Vitamin-C- and isovitamin-C-derived chemistry, Part I. : synthesis of 2,3-dideoxy derivatives of the ascorbic acids

Citation for published version (APA):

Vekemans, J. A. J. M., Boerekamp, J. G., Godefroi, E. F., & Chittenden, G. J. F. (1985). Vitamin-C- and isovitamin-C-derived chemistry, Part I. : synthesis of 2,3-dideoxy derivatives of the ascorbic acids. *Recueil des Travaux Chimiques des Pays-Bas*, 104(10), 266-272. <https://doi.org/10.1002/recl.19851041005>

DOI:

[10.1002/recl.19851041005](https://doi.org/10.1002/recl.19851041005)

Document status and date:

Published: 01/01/1985

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Vitamin-C- and isovitamin-C-derived chemistry.

Part I. Synthesis of 2,3-dideoxy derivatives of the Ascorbic acids

Jozef A. J. M. Vekemans, Jack Boerekamp and Erik F. Godefroi*

Department of Chemical Technology, Section Technical Organic Synthesis,
University of Technology Eindhoven, The Netherlands

and

Gordon J. F. Chittenden

Department of Organic Chemistry, Catholic University Nijmegen, The Netherlands
(Received April 29, 1985)

Abstract. 5,6-*O*-Isopropylidene-L-gulono- and -D-mannono-1,4-lactones are converted into 2-(dimethylamino)-1,3-dioxolane derivatives on treatment with *N,N*-dimethylformamide dimethyl acetal in chloroform with azeotropic removal of the methanol thus formed. Quaternisation of the products with iodomethane, followed by thermal decomposition yields the corresponding C(4)-substituted enantiomeric butenolides. Some aspects of the reactions, the characterisation of the products, and further transformations are described.

Introduction

L-Ascorbic acid (L-*threo*-hex-2-enono-1,4-lactone, **1**) is an important biomolecule. The present scale of its industrial production qualifies it as a cheap bulk chemical. Its methods of production, chemistry and biochemistry have been reviewed^{1–3}. It has, so far, found little application as an intermediate in organic synthesis. The chemical reactions of the isomeric D-isoascorbic acid (D-*erythro*-hex-2-enono-1,4-lactone, **2**), also commercially available and cheaper, remain virtually unexplored. Recently **1** has been used as starting material for the synthesis of R-GABOB⁴. Its behaviour as a *Michael*-type donor with acrolein⁵ and with 2-methyl-2,5-dimethoxy-2,5-dihydrofuran⁶ has also been studied. Current research interests required investigating procedures for converting readily available **1** and **2** into synthetically useful chiral structural units. Deoxygenation of the 2,3-enediol functions for example, would produce the dihydroxyethyl-substituted butenolides **3** and **4**. The configurations at C(4) and C(5) would be retained and correspond to those present in the parent L-gulonic and D-mannonic acids.

Butenolide-containing systems are encountered⁷ frequently in natural products. A number of asymmetric 4-substituted butenolides have been synthesised from chiral lactones⁸ derived from glutamic acid and by chiral reduction⁹ of acylated alkynes. The recently described synthesis¹⁰ of compounds **6a,b** from the D-ribonolactones **5a,b** and the subsequent use¹¹ of **6a** as a synthon are noteworthy.

- ¹ B. M. Tolbert, M. Downing, R. W. Carlsson, M. K. Knight and E. M. Baker, *Ann. N.Y. Acad. Sci.* **258**, 48 (1975).
- ² T. C. Crawford and S. A. Crawford, *Adv. Carbohydr. Chem. Biochem.* **37**, 79 (1980).
- ³ P. A. Seib and B. M. Tolbert, "Ascorbic Acid: Chemistry, Metabolism, and Uses", *Advances in Chemistry, Series 200*, Am. Chem. Soc., Washington DC, 1982.
- ⁴ M. E. Jung and T. C. Shaw, *J. Am. Chem. Soc.* **102**, 6304 (1980).
- ⁵ G. Fodor, R. Arnold, T. Mohacsi, I. Karle and J. Flippen-Anderson, *Tetrahedron* **39**, 2137 (1983).
- ⁶ G. Fodor, K. Sussangkarn, H. Mathelier, R. Arnold, I. Karle and C. George, *J. Org. Chem.* **49**, 5064 (1984).
- ⁷ See i.a. D. C. Aldridge and W. B. Turner, *J. Chem. Soc. (C)*, 2433 (1971); T. C. McMorris, R. Seshadri and T. Arunachalam, *J. Org. Chem.* **39**, 669 (1974); J. S. Brimacombe, A. W. Murray and Z. Ul-Haque, *Carbohydr. Res.* **45**, 45 (1975); J. Fayos, F. Fernandez-Gadea, C. Pascual, A. Perales, F. Piozzi, M. Rico, B. Rodriguez and G. Savona, *J. Org. Chem.* **49**, 1789 (1984); R. G. Brereton, M. J. Garson and J. Staunton, *J. Chem. Soc., Perkin I*, 1027 (1984).
- ⁸ M. Taniguchi, K. Koga and S. Yamada, *Tetrahedron* **30**, 3547 (1974); K. Tomioka, T. Ishiguro and K. Koga, *J. Chem. Soc., Chem. Commun.* 652 (1979); *Ibid.*, *Tetrahedron Lett.* 2973 (1980).
- ⁹ R. S. Brinkmeyer and V. M. Kapoor, *J. Am. Chem. Soc.* **99**, 8339 (1977); J. P. Vigneron and V. Bloy, *Tetrahedron Lett.* 1735 (1980); J. P. Vigneron and J. M. Blanchard, *Tetrahedron Lett.* 1739 (1980); M. M. Midland and A. Tramontano, *Tetrahedron Lett.* 3549 (1980).
- ¹⁰ P. Camps, J. Font and O. Ponsati, *Tetrahedron Lett.* 1735 (1980); P. Camps, J. Cardellach, J. Font, R. M. Ortuno and O. Ponsati, *Tetrahedron* **38**, 2395 (1982); J. Cardellach, J. Font and R. M. Ortuno, *J. Heterocyclic Chem.* **21**, 327 (1984); R. E. Ireland, R. C. Anderson, R. Badoud, B. J. Fitzsimmons, G. J. McGarvey, S. Thaisrivongs and C. S. Wilcox, *J. Am. Chem. Soc.* **105**, 1988 (1983).
- ¹¹ S.-Y. Chen and M. M. Joullie, *J. Org. Chem.* **49**, 2168 (1984).

Compounds **3** and **4** constitute the two diastereoisomeric C(5)-(hydroxymethyl) homologues of **6a** and would be, therefore, of considerable synthetic interest. Syntheses of **3** and **4** and of some derivatives are now described.

Results and discussion

The reduction of an aqueous solution of **1**, by a slight modification of a published¹² procedure yielded L-gulonono-1,4-lactone, **7** (60–70% yield). The intended dehydroxylation of C(2) and C(3) required the prior protection of the hydroxyl groups at C(5) and C(6). The treatment of **7** or its D-enantiomer with acidified acetone has been shown to yield the corresponding 2,3:5,6-di-O-isopropylidene derivatives¹³, the D-isomer of which has been reported to give the corresponding 2,3-O-isopropylidene compound¹⁴ by selective acid hydrolysis. The use of acetone/anhydrous copper(II) sulphate in the D series gave a low yield of the 5,6-O-isopropylidene acetal¹⁵, which was also obtained in improved yield, but on a small scale¹⁶, by the use of 2-methoxypropene in *N,N*-dimethylformamide solution, catalysed by toluene-*p*-sulphonic acid. When **7** was treated with 2,2-dimethoxypropane/acetone in the presence of tin(II) chloride¹⁷, 5,6-O-isopropylidene-L-gulonono-1,4-lactone (**8a**) was obtained in 60% yield. This procedure proved satisfactory on a 100-g scale. Examination of the reaction mother liquors by TLC showed them to contain **7**, **8a** and the corresponding 2,3:5,6-diacetal. No attempts were made at separation but the concentrated residues were treated with dilute acid to regenerate *ca.* 25% of re-usable **7**.

Similar treatment of **7** with 1,1-dimethoxycyclohexane/tin(II) chloride in *N,N*-dimethylformamide solution gave the corresponding 5,6-O-cyclohexylidene acetal **8b** also in ~60% yield (Scheme 1).

Scheme 1. (a) Pd-C, H_2 ; (b) $\text{R}'_2\text{C(OMe)}_2$, SnCl_2 .

Attention was then directed towards the introduction of a double bond between C(2) and C(3) in compounds **8a** and **8b**. The synthesis of olefins from vicinal diols has been reviewed¹⁸ recently. For *cis*-diols the desulphurisation of the derived thionocarbonates (Corey–Winter method¹⁹), the fragmentation of the corresponding 2-ethoxy- or 2-(dimethylamino)-1,3-dioxolanes (Eastwood methods²⁰) or the thermal decomposition of the analogous 2-trimethylammonium iodides (Hanessian method²¹) are currently the most adopted procedures. The Eastwood orthoformate method was attempted initially, as this approach had proven¹⁰ superior to the Corey–Winter and Hanessian routes in the conversion of **5a,b** into **6a,b**. Lactone **8a**, on treatment with triethyl orthoformate in the presence of catalytic amounts of benzoic acid, gave compound **9** (62%). Pyrolysis of this derivative led to intractable mixtures, which were not studied further.

The trimethylammonium acetal approach (Hanessian method²¹) was next examined and adapted thus. A chloroform suspension of compound **8a** was heated under gentle reflux in the presence of (dimethoxymethyl)dimethylamine (DMF dimethyl acetal) with continuous removal of the methanol that was formed, as the lower-boiling azeotrope. Evaporation of the reaction mixture *in vacuo* at 50°C gave solid material, the NMR spectrum of which displayed, *inter alia*, two closely separated methine (CH) singlets at 5.51 and 5.48 ppm respectively, of approximately equal intensity, suggesting that the product **12a** was an *exo/endo* mixture. Additional information was then obtained by conducting NMR-monitored control experiments. The reaction of **8a** with DMF dimethyl acetal in deuteriochloroform solution, at room temperature, indicated the rapid disappearance of starting material, with the production of methanol and the appearance of two isomeric products, in the ratio 3/7. These exhibited signals at 5.51 and 5.17 ppm (methine protons) in addition to the protons of a methoxy group at 3.73 ppm, suggesting the presence of the C(2)–O or C(3)–O open-chain acetals **10a** (R + S) or **11a** (R + S)**, resulting from exchange of only one methoxy group in DMF dimethyl acetal with the substrate **8a**. When the reaction mixture was concentrated *in vacuo* at 50°C, and then re-dissolved in deuteriochloroform, the NMR spectrum was identical to that of product **12a** (*vide supra*). The addition of methanol to the solution of **12a** caused reversion to the original mixture of open-chain acetals **10a** or **11a** (Scheme 2). The question of which pair of open-chain acetals **10a** (R + S) or **11a** (R + S) largely preponderates in the equilibrium mixture remains unresolved presently. The spectral data are insufficiently definitive for the assignment of the relevant signals to either **10a** or **11a**. If it is assumed that their formation is a kinetically controlled process, the production of **10a** epimers would be favoured since the C(2)-hydroxyl is probably more nucleophilic than that on C(3). However, the experimental evidence and the generally accepted $\text{S}_{\text{N}}1$ nature of aminoacetal processes²² should imply that the ratio **10a/11a** is determined by a thermodynamically controlled trans-acetalation equilibrium, in which the **11a** epimers are the more stable entities. The ionisation of the acetal C–O bond in **12a** towards C(2)–O would generate a better leaving group than if this were to occur towards C(3)–O; following the same line of reasoning, **10a** should revert more easily to **8a** than **11a** should. The formation of **11a** should, therefore, be favoured. The relatively large 1,3-interaction between the C(2)–O aminoacetal function and the exocyclic 1,3-dioxolane group in **10a** could be an additional destabilising factor.

** One of the referees pointed out that the observed NMR signals must be attributed to two epimers, **10a** (R + S) or **11a** (R + S), rather than to all four possible products as suggested originally; this does not exclude the presence of minor quantities of the other pair of epimers.

¹² G. C. Andrews, T. C. Crawford and B. E. Bacon, *J. Org. Chem.* **46**, 2976 (1981) and references cited.

¹³ M. Matsui, M. Okada and M. Ishidate, *Yakugaku Zasshi* **86**, 110 (1966); *C.A.* **64**, 15967a (1966); L. M. Lerner, B. D. Kohn and P. Kohn, *J. Org. Chem.* **33**, 1780 (1968).

¹⁴ L. M. Lerner, *Carbohydr. Res.* **9**, 1 (1969).

¹⁵ R. K. Hulyalkar and J. K. N. Jones, *Can. J. Chem.* **41**, 1898 (1963).

¹⁶ C. Copeland and R. V. Stick, *Aust. J. Chem.* **31**, 1371 (1978).

¹⁷ G. J. F. Chittenden, *Carbohydr. Res.* **87**, 219 (1980).

¹⁸ E. Block, "Organic Reactions", chapter 2, W. G. Dauben ed., J. Wiley and Sons, N.Y., 1984, p. 457.

¹⁹ E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.* **85**, 2677 (1963).

²⁰ J. S. Josan and F. W. Eastwood, *Aust. J. Chem.* **21**, 2013 (1968); F. W. Eastwood, K. J. Harrington, J. S. Josan and J. L. Pura, *Tetrahedron Lett.* 5223 (1970).

²¹ S. Hanessian, A. Bargiotti and M. LaRue, *Tetrahedron Lett.* 737 (1978).

²² H. Meerwein, W. Florian, N. Schön and G. Stopp, *Justus Liebigs Ann. Chem.* **641**, 1 (1961).

Further studies on a number of model systems would be required to clarify these points.

Scheme 2. (a) $(\text{MeO})_2\text{CHNMe}_2$, CHCl_3 , R.T.; (b) removal of volatiles (MeOH); (c) MeOH.

The treatment of compound **8a** with DMF dimethyl acetal in tetrahydrofuran or 1,2-dimethoxyethane solution led to a slower formation of product **12a**, whereas extensive decomposition occurred when the reaction was conducted in boiling acetonitrile. Compound **12a** can be stored for long periods below -10°C , but rapidly decomposes on being kept at room temperature.

The behaviour of compound **8b** with DMF dimethyl acetal paralleled that of **8a**, producing, on azeotropic removal of methanol, **12b**, as an *exo/endo* mixture. The intermediacy of C(2)-O- or C(3)-O-substituted open-chain acetals was also demonstrated by ^1H NMR spectroscopy. The appearance of two distinct methine proton signals at 5.51 and 5.13 ppm respectively, and that of the methoxy group at 3.74 ppm characterised the products. The removal of the solvent and methanol *in vacuo* at 50°C , followed by addition of deuteriochloroform gave material whose spectrum was identical to that of **12b**, obtained directly from the reactants, and exhibiting two closely separated methine proton signals near to 5.50 ppm.

Heating a solution of **12a** or **12b** in acetonitrile or acetone under reflux in the presence of iodomethane yielded the corresponding quaternary salts **13a** or **13b**. Better yields are here obtainable, however, by the addition of **12a** or **12b** to neat iodomethane at 50°C . The *exo/endo* mixtures of **13a** and **13b**, isolated in $\sim 80\%$ yield, were thermally unstable and were not purified further (Scheme 3).

Scheme 3. a $R' = \text{Me}$; b $R'R' = (\text{CH}_2)_5$.

The initial studies on the thermal decomposition of the quaternary salts were carried out with **13a**. A complex mixture of products was obtained when a suspension of **13a** was heated under reflux in toluene. When the reaction was performed in boiling acetonitrile, in which **13a** is moderately soluble, a precipitate of trimethylammonium iodide was

formed rapidly; the concomitant evolution of CO_2 facilitated the monitoring of the reaction.

Processing of the reaction mixture gave the butenolide **14a** (85%) and a closely related product ($\sim 10\%$), as demonstrated by ^1H NMR spectroscopy. TLC and GLC showed the minor compound to be less polar and more volatile than the major product **14a**. Attempted separation of the mixture by crystallisation or fractional distillation was unsuccessful, whilst attempted separation on alumina or silica gel (chloroform/ethyl acetate) led to extensive decomposition in the former, partial deprotection in the latter case. Therefore crude **14a** was heated under reflux with acidified methanol to give, after chromatography (silica gel, chloroform/methanol) and crystallisation, pure 2,3-dideoxy-L-ascorbic acid, **3** (46%). This on treatment with acidified acetone yielded pure **14a**. Later studies showed that addition of acetone to the elution solvent inhibited deprotection of **14a** during chromatography on silica gel, thus allowing separation from its closely related by-product and purification.

The analogous decomposition of compound **13b** by heating it under reflux in acetonitrile proceeded less satisfactorily, possibly due to the steric bulk of the cyclohexylidene protecting group, having an adverse effect on the acetal deprotonation. The remaining dehydroxylation studies were consequently carried out only on isopropylidene-protected substrates (Scheme 4).

Scheme 4. a $R' = \text{Me}$ b $R'R' = (\text{CH}_2)_5$.

(a) MeCN, reflux (with elimination of $\text{Me}_3\text{N}\cdot\text{HI}$ and CO_2); (b) MeOH, H^+ ; (c) Me_2CO , H^+ (to **14a**).

The nature of the by-product formed during the transformation of **13a** into **14a** was intriguing, as the enhanced acidity of the C(4) proton in the butenolide **14a** may have made the molecule more susceptible to isomerisation at this position. This was verified as follows. A 0.5-molar solution of **14a** in deuteriochloroform was treated with one equivalent of triethylamine and was monitored continuously by ^1H NMR. A second set of proton signals, occurring at 7.55 and 4.81 ppm, developed in addition to those at 7.39 and 5.04 ppm, attributable to H(3) and H(4) in **14a**. This suggested that isomerisation had occurred. An equilibrium was apparently reached after *ca.* 3 h, resulting in a 3/5 mixture of the original **14a** and the corresponding L-erythro epimer **15a**, identical to the previously mentioned by-product. After a longer reaction period ($t_{1/2}$ to 4 days), additional NMR signals were observed, attributable to acetone and to the dienolactones **16E,Z**, arising through the uncommon elimination²³ of acetone from either isomer. The crude equilibration (*ca.* 3 h) reaction mixture, after neutralisation, was chromatographed on silica gel (pentane/acetone, 7/1) to give pure **15a**, which on subsequent hydrolysis (2-propanol-concentrated hydrochloric acid, 24/1) furnished 2,3-dideoxy-L-isoascorbic acid, **17** (Scheme 5).

²³ S. J. Eitelman, R. K. Hall and A. Jordaan, J. Chem. Soc., Chem. Commun. 923 (1976).

Scheme 5

Compound **17** is of interest since it represents the optical antipode of the target compound **4**, the synthesis of which is now described.

Catalytic reduction of **2**, in a similar manner as described for **1**, gave D-mannono-1,4-lactone, **18** (50%). Treatment of **18** with a boiling mixture of 2,2-dimethoxypropane/acetone/tin(II) chloride yielded the corresponding 5,6-O-isopropylidene derivative **19** (77%), the melting point of which was considerably higher than that reported²⁴. Subsequent reaction of **19** with DMF dimethyl acetal gave the diacetal **20**, the formation of which was shown to proceed via open-chain monoacetals, analogous to **10a** or **11a** (¹H NMR). Compound **20** could not be obtained crystalline and was converted directly into the solid quaternary salt **21** by treatment with iodomethane at 5°C. Heating a suspension of **21** in acetonitrile or 1,2-dimethoxyethane under reflux gave butenolide **22**, which was purified by silica gel chromatography (pentane/acetone, 7/1) (Scheme 6).

Scheme 6. (a) $\text{Pd}-\text{C}$, H_2 ; (b) $\text{Me}_2\text{C}(\text{OMe})_2$, SnCl_2 , Me_2CO ; (c) $(\text{MeO})_2\text{CHNMe}_2$, CHCl_3 , reflux; (d) MeI ; (e) MeCN , reflux; (f) 2-PrOH , H^+ ; (g) Me_2CO , H^+ .

The intermediates in the D-erythro series (**20**, **21**) were far more difficult to manipulate than their L-threo analogs. The conversion of **19** to **22** was thereafter performed as a one-pot reaction sequence to give after hydrolysis of crude **22** in acidified 2-propanol, 2,3-dideoxy-D-isoascorbic acid, **4** (18%), precursor **18** (7%) and approximately 10% of a compound $\text{C}_6\text{H}_7\text{IO}_4$ (yields of crystallised materials are based on lactone **19**).

Comparison of the ¹H MR spectrum of this compound with that of **4** indicated the absence of a resonance due to H(2) and featured simplified signals for H(3) and H(4), with a 0.32-ppm downfield shift for the former. The material was therefore assigned structure **23** and was thought to have arisen from $\text{S}_{\text{N}}2$ attack at C(2) in compound **21** by iodide ion, to give an iodoformate, subsequent elimination of formic acid and hydrolysis. The intermediacy²² and isolation²⁵ of iodoformates have been described previously. The *cis* elimination of formic acid is facilitated presumably by the carbonyl- and iodo-induced enhancement of the acidity of H(2) (Scheme 7).

Scheme 7

The ¹H NMR spectra of **15a** and **22** (L- and D-erythro) were superimposable, but differed significantly from that of **14a** (L-threo), both featuring a downfield H(3) resonance shift (7.63 vs. 7.48 ppm), an upfield H(4) resonance shift (4.89 vs. 5.09 ppm), a higher H(4)–H(5) vicinal coupling constant (J 7.5 vs. 4.0 Hz) and a more compact multiplet for H(5), H(6) and H(6'). The acetonide **22** also underwent triethylamine-induced isomerisation at C(4), producing an equilibrium mixture with approximately the same *threo*/*erythro* ratio (3/5) as that observed previously from compound **14a**. Compounds **4** and **17** showed equal specific rotations, but of opposite sign (-187 and $+187^\circ$ respectively; cf. L-threo isomer **3**: -120°). It is of interest to compare these values with that (-145°) reported¹⁰ for the D-ribonolactone analog **6a**, since the latter's negative sign of rotation must be dictated by the *S* configuration at C(4).

Concluding remarks

Butenolides **3** and **4**, derived from the relatively inexpensive and plentiful ascorbic acids **1** and **2**, represent potential key intermediates for carbohydrate synthesis. They feature opposing stereochemistry at C(5) and identical *S* configurations at C(4). Our studies have demonstrated their practically

²⁴ E. H. Goodyear and W. N. Haworth, J. Chem. Soc. 3136 (1927).

²⁵ R. E. Ireland and J.-P. Vever, Can. J. Chem. **59**, 572 (1981).

feasible base-catalysed inversions at C(4). They are, in principle, amenable for the regio- and stereoselective introduction of functionality at C(2) and C(3). These options, in combination with described methodologies for reducing 1,4-lactones to lactols²⁶, offer an unexplored strategy for preparing modified monosaccharides. The concept is presently under active investigation.

Experimental

General

The authors thank Mr. H. Eding for microanalytical data. A generous sample of (dimethoxymethyl)dimethylamine (DMF dimethyl acetal) was kindly supplied by Fine Organics, Ltd. Peterlee, County Durham, Great Britain. 60 MHz ¹H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer with TMS as internal standard. Melting points, recorded on a Fischer-Johns block, are uncorrected. Optical rotations were determined on an Optical Activity AA-10 polarimeter. Chromatography was carried out on silica gel (Merck, 0.063–0.20 mm).

L-Gulono-1,4-lactone, **7**¹²

A mixture of L-ascorbic acid, **1** (352.2 g, 2 mol) and 10% Pd-C (Merck, 12.5 g) in water (1 l) was hydrogenated at 50°C and 5.25 atm for 50 h. Removal of the catalyst, concentration of the filtrate to 500 ml and pouring the hot residue onto stirred acetone (2.25 l) afforded **7** (225 g, 63%), m.p. 184–186°C (lit.¹² 183–185°C). C₆H₁₀O₆ (178.11) calcd.: C 40.45, H 5.66; found: C 40.7, H 5.7. $[\alpha]_D^{20} + 55.1^\circ$ (c 2.06, H₂O) [lit.¹² $[\alpha]_D^{25} + 55.2^\circ$ (H₂O)]. ¹H NMR (DMSO-*d*₆) δ: 5.69 (d, *J* 7.5 Hz, 1); 5.23 (d, *J* 3.75 Hz, 1); 4.90 (d, *J* 4.5 Hz, 1); 4.59 (t, *J* 5.5 Hz, 1); 4.5–4.1 (m, 3); 3.9–3.35 (m, 3).

5,6-O-Isopropylidene-L-gulono-1,4-lactone, **8a**^{15,27}

To suspension of **7** (89 g, 0.50 mol), heated under reflux in dry acetone (250 ml), containing anhydrous SnCl₂ (0.15 g), was added dropwise during 30 min a solution of 2,2-dimethoxypropane (56 g, 0.54 mol) in acetone (250 ml). The mixture was boiled under reflux for an additional h. Pyridine (0.5 ml) was then introduced, followed by acetone (500 ml). Subsequent cooling on ice and filtration afforded insoluble starting material (13.5 g, 15%). The filtrate was evaporated under reduced pressure to leave a solid residue which, on trituration with ice-cold 2-propanol (400 ml), provided impure **8a** (69 g, m.p. 160–162°C). Filtration over silica gel (acetone) gave **8a** (66 g, 60%, m.p. 166–167°C). A sample recrystallised from ethyl acetate had m.p. 167–168°C. C₉H₁₄O₆ (218.18) calcd.: C 49.54, H 6.47; found: C 49.4, H 6.4. $[\alpha]_D^{20} + 61^\circ$ (c 1.11, H₂O). ¹H NMR (DMSO-*d*₆) δ: 5.79 (d, *J* 7.5 Hz, 1); 5.35 (d, *J* 4 Hz, 1); 4.5–3.6 (m, 6); 1.35 (s, 3); 1.29 (s, 3).

5,6-O-Cyclohexylidene-L-gulono-1,4-lactone, **8b**

A suspension of **7** (53.5 g, 0.30 mol) and 1,1-dimethoxycyclohexane²⁸ (45 g, 0.31 mol) in dry DMF (50 ml) was added during 30 min to a solution of anhydrous SnCl₂ (0.10 g) in DMF (10 ml) at 85°C. The mixture was kept at this temperature for another 30 min and was then, after cooling, poured into a stirred mixture of ice-cold brine and diethyl ether (3/1). The crystalline product was isolated by filtration. Adhering water was removed azeotropically with toluene, containing pyridine (0.5%). Evaporation of the solvent left **8b** (43.5 g, 56%, m.p. 172–175°C). A small amount was recrystallised from water to give an analytical sample, m.p. 176–178°C. C₁₂H₁₈O₆ (258.24) calcd.: C 55.81, H 7.02; found: C 56.1, H 7.3. $[\alpha]_D^{20} + 26^\circ$ (c 1.35, acetone). ¹H NMR (DMSO-*d*₆) δ: 5.76 (d, *J* 7 Hz, 1); 5.32 (d, *J* 4 Hz, 1); 4.5–3.6 (m, 6); 1.54 (s, 10).

2,3-O-(Ethoxymethylidene)-5,6-O-isopropylidene-L-gulono-1,4-lactone, **9**

A mixture of **8a** (20.0 g, 0.092 mol), benzoic acid (0.1 g) and triethyl orthoformate (30 ml) was heated during 1 h at 110°C, while removing the produced ethanol. Subsequent short-path vacuum distillation afforded an oil (23.5 g), producing crystalline **9a** (14.1 g, 62%) on trituration with diisopropyl ether. M.p. 81–82°C, C₁₂H₁₈O₇ (274.27) calcd.: C 52.55, H 6.62; found: C 52.5, H 6.1. ¹H NMR (CDCl₃) δ: 5.94 and 5.93 (2s, 1) 5.0–3.7 (m, 6); 3.58 (q, *J* 7 Hz, 2); 1.48 (s, 3); 1.40 (s, 3); 1.18 (t, *J* 7 Hz, 3).

2,3-O-[(Dimethylamino)methylidene]-5,6-O-isopropylidene-L-gulono-1,4-lactone, **12a**

To a suspension of **8a** (54.5 g, 0.25 mol) in CHCl₃ (500 ml), heated to gentle reflux, was added dropwise (dimethoxymethyl)dimethylamine (DMF dimethyl acetal) (32 g, 0.27 mol), while removing the produced methanol azeotropically and monitoring the reaction via the b.p. and the density of the distillate. When no more methanol was evolved (~2 h), the solution was evaporated exhaustively *in vacuo* at 50°C, leaving solid, pink material which, on trituration with diethyl ether, gave **12a** (68 g, ~100%), as an *exo/endo* mixture. The amine, being unstable at room temperature, was stored below –10°C. M.p. 118–119°C (decomp.). ¹H NMR (CDCl₃) δ: Major: 5.51 (s, 1); 4.95 (d, *J* 6 Hz, 1); 4.70 (dd, *J* 6 and 2 Hz, 1); 4.5–3.7 (m, 4); 2.33 (s, 6); 1.44 (s, 3); 1.37 (s, 3). Minor: 5.48 (s, 1), 4.79 (m, 2); 4.5–3.7 (m, 4); 2.33 (s, 6); 1.44 (s, 3); 1.37 (s, 3).

5,6-O-Cyclohexylidene-2,3-O-[(dimethylamino)methylidene]-L-gulono-1,4-lactone, **12b**

Compound **8b** (32.2 g, 0.125 mol) was converted to **12b** (39 g, ~100%) (*exo/endo* mixture) as described for **12a**. M.p. 117–118°C (decomp.). ¹H NMR (CDCl₃) δ: Major: 5.50 (s, 1); 4.95 (d, *J* 5.5 Hz, 1); 4.71 (dd, *J* 5.5 and 1.5 Hz, 1); 4.55–3.7 (m, 4); 2.40 (s, 6); 1.63 (s, 10). Minor: 5.50 (s, 1); 4.80 (m, 2); 4.55–3.7 (m, 4); 2.38 (s, 6); 1.63 (s, 10).

5,6-O-Isopropylidene-2,3-O-[(trimethylammonio)methylidene]-L-gulono-1,4-lactone iodide, **13a**

Compound **12a** (27.3 g, 0.1 mol) was added portionwise to ice-cold, stirred iodomethane (25 ml, 0.4 mol). The mixture was stored overnight at 5°C and was then freed of excess reagent under reduced pressure below 40°C (bath). Acetone trituration of the resulting solid produced quaternary salt **13a** (34.5 g, 82%), m.p. ~150°C (decomp.) as an *exo/endo* mixture. ¹H NMR (DMSO-*d*₆) δ: Major: 6.27 (br s, 1); 5.62 (m, 2); 4.64 (dd, *J* 6 and 2 Hz, 1); 4.31 (q, *J* 6 Hz, 1); 4.3–3.75 (m, 2); 3.00 (s, 9); 1.36 (s, 6). Minor: 6.14 (br s, 1); 5.48 (m, 2); 4.79 (dd, *J* 6 and 2 Hz, 1); 4.31 (q, *J* 6 Hz, 1); 4.3–3.75 (m, 2); 3.00 (s, 9); 1.33 (s, 6).

5,6-O-Cyclohexylidene-2,3-O-[(trimethylammonio)methylidene]-L-gulono-1,4-lactone iodide, **13b**

Portionwise introduction of **12b** (39.1 g, 0.125 mol) in ice-cold, stirred iodomethane (39 ml, 0.625 mol) and removal of the excess reagent below 40°C (bath) after 18 h at 5°C, left solid product. This was trituated with acetone/diethyl ether (2/1, 125 ml) to leave slightly yellow **13b** (46.4 g, 82%) as a mixture of 2 diastereoisomers, m.p. ~150°C (decomp.). ¹H NMR (DMSO-*d*₆) δ: Major: 6.26 (br s, 1); 5.67 (d, *J* 6 Hz, 1); 5.48 (dd, *J* 6 and 2 Hz, 1); 4.65 (dd, 6 and 3.75 Hz, 1); 4.29 (q, *J* 6 Hz, 1); 4.25–3.9 (m, 2); 3.01 (s, 9); 1.53 (s, 10). Minor: 6.16 (br s, 1); 5.47 (m, 2); 4.8–3.8 (m, 4); 3.01 (s, 9); 1.53 (s, 10).

2,3-Dideoxy-L-threo-hex-2-enono-1,4-lactone, **3**

A stirred suspension of **13a** (104 g, 0.25 mol) in dry acetonitrile was brought to reflux, resulting, after 15 min, in a clear solution and subsequent deposition of a new insoluble material and evolution of CO₂. After 1 h no more gas was evolved and the mixture was cooled and filtered. Washing of the solid with acetonitrile left trimethylammonium iodide (38.9 g, 84%). The filtrate was evaporated under reduced pressure and the residue was freed of some tarry contaminants by the addition of dry diethyl ether (1 l), followed by decantation. Solvent removal left an oil (46.7 g, ~100%), consisting according to NMR data for 85% of **14a** [H(4), 5.05 ppm; H(3), 7.39 ppm] and 10% of C(4)-epimeric **15a** [(4), 4.81 ppm; H(3), 7.56 ppm]. The residue was taken up in a mixture of 2-propanol (600 ml) and conc. HCl (25 ml). After 18 h solvent was removed *in vacuo*, leaving an oil which was chromatographically purified (CHCl₃/MeOH,

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7/1 → 4/1). The solvent-free product was triturated with ice-cold acetonitrile to give pure **3** (16.4 g, 46%), m.p. 83–85°C. Analytical material from acetonitrile/diisopropyl ether had m.p. 85–86°C. $C_6H_8O_4$ (144.13) calcd.: C 50.00, H 5.59; found: C 49.9, H 5.7. $[\alpha]_D^{20}$ –120° (c 1.00, H_2O). 1H NMR (acetone- d_6) δ : 7.72 (dd, *J* 6 and 1.5 Hz, 1); 6.14 (dd, *J* 6 and 2 Hz, 1); 5.25 (ddd, *J* 3, 2 and 1.75 Hz, 1); 4.3 (d, *J* 5.5 Hz, 1); 4.1 (t, *J* 5.5 Hz, 1); 4.0–3.6 (m, 3).

2,3-Dideoxy-5,6-O-isopropylidene-L-threo-hex-2-enono-1,4-lactone, **14a**

A solution of pure **3** (1.44 g, 0.01 mol) in acetone (10 ml) was treated with anhydrous HCl in 2-propanol (1 drop, 5 M). Removal of the solvent after 18 h and filtration over silica gel (pentane/acetone, 3/1) gave a colourless oil, which solidified on cooling. It was triturated with pentane to yield pure acetone **14a** (1.38 g, 75%), m.p. 37.5–38.5°C. $C_9H_{12}O_4$ (184.19) calcd.: C 58.69, H 6.57; found: C 58.4, H 6.8. $[\alpha]_D^{20}$ –132° (c 1.09, $CHCl_3$). 1H NMR ($CDCl_3$) δ : 7.48 (dd, *J* 6 and 1.75 Hz, 1); 6.16 (dd, *J* 6 and 2.25 Hz, 1); 5.09 (ddd, *J* 3.75, 2.25 and 1.75 Hz, 1); 4.39 (ddd, *J* 6.5, 5.5 and 3.75 Hz, 1); 4.09 (dd, *J* 8 and 6.5 Hz, 1); 3.83 (dd, *J* 8 and 5.5 Hz, 1); 1.40 (s, 3); 1.33 (s, 3).

C(4) Epimerisation of **14a** (L-threo) to **15a** (L-erythro)

Reaction conditions were initially optimised via small-scale NMR monitoring. A solution of **14a** (0.046 g, 2.5×10^{-4} mol) in $CDCl_3$ (0.5 ml), containing NEt_3 (0.036 ml, 2.5×10^{-4} mol), produced after a few min, besides the original H(4) and H(3) absorptions at 5.04 and 7.39 ppm, a second set of H(4) and H(3) signals at 4.81 and 7.55 ppm, indicative of **15a** being formed. No further changes were noted after 3 h, resulting in an NMR-established equilibrium mixture consisting for 3/8 of **14a** and 5/8 of **15a**. A slow concurring acetone elimination ($t_{1/2}$ ~4 days) to **16E,Z**, as evidenced by additional NMR signals at δ : 2.14 (s) (acetone)/7.29 (d, *J* 5.5 Hz, H(3)); 5.44 (t, *J* 6.5 Hz, =CH–CH₂); 4.45 (d, *J* 7 Hz, =CH–CH₂) (**16** major)/7.79 d, 6 Hz, H(3); 5.71 (t, *J* 7.5 Hz, =CH–CH₂); 4.39 (d, *J* 6.5 Hz, =CH–CH₂) (**16** minor), was noted.

The process was adapted for preparative purposes as follows. A solution of **14a** (0.920 g, 0.005 mol) and NEt_3 (0.505 g, 0.005 mol) in $CHCl_3$ (10 ml) was kept at room temperature for 3 h. The solution was then extracted 3 times with saturated NH_4Cl solution. Drying of the organic phase and solvent removal left a spectrally-assayed mixture of **14a** and **15a**. Column chromatography (pentane/acetone, 7/1) gave the faster moving **15a** (0.515 g, 56%) as an ultimately crystallising oil, m.p. 32–33°C. 1H NMR ($CDCl_3$) δ : 7.63 (dd, *J* 6 and 2 Hz, 1); 6.18 (dd, *J* 6 and 2 Hz, 1); 4.88 (td, *J* 2 and 7.5 Hz, 1); 4.2–3.8 (m, 3); 1.45 (s, 3); 1.35 (s, 3).

2,3-Dideoxy-L-erythro-hex-2-enono-1,4-lactone, **17**

Compound **15a** (0.515 g, 0.0028 mol) was dissolved in 2-propanol (10 ml), containing conc. HCl (0.4 ml). After 18 h at room temperature, solvent was removed and the residue was chromatographed ($CHCl_3/MeOH$, 7/1) to furnish, on recrystallisation from ethyl acetate, **17** (0.290 g, 40% based on **14a**). M.p. 94–95°C. $C_6H_8O_4$ (144.13) calcd.: C 50.00, H 5.59; found: C 50.2, H 5.5. $[\alpha]_D^{20}$ +187° (c 0.70, H_2O). 1H NMR (acetone- d_6) δ : 7.76 (dd, *J* 6 and 1.75 Hz, 1); 6.12 (dd, *J* 6 and 2.25 Hz, 1); 5.13 (ddd, *J* 4.5, 2.25 and 1.75 Hz, 1); 4.3 (d, *J* 5 Hz, 1); 3.9 (t, *J* 5 Hz, 1); 3.8–3.6 (m, 3).

D-Mannono-1,4-lactone, **18**¹²

D-Isoscorbic acid, **2** (176.1 g, 1 mol) and 10% Pd-C (Merck, 10 g) were suspended in water (400 ml). After hydrogenation at room temperature in a Parr apparatus at 60 psi for 12 days, the catalyst was removed and the filtrate was evaporated *in vacuo*. The residue was taken up in boiling 94% 2-propanol (850 ml), cooled on ice and filtered to leave, on washing with 2-propanol and diethyl ether, pure **18** (91.1 g, 51%), m.p. 151–152°C (lit.¹² 151–152°C). $C_6H_{10}O_6$ (178.14) calcd.: C 40.45, H 5.66; found: C 40.4, H 5.4. $[\alpha]_D^{20}$ +51.2° (c 2.00, H_2O) [lit.¹² $[\alpha]_D^{20}$ +51.3° (H_2O)]. 1H NMR (DMSO- d_6) δ : 5.64 (d, *J* 7.5 Hz, 1); 5.19 (d, *J* 3.5 Hz, 1); 4.76 (d, *J* 6 Hz, 1); 4.51 (t, *J* 5.5 Hz, 1); 4.5–4.0 (m, 3); 3.9–3.3 (m, 3).

5,6-O-Isopropylidene-D-mannono-1,4-lactone, **19**

To a suspension of **18** (44.5 g, 0.25 mol) and 2,2-dimethoxypropane (27.5 g, 0.265 mol) in boiling acetone (250 ml) was added anhydrous $SnCl_2$ (0.075 g). The mixture became homogeneous within 5 min and the reaction was quenched after 15 min by addition of pyridine (0.25 ml). The solution was evaporated under reduced pressure to give a

white waxy solid, which on trituration with CH_2Cl_2 (300 ml) and washing with dry diethyl ether (250 ml), afforded crude **19** (46.2 g), m.p. 132–134°C. Silica gel filtration (5% acetone in ethyl acetate) removed traces of **18**, ultimately leaving pure **19** (41.9 g, 77%), m.p. 138–139°C (lit.²⁴ 133°C). $C_9H_{14}O_6$ (218.21) calcd.: C 49.54, H 6.47; found: C 49.8, H 6.4. $[\alpha]_D^{20}$ +59° (c 1.20, H_2O) [lit.²⁴ $[\alpha]_D^{20}$ +55.4° (H_2O)]. 1H NMR (DMSO- d_6) δ : 5.73 (d, *J* 7.5 Hz, 1); 5.38 (d, *J* 4 Hz, 1); 4.5–3.7 (m, 6); 1.34 (s, 3); 1.28 (s, 3).

2,3-O-[(Dimethylamino)methylidene]-5,6-O-isopropylidene-D-mannono-1,4-lactone, **20**

To a suspension of **19** (9.81 g, 0.050 mol) in $CHCl_3$ (100 ml), brought to gentle reflux, was added dropwise DMF dimethyl acetal (6.5 g, 0.055 mol). The produced methanol was distilled off azeotropically during ~4 h and then the reaction mixture was completely freed of volatiles below 50°C, to leave a red-brown oil (13.7 g). This failed to crystallise and was converted directly to **21**. 1H NMR ($CDCl_3$) δ : Major: 5.56 (s, 1); 4.95 (d, *J* 6 Hz, 1); 4.70 (dd, *J* 6 and 3 Hz, 1); 4.45–3.85 (m, 4); 2.31 (s, 6); 1.44 (s, 3); 1.36 (s, 3). Minor: 5.46 (s, 1); 4.75 (m, 2); 4.45–3.85 (m, 4); 2.34 (s, 6); 1.44 (s, 3); 1.36 (s, 3).

5,6-O-Isopropylidene-2,3-O-[(trimethylammonio)methylidene]-D-mannono-1,4-lactone iodide, **21**

Crude **20** (13.7 g, 0.05 mol) was added portionwise with stirring to ice-cold iodomethane (12.5 ml, 0.2 mol). After storing at 0°C for 24 h, the excess of reagent was removed below 40°C (bath) to leave a solid residue. This was triturated with acetone to provide colourless **21** (8.24 g, 38% based on **19**), m.p. ~150°C (decomp.). 1H NMR (DMSO- d_6) δ : Major: 6.36 (br s, 1); 5.75 (d, *J* 6 Hz, 1); 5.48 (dd, *J* 6 and 3.75 Hz, 1); 4.78 (dd, *J* 6 and 3.75 Hz, 1); 4.46 (q, *J* 6 Hz, 1); 4.01 (dd, *J* 9 and 6 Hz, 1); 3.88 (dd, *J* 9 and 6 Hz, 1); 2.98 (s, 9); 1.38 (s, 3); 1.32 (s, 3).

2,3-Dideoxy-5,6-O-isopropylidene-D-erythro-hex-2-enono-1,4-lactone, **22**

A suspension of **21** (4.15 g, 0.01 mol) in dry acetonitrile (20 ml) was heated under reflux for 1 h. The isolation procedure, as described for **14a**, gave a crude oil (1.45 g), consisting for 60% (NMR-determined) of **22**. Column chromatography (pentane/acetone, 7/1) furnished pure **22** (0.89 g, 48%), m.p. 33–34°C. $C_9H_{12}O_4$ (184.19) calcd.: C 58.69, H 6.57; found: C 58.5, H 6.4. $[\alpha]_D^{20}$ –154° (c 1.01, $CHCl_3$). 1H NMR ($CDCl_3$) δ : 7.63 (dd, *J* 6 and 2 Hz, 1); 6.19 (dd, *J* 6 and 2 Hz, 1); 4.89 (td, *J* 2 and 7.5 Hz, 1); 4.2–3.8 (m, 3); 1.46 (s, 3); 1.36 (s, 3).

2,3-Dideoxy-D-erythro-hex-2-enono-1,4-lactone, **4** and 2,3-dideoxy-2-iodo-D-erythro-hex-2-enono-1,4-lactone, **23** (one-pot procedure)

To a solution of **19** (21.8 g, 0.10 mol) in dry 1,2-dimethoxyethane (250 ml) was added at reflux temperature DMF dimethyl acetal (13.1 g, 0.11 mol) in 30 min. Methanol was removed azeotropically, while keeping the concentration constant by adding fresh 1,2-dimethoxyethane (~4 h), to afford an orange-red solution. After concentration to 100 ml, cooling at 0°C and treatment with iodomethane (25 ml, 0.4 mol) during 1 h, the excess of reagent was slowly distilled off. Finally the reaction mixture was heated under reflux during an additional h. On cooling, the precipitate was removed by filtration, the filtrate was evaporated *in vacuo*. The residue was taken up in dry diethyl ether (600 ml) and insoluble, tarry material was discarded. The ethereal solution was concentrated, leaving an oil (15.9 g), whose NMR spectral data indicated the presence of 3 major products. The oily material was dissolved in a mixture of 2-propanol (100 ml) and conc. HCl (4 ml) at room temperature, depositing after 18 h crystalline D-mannono-1,4-lactone **18** (1.53 g, 7%). The supernatant liquid was evaporated and the residue was chromatographed ($CHCl_3/MeOH$, 9/1 → 5/1), to give as first component **23** (2.65 g, 10%), m.p. 95–96°C (ethyl acetate). $C_6H_7IO_4$ (270.03) calcd.: C 26.69, H 2.61; found: C 26.9, H 2.5. $[\alpha]_D^{20}$ –52° (c 1.16, H_2O). 1H NMR (acetone- d_6) δ : 8.03 (d, *J* 2 Hz, 1); 5.15 (dd, *J* 4.5 and 2 Hz, 1); 4.44 (d, *J* 5 Hz, 1); 3.94 (t, *J* 5 Hz, 1); 3.9–3.7 (m, 3).

The second component, recrystallised from ethyl acetate, gave **4** (2.54 g, 18%), m.p. 93.5–94.5°C. $C_6H_8O_4$ (144.13) calcd.: C 50.00, H 5.59; found: C 49.8, H 5.3. $[\alpha]_D^{20}$ –187° (c 0.69, H_2O). 1H NMR (acetone- d_6) δ : 7.75 (dd, *J* 6 and 1.75 Hz, 1); 6.11 (dd, *J* 6 and 2.25 Hz, 1); 5.13 (ddd, *J* 4.5, 2.25 and 1.75 Hz, 1); 4.3 (d, *J* 5 Hz, 1); 3.9 (t, *J* 5 Hz, 1); 3.8–3.6 (m, 3).

Acknowledgements

The capable assistance of undergraduate students *M. van Alphen*, *M. Heuts* and *R. de Bruyn* and of Mr. *W. van 't Hof* (M.S.) is gratefully acknowledged. We also thank Dr. *Marcel Janssen* and Mr. *Jef Dockx* of Janssen Pharmaceutica, Beerse,

Belgium and Dr. *Jan Batelaan*, AKZO Corporate Research, Arnhem, The Netherlands for stimulating discussions and for providing some supporting data. Responsible author (*E.F.G.*) expresses his thanks to colleague *Hessel van der Baan*, without whose intervening good offices this work would not have been possible.

Recl. Trav. Chim. Pays-Bas **104**, 272–276 (1985)

0165-0513/85/10272-05\$1.75

Mechanistic photochemical studies on the 1,3-acyl shift and oxa-di- π -methane rearrangement of two $\beta,\gamma\cdot\gamma',\delta'$ -dienones[†]

Margareth J. C. M. Koppes and Hans Cerfontain*

Laboratory for Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129,
1018 WS Amsterdam, The Netherlands
(Received March 12th, 1985)

Abstract. The photochemical rearrangement of the two 2-(2-alkenyl)-2-(1-cyclopentenyl)cyclopentanones (*E*)-**1a** and (*E*)-**2a** have been studied under conditions of both direct (λ 300 nm) and triplet-sensitized irradiation in order to determine the applicability of 2-alkenyl moieties as intramolecular quenchers of the lowest excited triplet states of the β,γ -enone chromophore.

The $\beta,\gamma\cdot\gamma',\delta'$ -dienone (*E*)-**1a**, upon direct irradiation, exhibits a reversible 1,3-AS shift (1,3-AS) leading to an eventual photostationary state $\{[(E)\text{-}1a]/[(E)\text{-}1b]\}_{\text{pss}} = 4.0 \pm 0.8$, whereas triplet photosensitization of (*E*)-**1a** gives the ODPM isomer (*E*)-**1c**. Both processes occur without (*E*)-(Z) isomerization of the 2-butenyl side-chain. Direct irradiation of (*E*)-**2a** yields, albeit very inefficiently, the 1,3-AS compound (*E*)-**2b** ($\Phi < 0.001$) as the primary product which, upon electronic excitation, forms, in competing reactions, (*E*)-**2a** ($\Phi = 0.18$) and (*Z*)-**2b** ($\Phi = 0.035$). Upon triplet photosensitization of both (*E*)-**2a** and (*E*)-**2b**, only (*E*)-(Z) isomerization of the styryl side-chain is observed. The eventual photostationary state in the direct irradiation equals $\{[(E)\text{-}2a]/[(Z)\text{-}2a]/[(E)\text{-}2b]/[(Z)\text{-}2b]\}_{\text{pss}} = (33 \pm 1)/(33 \pm 1)/(17 \pm 1)/(17 \pm 1)$.

The differences in photochemical behaviour of the $\beta,\gamma\cdot\gamma',\delta'$ -dienone substrates and their 1,3-AS products are discussed with special emphasis being placed upon the triplet energies of the 2-alkenyl chromophores relative to those of the β,γ -enone chromophores and the occurrence of CT interaction which enhances the internal conversion of the $S^1(n\pi^*)$ states of the β,γ -enone chromophores.

Introduction

The photochemistry of β,γ -enones has been intensively studied. The most general reactions displayed by these substrates are isomerizations via a 1,3-acyl shift (1,3-AS) and a 1,2-acyl shift which is usually referred to as oxa-di- π -methane (ODPM) rearrangement. The results of a series of investigations²⁻⁴ permit the conclusion to be drawn that the ODPM rearrangement arises from the lowest $^3(\pi\pi^*)$ state of the enones, which is usually the lowest excited triplet. The mechanism of the 1,3-AS process is far less clearly established. Early studies indicated that the 1,3-AS process occurred only upon direct irradiation and was not quenched by typical triplet quenchers, whereas the acetone- (*i.e.* triplet)-sensitized irradiation resulted in an ODPM rearrangement⁵⁻⁷. The simplest logical conclusion was that the 1,3-AS process originated from the lowest excited singlet state, *i.e.* the $(n\pi^*)$ state^{8,9}. Later it was suggested that this isomerization, at least for certain systems, might proceed from the excited triplet state¹⁰⁻¹⁴. Evidence for this assignment was obtained from studies involving differential sensitization and quenching of the photoreactions¹⁵, temperature dependence of quantum efficiencies for fluorescence and product for-

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