] J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, 1968, **90**, 4303.
[79] W. E. Barnett and J. C. McKenna, *Tetrahedron Letters*, 1971, 227.
[80] G. L. Thompson, W. E. Heyd, and L. A. Paquette, *J. Amer. Chem. Soc.*, 1974, **96**, 3177.
[81] B. Lythgoe, M. E. N. Nambudiry, and J. Tideswell, *Tetrahedron Letters*, 1977, 3685.
[82] H. W. Whitlock jun., *J. Amer. Chem. Soc.*, 1962, **84**, 3412.
[83] K. Alder, R. Hartmann, and W. Roth, *Chem. Ber.*, 1960, **93**, 2271.
[84] T. Adams and R. M. Moriarty, *J. Amer. Chem. Soc.*, 1973, **95**, 4071.



(94)



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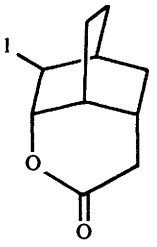

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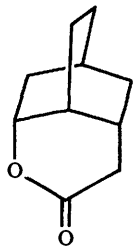


(97)

The bromolactones of norborn-5-en-2,3-*endo-cis*-dicarboxylic acid and cyclohex-4-en-1,2-dicarboxylic acid[38,85] were analogously debrominated (hydrogen–palladium-on-charcoal, potassium acetate–ethanol). However in certain examples this procedure resulted in some bromolactones reverting to the parent unsaturated acid *e.g.* oleanolic acid bromolactone (84)→oleanolic acid (83).[85]

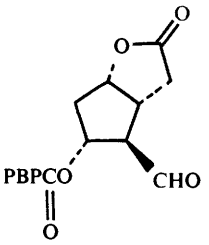
Iodolactonization followed by deiodination has played a vital role in the synthesis of the Corey aldehyde (98), an important intermediate in prostaglandin synthesis. The unsaturated acid (99) is converted to the iodolactone (100), and after protection of the hydroxyl group as in (101) the iodine is removed by reduction to afford (102). Removal of the protecting group of the primary alcohol gave (103) which afforded the required aldehyde (98) on oxidation with Collins reagent.[26,27,86] An alternative route to the Corey aldehyde (98) was developed at I.C.I.[87] and involves iodolactonization of lactone (104) to afford (105) from which (98) may be derived. In Corey's epoxide displacement route to prostaglandin synthesis[88] the key intermediate is the epoxy-lactone (108),

[85] D. A. Denton, F. J. McQuillan, and P. L. Simpson, *J. Chem. Soc.*, 1964, 5535.

[86] E. W. Yankee, U. Axen, and G. L. Bundy, *J. Amer. Chem. Soc.*, 1974, **96**, 5865; E. J. Corey and H. E. Ensley, *J. Amer. Chem. Soc.*, 1975, **97**, 6908; E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, 1973, **95**, 6831; E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 1491; E. J. Corey, S. Terashima, P. W. Ramwell, R. Jessup, N. M. Weinshenker, D. M. Floyd, and G. A. Crosby, *J. Org. Chem.*, 1972, **37**, 3043; E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, 1970, **92**, 397.

[87] E. D. Brown, R. Clarkson, T. J. Leaney, and G. E. Robinson, *J.C.S. Chem. Comm.*, 1974, 642.

[88] E. J. Corey and R. Noyori, *Tetrahedron Letters*, 1970, 311.



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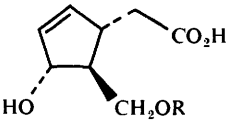

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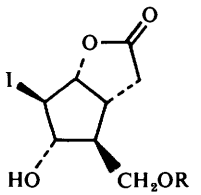
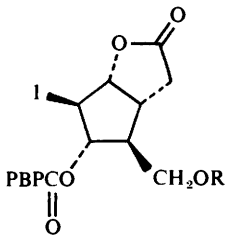
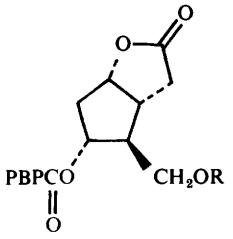


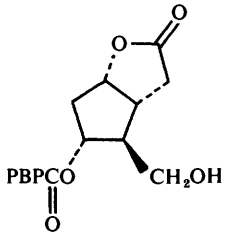
(100)



(101)

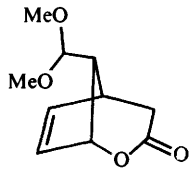


(102)

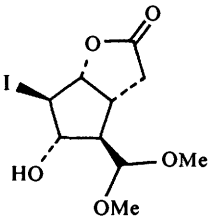


(103)

For (98)-(103) R = CH_3 or CH_2Ph, PBP = $-C_6H_4-C_6H_5$-*p*

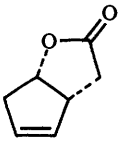


(104)

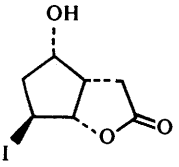


(105)

which can be obtained in fair yield from the unsaturated lactone (106) *via* the iodolactone (107), although direct epoxidation of (106) was developed to give better yields. In a short synthesis of primary prostaglandins, the ketone (110)



(106)



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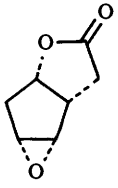
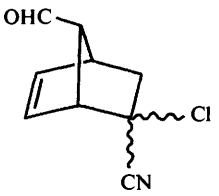
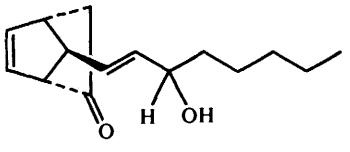


(108)

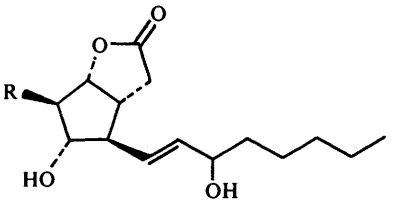
derived from 5-chloro-5-cyano-7-*syn*-formylbicyclo[2,2,1]hept-2-ene (109) underwent Baeyer–Villiger oxidation with alkaline peroxide and the resultant hydroxylactone was subjected to iodolactonization *in situ*. The hydroxy iodolactone (111a) obtained was deiodinated with tri-n-butyltin hydride to give (111b).[89] This synthesis is important because it obviates the necessity for protecting groups.



(109)

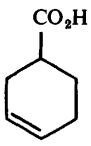


(110)

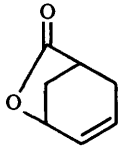


(111) a; X = I
b; X = H

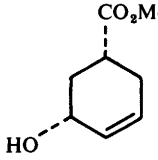
As part of an enantioconvergent approach to prostanoid synthesis developed by Trost[90] the unsaturated acid (112) was converted *via* the iodolactone into the unsaturated lactone (113) and hence to the two enantiomers (114). In a simple

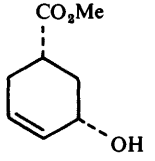


(112)



(113)

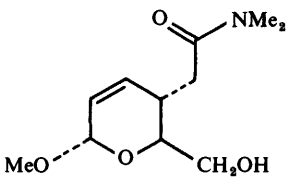




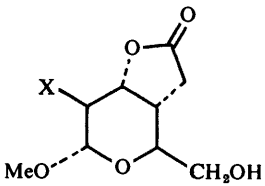
(114)

stereocontrolled synthesis of thromboxane B_2 from D-glucose,[23] an essential stage involved the treatment of the dimethylamide (115) with three equivalents of iodine in tetrahydrofuran–water for one hour at 0 °C, which afforded the oily iodolactone (116a). Deiodination of (116a) with tri-n-butyltin hydride gave quantitatively the hydroxylactone (116b).

[89] E. D. Brown and T. J. Lilley, *J.C.S. Chem. Comm.*, 1975, 39.
[90] B. M. Trost, J. M. Timko, and J. L. Stanton, *J.C.S. Chem. Comm.*, 1978, 436.

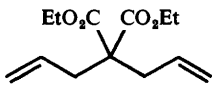


(115)

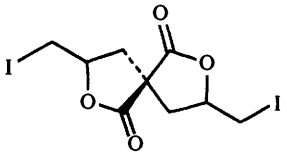


(116) a; X=I
b; X=H

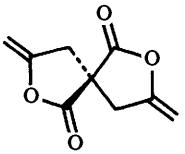
Process 4 (Dehydrohalogenation of halolactones to afford Unsaturated Lactones).— The dehydrohalogenation of halolactones affords unsaturated lactones. This has nowhere proved more important than in the synthesis of γ-methylene-butyrolactones *via* the dehydroiodination, with diazabicycloundecane (DBU) or diazabicyclononene (DBN), of the iodolactones derived from pent-4-enoic acids.[91] Elimination conditions were devized to allow for the isolation of the γ-methylenebutyrolactones virtually free from their endocyclic double bond isomers, a problem that hampered earlier attempts at their synthesis. The novel spiro-bis-γ-methylenebutyrolactone (119) was prepared from the lactone (118)



(117)

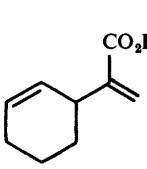


(118)

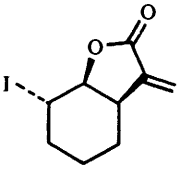


(119)

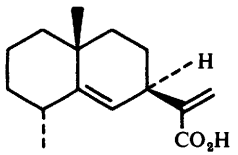
derived from diethyl diallylmalonate (117). α-Methylene lactones are important as potential anti-tumour agents, and the iodolactonization of α-substituted acrylic acids like (120)[92] and (122)[93] provides a valuable direct route to this structural unit. The iodo-γ-methylene lactone (121) may be either deiodinated (tri-n-butyltin hydride) to remove the iodine atom or dehydroiodinated (DBN) to introduce another double bond.[54] This latter alternative was used in the first total synthesis of the allergenic sesquiterpene (±)-frulanolide (125).[93] The



(120)



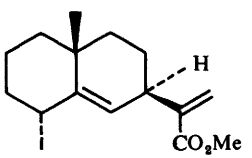
(121)



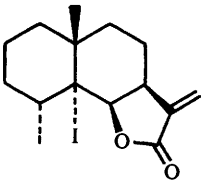
(122)

[91] V. Jäger and H. J. Günther, *Tetrahedron Letters*, 1977, 2543.
[92] J. P. Marino and D. M. Floyd, *J. Amer. Chem. Soc.*, 1974, **96**, 7138.
[93] W. C. Still and M. J. Schneider, *J. Amer. Chem. Soc.*, 1977, **99**, 948.

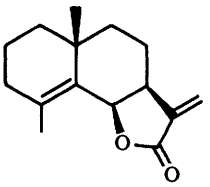
unsaturated ester (123) was saponified to afford (122), which was converted to the crystalline iodolactone (124) on treatment with potassium tri-iodide in aqueous sodium bicarbonate at 25 °C. Dehydroiodination to afford (125) was



(123)



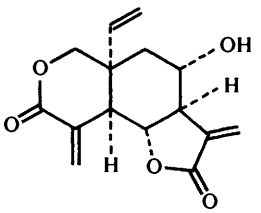
(124)



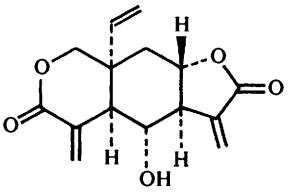
(125)

achieved on reaction of (124) with DBU in tetrahydrofuran. Dehydroiodination with DBN of iodolactones has also proved to be invaluable in the synthesis of certain prostaglandins.[94] The process of iodolactonization followed by dehydroiodination was successfully employed in the total synthesis of the tumour inhibitors (±)-vernolepin (126) and (±)-vernomenin (127).[95] The synthesis involved preparation of the acid (128) and its conversion into the iodolactone (129), which on treatment with DBU smoothly afforded (in 87% yield) the dienone lactone (130) required for the synthesis of (126) and (127).

Ganem and Holbert[96] utilized the bromolactone (13; R = CH_2OH) in the



(126)



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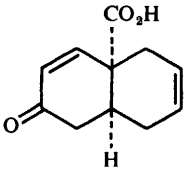
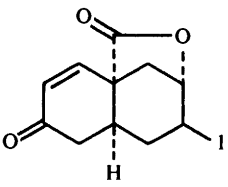
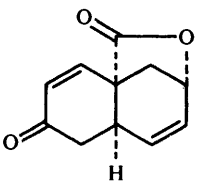


(128)



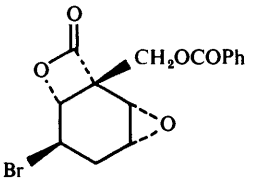
(129)



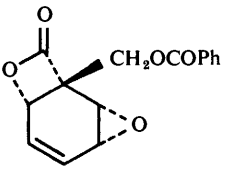
(130)

[94] E. J. Corey and J. Mann, *J. Amer. Chem. Soc.*, 1973, **95**, 6832.
[95] S. Danishefsky, P. I. Schuda, T. Kitahara, and S. J. Etheredge, *J. Amer. Chem. Soc.*, 1977, **99**, 6066.
[96] G. W. Holbert and B. Ganem, *J. Amer. Chem. Soc.*, 1978, **100**, 352.

total synthesis of senepoxide and seneol. Benzoylation of (13; R = CH_2OH) and epoxidation of the resultant ester produced (131), which was smoothly dehydrobrominated with DBU to the olefinic epoxylactone (132) *en route* to senepoxide and seneol.

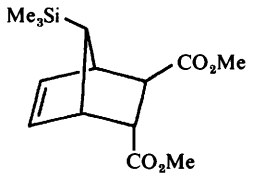


(131)

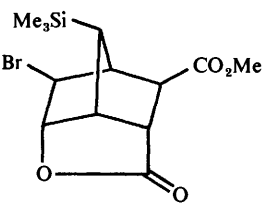


(132)

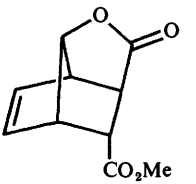
The keto ester (137) was required by Fleming[97] for a total synthesis. It had earlier been prepared in low yield, and Fleming devised a superior route involving bromolactonization. The Diels–Alder adduct (133) of dimethyl fumarate and trimethylsilylcyclopentadiene was converted to the bromolactone (134), which on treatment with methanolic silver nitrate produced the unsaturated hydroxy ester (136) *via* the unsaturated lactone (135). Oxidation of (136) then led to (137).



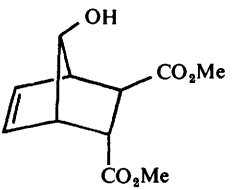
(133)



(134)



(135)



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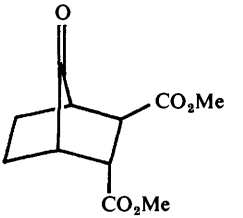
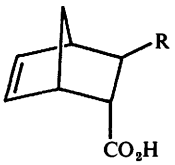


(137)

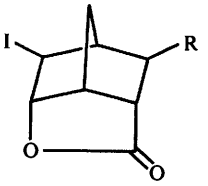
Process 5 (Transformation of Iodolactones into other Products).—Processes 3 and 4 previously described are the main routes for the transformation of iodolactones. There are, however, a number of examples in which other procedures are employed.

[97] I. Fleming and J. P. Michael, *J.C.S. Chem. Comm.*, 1978, 245.

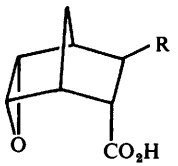
The *exo*-epoxidation of norbornene double bonds occurs readily with the use of a peracid. However due to the preference for *exo* attack on norbornene it is much more difficult to obtain the corresponding *endo* epoxides. However acids of type (138) may be converted into iodolactones (139) which on treatment with sodium or potassium hydroxide in dimethylformamide may be converted into mixtures of *endo* epoxy-acids (140) and keto acids (141).[98] When R = CH_2Cl,



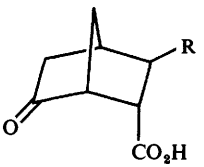
(138)



(139)

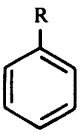


(140)

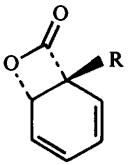


(141)

(140) is the sole product; when R = H, (140) and (141) are produced in the ratio of 83:17. Ganem and co-workers[30] found that the bromo-β-lactones (13), underwent dehydrobromination and decarboxylation on treatment with suitable bases to give simple aromatics (142). They considered that the reaction proceeded through the intermediacy of the β-lactones (143) although spectroscopic experiments failed to detect such species.

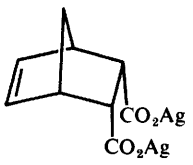


(142)

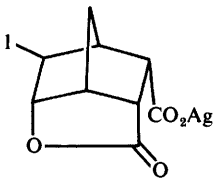


(143)

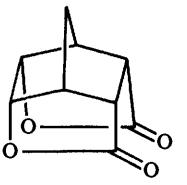
When olefinic dicarboxylic acids undergo halolactonization the halogen atom of the initially formed halolactone has the potential to serve as a leaving group for intramolecular attack by another carboxyl function to afford a dilactone (assuming favourable stereochemical requirements are satisfied). Yoshikoshi[99] observed that the highest yields of the norbornane dilactone (146) *via* iodolactone



(144)



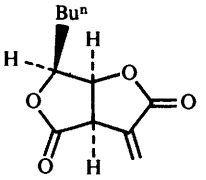
(145)



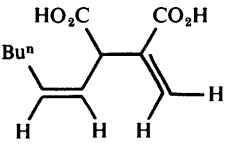
(146)

[98] H. Christol, J. Coste, and F. Plénat, *Tetrahedron Letters*, 1972, 1143.
[99] M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, 1975, **40**, 1932.

(145) resulted when the silver salt (144) of norbornene *endo cis* dicarboxylic acid was treated with iodine and silver acetate in dimethyl sulphoxide. These conditions are general for the production of other dilactones from their corresponding unsaturated acids, and were employed in the synthesis of (±) 4-*epi*-cardensolide (147) from the dicarboxylic acid (148). Similarly[100] cyclic

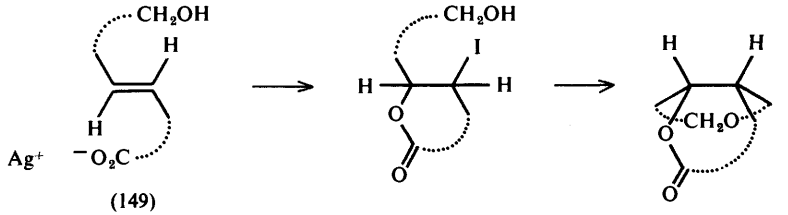


(147)



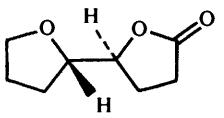
(148)

ether lactones (150) were obtained from the silver salts of unsaturated hydroxy acids (149) on treatment with iodine followed by silver acetate in dimethylformamide. The reactions are highly stereospecific as exemplified by the exclusive formation of the diastereoisomer (151) from the unsaturated hydroxy acid (152). A further example of nucleophilic substitution for the halogen of a

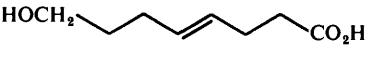


(149)

(150)



(151)



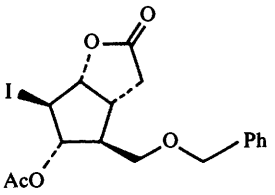
(152)

halolactone was observed on treatment of the iodolactone (153) with silver acetate.[101] The solvolysis is stereospecific due to the *vicinal* participation of the acetate function, and leads to the formation of a mixture of hydroxy acetates (154a, b), which may be hydrolysed to the diol (154c) *en route* to 10α-hydroxyprostaglandins.

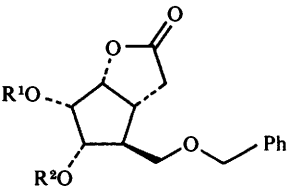
5 Conclusion

Halolactonization has a long history, and the realisation of its value in synthesis

[100] M. Kato, M. Kageyama, and A. Yoshikoshi, *J.C.S. Perkin I*, 1977, 1305.
[101] P. Crabbé, A. Guzmán, and E. Verlarde, *Chem. Comm.*, 1972, 1126.



(153)



(154) a; R^1 = Ac, R^2 = H
b; R^1 = H, R^2 = Ac
c; R^1 = R^2 = H

and in structure determination has grown steadily as the mechanistic intricacies of the reaction have been unravelled. We have aimed to give a summary of the more important mechanistic detail, and provide illustrative examples of the synthesis and synthetic utility of halolactones. Although the reaction has been well utilized since the beginning of the century, it continues to be of value in contemporary synthetic chemistry. There is every indication that this versatile reaction will continue to be of use in the future.

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