Anthracyclinones. 5.[1] Glucosaccharino-1,4-lactone as a Chiral Template for the Synthesis of New Anthracyclinones

Brigitte Deguin, Jean-Claude Florent, and Claude Monneret*,†

Département de Pharmacognosie, U.A. au CNRS no. 484, Faculté des Sciences Pharmaceutiques et Biologiques, 75270 Paris Cédex 06, France

Received December 5, 1989

Alkylation of dimethoxybenzene **16** with the chiral aldehyde derivative **14** prepared in six steps from α-D-glucosaccharino-1,4-lactone **3** afforded the adduct **17**. After suitable transformation of **17**, A ring closure was stereoselectively performed using $SnCl_4$ at −70 °C, giving **20**. The tetralin-type quinone monoketal **23** obtained from **20** was then condensed with **27**, and complete deprotection of anthracyclinones **28** and **29** led to 9-deacetyl-8(*R*)-hydroxy-9-methyl-4-demethoxydaunomycinone (**6**). On the other hand, **39**, easily obtained from **14**, was condensed with leucoquinizarin **31** to give after oxidation, intramolecular Marschalk reaction and benzylic deoxygenation, the corresponding 7-deoxyaglycon **7**.

Introduction

The broad therapeutic efficacy of the anthracycline antibiotics doxorubicin and daunoribicin[2] has prompted an extensive search for analogues with reduced side effects. For some time, our laboratory has been engaged in a broad program to develop chiral pool syntheses of new aglycon moieties and therefore various syntheses of anthracycline glycosides. For example, in previous papers[3] we have shown that α-D-isosaccharino-1,4-lactone **1** (or its *O*-isopropylidene derivative **2**), obtained in good yield from lactose,[4] is a useful synthon for the preparation of (+)-4-demethoxy-9-deacetyl-9-(hydroxymethyl)daunomycinone **5**, and corresponding potent antitumor anthracyclines.[5]

In this paper we report that α-D-glucosaccharinolactone **3**, which is readily available by alkaline treatment of fructose[6] and isolated as its *O*-isopropylidene derivative **4**,[7] is also an attractive starting material for preparing new anthracyclinones. Thus, the syntheses of aglycon **6** and its corresponding 7-deoxy analogue **7** using **4** as the precursor of ring A carbons C(7)–C(10) are described. In our sequence the chirality of C(2) and C(3) (sugar numbering) in **4** is transferred to C(8) and C(9) in the anthracyclines **6** and **7**.

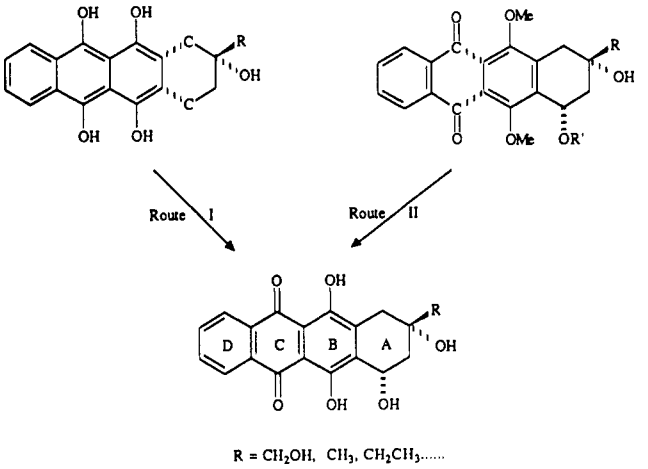
As previously reported[3] for the synthesis of **5**, two routes were examined for the construction of the tetracyclic nucleus of **6** involving condensation of the subunits AB and CD or condensation of the subunit A with leucoquinizarine as a BCD component (Scheme I). The key step in the latter route was an aldolization reaction between leucoquinizarin and a suitable aldehyde precursor of ring A, whereas in the former approach, the AB ring segment was constructed by ortho-alkylation of dimethoxybenzene[8] with the same kind of aldehyde derivative.

Our initial objective was thus the preparation of the crucial aldehyde intermediate from **4**.

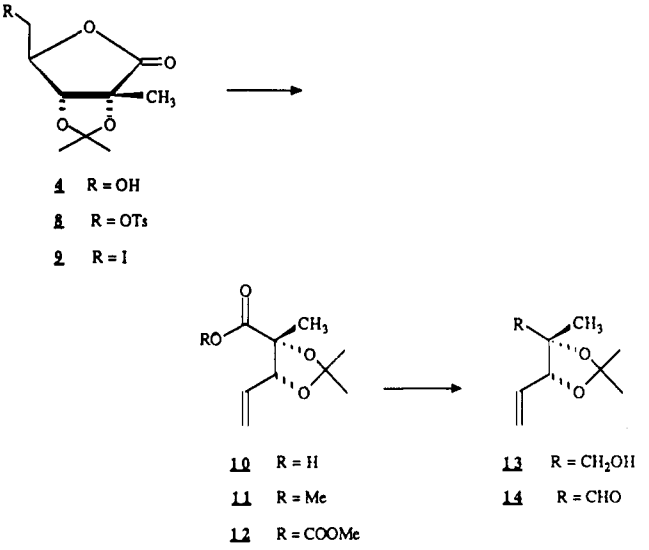
Synthesis of Aldehyde Derivative 14

The lactone **4** was transformed into the iodo derivative **9** in 77% overall yield in a two-step sequence involving formation of the tosylate **8**[9] by reaction with tosyl chloride in pyridine and subsequent exchange for iodine with sodium iodide in butanone (Scheme II). Fragmentation of the 6-iodolactone **9** by modification of the procedure described by Bernet and Vasella[10] (Zn, HOAc, aqueous THF) led almost quantitatively to the unsaturated acid **10**. The following step involved transformation of the unsaturated acid **10** into the corresponding aldehyde **14**.

Scheme I



Scheme II



In initial experiments LAH reduction (refluxing THF) of compound **9** afforded alcohols **13** along with **15**. For-

† Present address: Service de Chimie, Institut Curie, Section de Biologie, 26 rue d'Ulm, F-75231 Paris Cedex 05, France.

(1) For part IV, see: Genot, A.; Florent, J.-C.; Monneret, C. *Tetrahedron Lett.* **1989**, *30*, 711.

(2) Arcamone, F. In *Doxorubicin*; Academic Press: New York, 1981.

(3) (a) Bennani, F.; Florent, J.-C.; Koch, M.; Monneret, C. *Tetrahedron* **1984**, *40*, 4669. (b) Florent, J.-C.; Ughetto Monfrin, J.; Monneret, C. *J. Org. Chem.* **1977**, *52*, 1051. (c) Genot, A.; Florent, J.-C.; Monneret, C. *Ibid.* **1977**, *52*, 1057.

(4) Whistler, R. L.; BeMiller, J. N. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1963; Vol. II, p 477.

0022-3263/91/1956-0405$02.50/0

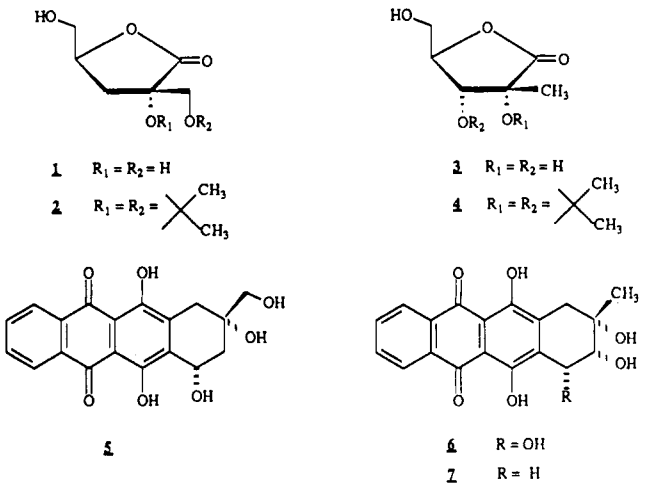
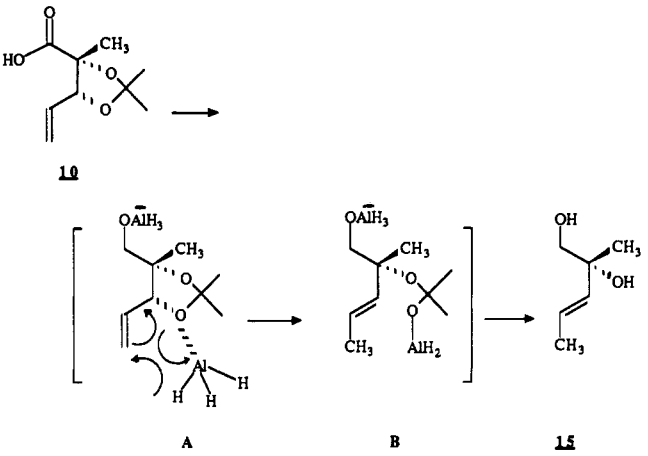


Figure 1.

Scheme III

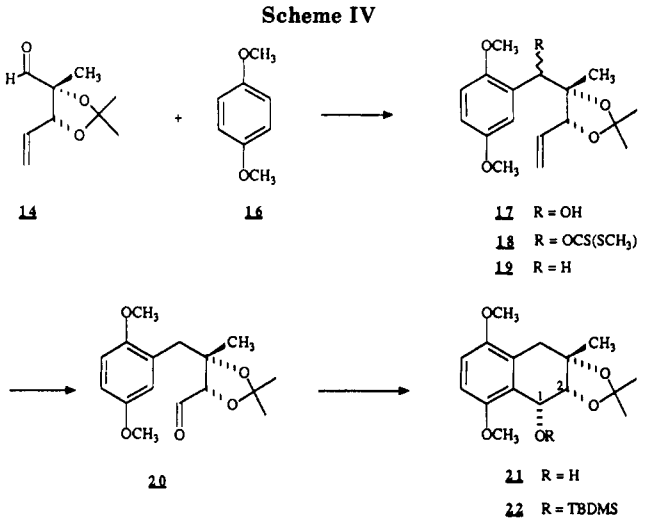


mation of the side product **15** may be explained as depicted in Scheme III through the formation of an alkoxyaluminum hydride derivative A. This intermediate may undergo a hydride intramolecular displacement with concerted migration of the double bond[11] according to a bimolecular mechanism S_N2' to give B and, then, **15** after the workup.

In order to avoid the formation of **15**, LAH reduction of **10** was attempted at room temperature. However, no reaction was observed, even in the presence of a large excess of LAH. An alternative route was thus followed which consisted of preparing alcohol **13** from either the methyl ester **11** or the mixed anhydride **12**.

The methyl ester **11** obtained by treatment of **10** with $MeSO_2Cl$-DMAP-MeOH[12] (28%) or with diazomethane (98%), was reduced with LAH in THF (25 °C) to give, quantitatively, the alcohol **13**. An efficient preparation of

Scheme IV



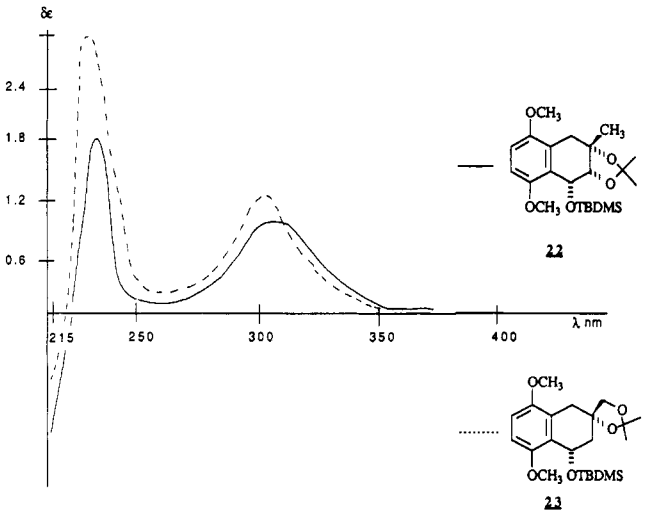


Figure 2.

13 by an alternative two-step sequence involved formation and LAH reduction (−40 °C) of the mixed anhydride **12**[13] (54% overall yield).

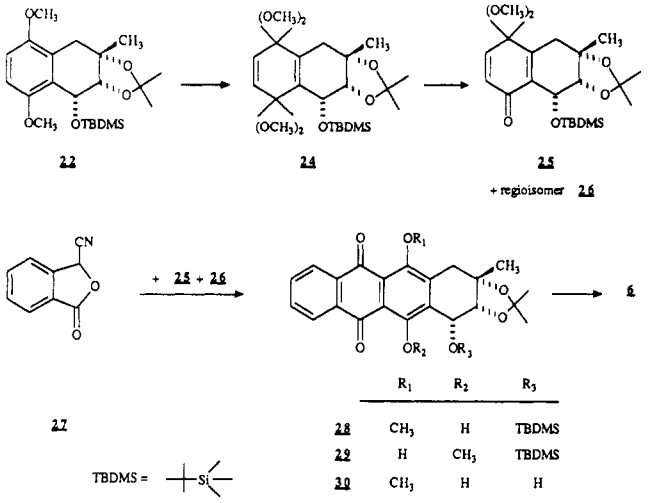
Finally, oxidation of **13** with pyridinium dichromate in dichloromethane containing traces of acetic acid[14] or by the Swern procedure[15] led to the aldehyde **14** in 93% and 80% yields, respectively. On the other hand, **14** was not obtained following attempted reduction of the methyl ester **11** with DIBAH.[16] This lack of reactivity is probably the result of steric hindrance.

Synthesis of Anthracyclinone 6

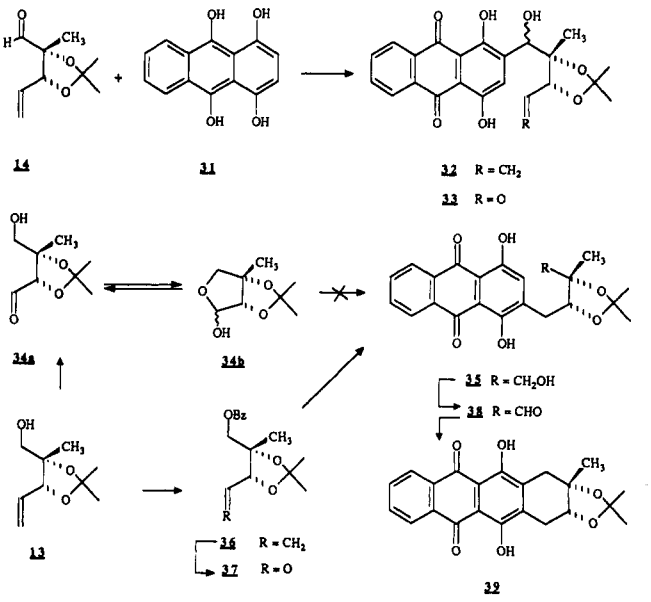
(a) Synthesis of the AB Ring Segment. Coupling of **14** with the lithio derivative of dimethoxybenzene **16** afforded the adduct **17** in 82% yield (Scheme IV). Radical deoxygenation[17] of the methyl dithiocarbonate **18** using Bu_3SnH led to **19**, which, after oxidation (OsO_4–$NaIO_4$),[18] gave the aldehyde derivative **20** (overall yield **17** → **20** ≈

(5) Florent, J.-C.; Genot, A.; Monneret, C. *J. Antibiot.* **1989**, *42*, 1823.
(6) Cf. ref 4, p 484 and references cited therein.
(7) Novak, J. J. K.; Sorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 857. Blair, M. G.; Kuenne, D. J. *J. Am. Chem. Soc.* **1957**, *79*, 6450. Lopez-Aparicio, F. J.; Cubero, I. I.; Olea, M. D. *Carbohydr. Res.* **1984**, *129*, 99.
(8) Shirley, D. A.; Johnson, J. R., Jr.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209. Shirley, D. A.; Hendrix, J. P. *Ibid.* **1968**, *11*, 217.
(9) Sowden, J. C.; Stroback, D. R. *J. Am. Chem. Soc.* **1960**, *82*, 3707.
(10) Bernet, B.; Vasella, A. *Helv. Chem. Acta* **1984**, *67*, 1328.
(11) Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 6661. Fraser-Reid, B.; Tam, S. Y.-K.; Radatus, B. *Can. J. Chem.* **1975**, *53*, 2005. Achmatowicz, O., Jr.; Szechner, B. *Tetrahedron Lett.* **1972**, 1205.
(12) Chandrasekaran, S.; Turner, J. V. *Synth. Commun.* **1982**, *12*, 727.
(13) Adams, J.; Milette, S.; Rokach, J.; Zamboni, R. *Tetrahedron Lett.* **1984**, *25*, 2179.
(14) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.
(15) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. Swern, D.; Manecuso, J. *Synthesis* **1981**, 165.
(16) Winterfeldt, E. *Synthesis* **1975**, 617.
(17) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(18) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

Scheme V



Scheme VI



50%). Ring closure of **20** was carried out in the presence of $SnCl_4$ at −78 °C to give the desired *cis*-tetralin (1*R*,2*R*,3*S*)-**21** (44% after purification). The 1*R* configuration of compound **21** was unambiguously deduced from comparison of the CD curve of its *O*-silyl ether derivative **22** with the CD curve of **23**,[3c] the structure of which was previously assigned by ^1H NMR. On the other hand, the 2*R* configuration of **21** was deduced from ^1H NMR. The coupling constant ($J_{1,2}$ = 4 Hz) can be interpreted as the result of a *cis*-vicinal relationship between H-1 and H-2 as shown by models (angle ≈40°).

In addition to **21**, three other side products were also obtained. Although this mixture could not be purified, the presence of the corresponding *trans*-tetralin 1*S*,2*R*,3*S* isomer may be postulated in addition to two other diastereomers (1*R*,2*S*,3*S* and 1*S*,2*S*,3*S*). These latter two compounds may arise via isomerization of the α-alkoxy aldehyde during the annelation reaction.

(b) Coupling of the AB and CD Segments. The elaboration of the tetracyclic skeleton of anthacyclinone was achieved following the general protocol described by Swenton et al.[19] in which a phtalide anion is condensed with tetralin-type monoketals. Thus, the ((*tert*-butyldimethylsilyl)oxy)tetralin **22**, prepared[20] from **21**, was subjected to anodic oxidation,[21] giving the quinone bisketal **24**. Selective hydrolysis of **24** in aqueous acetic acid afforded a mixture of monoketals **25** and **26**, which, on reaction with the anion of 3-cyano-1(3*H*)-isobenzofuranone (**27**),[22] gave a mixture of regioisomeric anthracyclinones **28** and **29** in 70% yield (see Scheme V). These compounds were not readily separable, but following desilylation of the mixture (Bu_4NF, 3 h), the 11-methoxy derivative **30** (72%) and the unreacted **29** (20%) were obtained pure, after chromatography. Steric hindrance can account for the stability of the silyl ether in **29** in *peri* position to the 6-methoxy ether. Then **30** yielded anthracyclinone **6** (89–90%) by treatment with BCl_3 at −78 °C.

(c) Route A + BCD. The condensation of aldehyde **14** with leucoquinizarin **31** in the presence of DBU[23] afforded, in low yield (33%), a mixture of diastereoisomeric alkylanthraquinones **32** (Scheme VI) which could not be separated by column chromatography. Since all attempts to deoxygenate or to oxidize the benzylic hydroxyl group were unsuccessful, oxidation of the terminal double bond (OsO_4–$NaIO_4$)[18] was carried out to give **33**. The intramolecular aldolization reaction of **33** under Marschalk conditions (NaOH, $Na_2S_2O_4$)[24] afforded a complex mixture that could not be characterized.

In order to avoid these difficulties due to the presence of two asymmetric carbons at C-7 and C-10, we turn our attention toward the synthesis of the 7-deoxy analogue **7** by the A + BCD route. The preparation of the two other aldehydes derivatives **34** and **37** from α-D-glucosaccharinolactone was therefore undertaken. Aldehyde **34** was readily obtained by oxidation (OsO_4–$NaIO_4$, 78%)[18] of unsaturated alcohol **13**, but subsequent efforts to obtain alkylanthraquinone **35** by condensation of **34** with leucoquinizarine **31** (Shaw,[23] Marschalk,[24] or Lewis[25] procedures) failed. This could be attributed to the fact that **34** exists preferentially in the cyclic hemiacetal form **34b** as indicated by ^1H NMR and IR spectra. Such an explanation is in agreement with previous observations reported with other cyclic hemiacetals either as furanosides[3b,26] or pyranosides.[27] To overcome this obstacle, the corresponding aldehyde **37** fixed in the open-chain form was prepared in a next experiment. This involved benzoylation of **13** prior to the oxidation step (**13** → **36** → **37**). For obtention of alkylanthraquinone **35**, condensation of **37** with leucoquinizarine **31** (DBU, DMF, room temperature, 5 min), benzylic deoxygenation ($Na_2S_2O_4$, H_2O, 80 °C, 30 min), and alcohol deprotection (NaOH 1 N, room temperature, 1 h) were carried out in a "one-pot" reaction and 60% overall yield. Using the Corey oxidation procedure[28] (*N*-chlorosuccinimide, Me_2S, Et_3N), **35** was easily transformed (>90%) into aldehyde **38**. Marschalk intramolecular reaction ($Na_2S_2O_4$, THF, H_2O, KOH, −10 °C, 30 min) of **38** followed by benzylic deoxygenation of the crude product ($Na_2S_2O_4$, DMF–H_2O, 80 °C, 30 min) gave the anthracyclinone **39** (**35** → **39**, 60% overall yield). Further acidic hydrolysis

(19) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625 and references cited therein.
(20) Corey, E. J.; Venkateswarlu, A.; Ogilive, K. K.; Iwacha, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 6190; *Tetrahedron Lett.* **1973**, 317.
(21) Henton, D.; McCreery, R.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369.
(22) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.
(23) Qureshi, S.; Shaw, G.; Burgess, G. E. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1557.
(24) Marschalk, C.; Koenig, J.; Ouroussoff, N. *Bull. Soc. Chim. Fr.* **1936**, 1545.
(25) Lewis, C. E. *J. Org. Chem.* **1970**, *35*, 2938.
(26) Krohn, K.; Heins, H. *Carbohydr. Res.* **1989**, *191*, 253.
(27) Mincher, D. J.; Shaw, G.; De Clercq, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 613.
(28) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

quantitatively afforded the target compound 7.

Experimental Section

General Methods. Melting points (Kofler hot stage microscope) are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer, calibrated against polystyrene film, and were expressed in cm^{-1}. ^1H NMR spectra at 270 MHz were obtained on a Bruker HX 270 in $CDCl_3$. Chemical shifts are expressed in ppm downfield from internal Me_4Si with the notations indicating the multiplicity of the signal (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). The coupling constants are expressed as J values in units of hertz. Mass spectra (DCI/NH_3 or EI) were recorded on a Nermag R 1010. For EI they were obtained at an ionizing voltage of 70 eV.

Silica gel for column (flash) chromatography was Merck silica gel 60 No. 9385. In all cases, the solvent systems used for the chromatographic separations were chosen such that on TLC an R_f of 0.25–0.30 was observed for the compound to be isolated.[29] Analytical thin-layer chromatographies were performed on Merck silica gel 60 F_{254}.

Ether solvents (THF and ether) were dried over sodium benzophenone and distilled, and dry CH_2Cl_2 was distilled over CaH_2.

Microanalyses were performed by the "Laboratoire de Microanalyse du CNRS," Gif-sur-Yvette and Lyon.

(-)-5-Iodo-2,3-*O*-isopropylidene-2-*C*-methyl-D-ribolactone (9). Sodium iodide (42 g, 0.29 mol) was added to a solution of 8[9] (90 g, 0.25 mol) in 2-butanone (800 mL), and the suspension was heated under reflux for 3 h. After cooling to room temperature and filtration, the resulting solution was evaporated under reduced pressure to ca. 100–150 mL, and the residue was diluted with water, extracted with ether, dried (Na_2SO_4), and concentrated to give **9** (75 g, 95%) as a pale yellow oil: $[\alpha]^{20}_D$ −50° (*c* 0.6, chloroform); IR (film) 1790 cm^{-1}; ^1H NMR δ 4.64 (dd, 1 H, J = 10, J' = 4.5, 4-H), 4.40 (s, 1 H, 3-H), 3.41 (dd, 1 H, J = 10, J' = 4.5, 4'a-H), 3.11 (dd, 1 H, J = 10, J' = 4.5, 4'b-H), 1.62 (s, 3 H, Me), 1.44 (s, 6 H, CMe_2); DCI/NH_3 m/z 330 ($M + NH_4^+$, base peak). Anal. Calcd for $C_9H_{13}O_4I$: C, 34.63; H, 4.19; I, 40.66. Found: C, 34.72; H, 4.25; I, 40.82.

(+)-(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-enoic Acid (10). To a cold solution (0 °C) of iodo derivative **9** (32 g, 102 mmol) in THF (450 mL) were successively added zinc powder (65 g), acetic acid (6.5 mL), and water (6.5 mL). The mixture was stirred vigorously at room temperature under an inert atmosphere for 3 h. After filtration through a pad of Celite, the filtrate was concentrated and the residue was diluted with EtOAc (≈500 mL). The organic solution was washed with 1 N aqueous HCl and H_2O, dried (Na_2SO_4), and evaporated under reduced pressure to give **10** (18 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ +23° (*c* 2.2, chloroform); IR (film) 3500, 3000, 1780, and 1600 cm^{-1}; ^1H NMR δ 5.83 (m, 1 H, 4-H), 5.50 (d, 1 H, J = 16.5, 5a-H), 5.38 (d, 1 H, J = 10.5, 5b-H), 4.43 (d, 1 H, J = 7, 3-H), 1.62 (s, 3 H), and 1.55 (s, 3 H) (CMe_2), 1.44 (s, 3 H, Me); DCI/NH_3 m/z 204 ($M + NH_4^+$), 187 ($M + H^+$). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.15; H, 7.63.

(-)-(2*R*,3*R*)-Methyl 2,3-Dihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-enoate (11). Method a. Triethylamine (0.74 mL, 5.4 mmol) and mesyl chloride (0.25 mL, 2.9 mmol) were added to a cooled solution (−40 °C) of **10** (500 mg, 2.7 mmol) in anhydrous dichloromethane (30 mL). After 1.5 h at −40 °C, MeOH (0.54 mL, 13.4 mmol) and DMAP (70 mg, 0.53 mmol) were added and the reaction mixture was allowed to reach room temperature. After 1 h, the solution was concentrated under reduced pressure, and the residue was diluted with ether. After filtration, the filtrate was concentrated and flash chromatography (hexane–EtOAc, 4:1) afforded 150 mg (28%) of **11**.

Method b. To a solution of **10** (2.6 g, 14 mmol) in ether (150 mL) was added dropwise, under inert atmosphere, an ethereal solution of diazomethane[30] until the starting material has disappeared as shown by TLC (hexane–acetone, 2:1). Concentration under reduced pressure afforded **11** (2.77 g, quantitative) as a colorless syrup: $[\alpha]^{20}_D$ −30° (*c* 1.6, chloroform) [lit.[31] $[\alpha]^{20}_D$ −36.4° (*c* 3.52, $CDCl_3$)]; IR (film) 1740, 1645, and 1190 cm^{-1}; ^1H NMR δ 5.75 (m, 1 H, 4-H), 5.46 (d, 1 H, J = 16.5, 5a-H), 5.28 (d, 1 H, J = 10.5, 5b-H), 4.33 (d, 1 H, J = 7, 3-H), 3.70 (s, 3 H, OMe), 1.62 (s, 3 H), 1.52 (s, 3 H), and 1.43 (s, 3 H) (Me and CMe_2).

(-)-(2*S*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-enol (13). (a) From 10. Lithium aluminum hydride (300 mg, 7.89 mmol) was carefully added to a cold solution (0 °C) of **10** (1 g, 5.37 mmol) in anhydrous THF (150 mL). The reaction mixture was stirred under reflux overnight and subjected to workup by successive addition of H_2O (0.3 mL), 15% aqueous NaOH (0.3 mL), and H_2O (0.9 mL). After the mixture was stirred for 24 h at room temperature, the salts were separated by filtration and the filtrate was concentrated under reduced pressure. Flash chromatography (hexane–EtOAc, 2:1) gave 280 mg of **13** and 170 mg of **15** (total yield 75%). Compound **15**: syrup; $[\alpha]^{20}_D$ −5.5° (*c* 1.6, chloroform); IR (film) 3500, 1660 cm^{-1}; ^1H NMR δ 5.73 (m, 1 H, 4-H), 5.51 (dd, 1 H, J = 16, J' = 2, 3 H), 3.46 (d, 1 H) and 3.39 (d, 1 H) (J = 14, 1-CH_2), 2.77 (s, 2 H, OH), 1.71 (dd, 1 H, J = 8, J' = 2, 3-H), 1.24 (s, 3 H, 2-Me); DCI/NH_3 m/z 134 ($M + NH_4^+$), 116 (M^+, base peak), 99, 85. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.10; H, 10.29.

(b) From 11. To a solution of **11** (500 mg, 2.5 mmol) in THF (100 mL) was added portionwise at 0 °C $LiAlH_4$ (150 mg, 3.9 mmol). The suspension was stirred at room temperature and treated sequentially with H_2O (0.15 mL), 15% aqueous NaOH (0.15 mL), and H_2O (0.45 mL). Workup as indicated above afforded 422 mg (98%) of **13** as a colorless syrup: $[\alpha]^{20}_D$ −8.5° (*c* 1, chloroform); IR (film) 3650, 1645, and 1380 cm^{-1}; ^1H NMR δ 5.86 (m, 1 H, 4-H), 5.46 (d, 1 H, J = 16.5, 5a-H), 5.28 (d, 1 H, J = 10.5, 5b-H), 4.33 (d, 1 H, J = 7, 3-H), 3.51 (d, 1 H, J = 11) and 3.29 (d, 1 H, J = 11) (AB syst., 1-CH_2), 2.44 (s, 1 H, OH), 1.51 (s, 3 H), 1.44 (s, 3 H) and 1.33 (s, 3 H) (Me and CMe_2); EIMS (relative intensity) m/z 173 (M + 1, 0.5), 157 (M − 15, 50), 141 (M − 31, 74), 83 (75), 69 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.82; H, 9.27.

(c) From Mixed Anhydride 12. Triethylamine (21 mL, 150 mmol) and methyl chloroformate (11.6 mL, 150 mmol) were added to a cold solution (0 °C) of **10** (14 g, 75.2 mmol) in dichloromethane (400 mL). After stirring for 2 h at 0 °C, the solvent was removed under reduced pressure and the residue was suspended into ether. After filtration and concentration, compound **12** was obtained (16.5 g) as an oil. This was immediately dissolved in THF (400 mL), and after cooling at −40 °C, $LiAlH_4$ (3.30 g, 86.8 mmol) was added. The mixture was stirred for 5 min, and the remaining $LiAlH_4$ was destroyed in usual manner. This gave 7 g (54%) of **13** after flash chromatography with hexane–acetone (5:1).

(-)-(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-enal (14). Method a. To a mixture of dry dimethyl sulfoxide (2 mL, 29 mmol) and anhydrous dichloromethane (30 mL) stirred under inert atmosphere at −60 °C was added trifluoroacetic anhydride (3 mL, 22 mmol) followed, after 10 min, by a solution of **13** (1.25 g, 7.26 mmol) in anhydrous CH_2Cl_2 (30 mL). The mixture was allowed to reach room temperature, and, after 30 min, triethylamine (6 mL, 43.4 mmol) was added. Further stirring for 40 min was followed by concentration under reduced pressure to ca. 10 mL, dilution with H_2O, and extraction with ether to give a crude product (1.3 g). Flash chromatography with dichloromethane–hexane (90:10) as eluent afforded 1 g (80%) of **14** as a syrup: $[\alpha]^{20}_D$ −41° (*c* 2, chloroform); IR (film) 1720 and 1600 cm^{-1}; ^1H NMR δ 9.57 (s, 1 H, 1-H), 5.77 (m, 1 H, 4-H), 5.51 (d, 1 H, J = 16, 5a-H), 5.35 (d, 1 H, J = 10, 5b-H), 4.44 (d, 1 H, J = 7, 3-H), 1.60 (s, 3 H), 1.50 (s, 3 H) and 1.36 (s, 3 H) (Me and CMe_2); EIMS (relative intensity) m/z 155 ($M^{\bullet+}$, 15.5), 141 ($M^{\bullet+}$ − 29, 100), 83 (100), 69 (50). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.68; H, 8.17.

Method b. Pyridinium dichromate (6.56 g, 17.4 mmol), freshly activated molecular sieves powder (17.5 g, 3-Å), and then anhydrous acetic acid (1.75 mL) were added successively to a solution of **13** (2.5 g, 14.5 mmol) in dry dichloromethane (250 mL). After stirring for 45 min at room temperature, the crude mixture was diluted with ether (50 mL), filtered through a short pad of silica gel, and evaporated under reduced pressure to give **14** as a pure product (2.30 g, 93%).

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(30) De Boer, T. T.; Backer, H. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 250.
(31) Hoffmann, R. W.; Ladner, W. *Chem. Ber.* **1983**, *116*, 1631.

(1*R*,2*S*,3*R*)- and (1*S*,2*S*,3*R*)-1-(2,5-Dimethoxyphenyl)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-ene (17). To a cold solution (0 °C) of dimethoxybenzene **16** (4 g, 28.9 mmol) in dry ether (50 mL) under argon atmosphere was added dropwise *n*-butyllithium (1.8 M) in hexane (16.6 mL). After the mixture was stirred at room temperature for 24 h and then cooled to −78 °C, aldehyde **13** (2.3 g, 13.5 mmol) in solution in dry ether (20 mL) was slowly added to the reaction mixture and stirring was maintained for 1 h at −78 °C. Addition of an aqueous saturated solution of ammonium chloride was followed by dilution with ether. The ether layer was washed with H_2O and dried over Na_2SO_4, and the solvent removed under reduced pressure. The resulting syrup was flash chromatographed with toluene–acetone (98:2) as eluent to afford 3.4 g (82%) of **17**: ^{1}H NMR δ 7.00–6.73 (m, 3 H, Ar), 6.42–6.10 (m, 1 H, 4-H), 5.60–5.31 (m, 2 H, 5a-H and 5b-H), 5.06–4.95 (2 d, 1 H, 1a-H and 1b-H), 4.50–4.40 (2 d, 1 H, H-3a and H-3b), 3.81 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.33 (d, 1 H, J = 7, OH) and 2.84 (d, 1 H, J = 7, OH), 1.72, 1.55, 1.45, 1.42, 1.37, and 1.06 (6 s, total 9 H, Me and CMe_2); DCI/NH_3 m/z 326 (M + NH_4^+), 309 (M + H^+), 235 (base peak), 167, 141.

(−)-(2*S*,3*R*)-5-(2,5-Dimethoxyphenyl)-3,4-dihydroxy-3,4-*O*-isopropylidene-4-methylpentene (19). Sodium hydride (50% suspension in oil, 75 mg, 7.5 mmol) was added to a cold solution (0 °C) of alcohol **17** (1.5 g, 4.9 mmol) in dry THF (50 mL) and, 30 min later, 0.87 mL (14.7 mmol) of carbon disulfide. The resulting mixture was stirred for 1.5 h at 0 °C before addition of methyl iodide (0.9 mL, 14.7 mmol). The mixture was allowed to reach room temperature and stirred overnight. The solvent was removed under reduced pressure, and the remaining residue was dissolved in toluene (30 mL) and filtered. To the filtrate containing **18** were added tributyltin hydride (1.57 mL, 5.9 mmol) and AIBN (20 mg). This mixture was refluxed under argon for 2.5 h. After cooling and filtration, the solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel with hexane–EtOAc (9:1) as eluent to give 840 mg (60%) of **19** as a crystalline compound: mp 42–43 °C; $[\alpha]^{20}_D$ −92° (*c* 1.3, chloroform); IR (Nujol) 2800, 1600 cm^{-1}; ^{1}H NMR δ 6.93 (d) and 6.75–6.20 (m) (3H-Ar, H), 6.00 (m, 1 H, 2-H), 5.48 (d, 1 H, J = 7, 1a-H), 5.37 (d, 1 H, J = 10, 1b-H), 4.37 (d, 1 H, J = 7, 3-H), 3.77 (s, 3 H), 3.75 (s, 3 H) (2 OMe), 2.84 (d, 1 H, J = 15) and 2.60 (d, 1 H, J = 15) (AB, 5-CH_2), 1.66 (s, 3 H), 1.39 (s, 3 H) and 1.13 (s, 3 H) (Me and CMe_2); EIMS (relative intensity) m/z 292 ($M^{\bullet+}$, 100), 277 (M − 15, 25), 151 (75), 141 (60). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.73; H, 8.28.

(−)-(2*S*,3*S*)-4-(2,5-Dimethoxyphenyl)-2,3-dihydroxy-2,3-*O*-isopropylidene-3-methylbutanal (20). To the cold solution (0 °C) of **19** (770 mg, 2.63 mmol) in a 1:1 mixture of ether and H_2O (160 mL) were added 1.3 mL of osmium tetraoxide in 2-methyl-2-propanol solution (2.5%) and sodium metaperiodate (5.64 g, 26.4 mmol). After the mixture was stirred for 48 h under an argon atmosphere at room temperature, the aqueous phase was separated and extracted with ether. Evaporation of ether under reduced pressure gave a dark residue (≈800 mg) which was chromatographed on silica gel with hexane–dichloromethane (95:5) as eluent to afford 610 mg (80%) of **20** as a colorless syrup: $[\alpha]^{20}_D$ −62° (*c* 1.2, chloroform); IR (film) 2820, 2720, and 1720 cm^{-1}; ^{1}H NMR δ 9.82 (s, 1 H, CHO), 6.88 (d) and 6.78 (m) (3 H, Ar-H), 4.25 (d, 1 H, J = 2, 2-H), 3.76 (s, 3 H), 3.74 (s, 3 H) (2 OMe), 2.91 (d, 1 H, J = 13), 2.66 (d, 1 H, J = 13) (AB, 4-CH_2), 1.72 (s, 3 H), 1.41 (s, 3 H), and 1.32 (s, 3 H) (Me and CMe_2); EIMS (relative intensity) m/z 294 ($M^{\bullet+}$, 45), 151 (M − 143, 45), 143 (73), 85 (100). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.40; H, 7.67.

(+)-(1*R*,2*R*,3*S*)-1,2,3-Trihydroxy-1,2,3,4-tetrahydro-2,3-*O*-isopropylidene-3-methyl-5,8-dimethoxynaphthalene (21). To a solution of aldehyde **20** (1.6 g, 5.44 mmol) in dry dichloromethane (50 mL) cooled at −78 °C was added dropwise under argon, 0.70 mL (6 mmol) of $SnCl_4$. The mixture was stirred for 2 h, quenched by addition of Et_3N (0.5 mL), and evaporated. The residue was diluted with dichloromethane and washed with an 1 N aqueous NaOH solution. The organic layer was dried (Na_2SO_4), and after concentration under reduced pressure, the crude residue (1.5 g) was chromatographed on silica gel with hexane–EtOAc (4:1) as eluent. Compound **21** (700 mg, 44%) was eluted first whereas the next fractions contained a mixture of several compounds which could not be separated. Recrystallization of **21** from hexane: mp 120 °C; $[\alpha]^{20}_D$ +33° (*c* 1.2, chloroform); ^{1}H NMR δ 6.77 (m, 2 H, Ar-H), 5.14 (d, 1, H, J = 4, 1-H), 4.19 (d, 1 H, J = 4, 2-H), 3.82 (s, 3 H) and 3.76 (s, 3 H) (2 OMe), 3.15 (d, 1 H, J = 16) and 2.57 (d, 1 H, J = 16) (AB, 4-CH_2), 1.43 (s, 3 H), 1.37 (s, 3 H), and 1.18 (s, 3 H) (Me and CMe_2); EIMS (relative intensity) m/z 294 ($M^{\bullet+}$, 10), 279 (M − 15, 10), 210 (M − 84, 75), 84 (100). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.51; H, 7.57.

(+)-(1*R*,2*R*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4-tetrahydro-1,2,3-trihydroxy-2,3-*O*-isopropylidene-3-methyl-5,8-dimethoxynaphthalene (22). Imidazole (1.7 g, 25 mmol) and *tert*-butyldimethylsilyl chloride (2.5 g, 16.6 mmol) were added to a solution of tetralin derivative **21** (620 mg, 2.1 mmol) in dry DMF (50 mL). The mixture was heated under reflux for 5 h and, after cooling, diluted with H_2O and extracted with ether. The organic layer was washed, dried (Na_2SO_4), and concentrated under reduced pressure. This afforded a residue (≈900 mg), which was chromatographed on silica gel with hexane–EtOAc (4:1) as eluent. Compound **22** was obtained (850 mg, 96.5%) as a syrup: $[\alpha]^{20}_D$ +17° (*c* 1.7 chloroform); IR (film) 1600, 1580, 1520, and 1380 cm^{-1}; ^{1}H NMR δ 6.75 (d, 1 H, J = 8) and 6.62 (d, 1 H, J = 8) (2H-Ar), 5.39 (d, 1 H, J = 4.5, 1-H), 3.80 (d, 1 H, 2-H), 3.71 (s, 6 H, 2 OMe), 3.18 (1 H, J = 13) and 3.03 (d, 1 H, J = 13) (AB, 4-CH_2), 1.51 (s, 3 H), 1.45 (s, 3 H), and 1.15 (s, 3 H) (Me and CMe_2), 0.74 (s, 9 H, *tert*-butyl), 0.07 (s, 3 H), and −0.19 (s, 3 H) (2 Me); DCI/NH_3 m/z 426 (M + NH_4^+), 408 (M + H^+), 393 (M − 15), 294 (100), 277 (100), 219 (100). Anal. Calcd for $C_{22}H_{36}O_5Si$: C, 64.50; H, 8.81. Found: C, 64.50; H, 8.74.

(1*R*,2*R*,3*S*)-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,5,8-hexahydro-1,2,3-trihydroxy-2,3-*O*-isopropylidene-3-methyl-5,5-dimethoxy-8-oxonaphthalene (25) and Its 8,8-Dimethoxy-5-oxo Isomer (26). Anodic oxidation of **22** (680 mg) was carried out as described by Swenton,[21] and the resulting crude bis(ketal) **24** was dissolved in acetone (150 mL) and stirred in the presence of aqueous 5% AcOH solution (30 mL) for 48 h at −20 °C. Extraction with ether followed by chromatography on silica gel with toluene–acetone (98:2) as eluent afforded 450 mg (64%) of a mixture of regioisomers **25** and **26**: DCI/NH_3 m/z 425 (M + H^+), 280 (100).

(7*R*,8*R*,9*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-7,8,9,10-tetrahydro-6,7,8,9-tetrahydroxy-8,9-*O*-isopropylidene-11-methoxy-9-methyl-5,12-naphthacenequinone (28) and Its 11-Hydroxy-6-methoxy Isomer (29). Condensation of cyanophthalide **27** (490 mg)[22] with the ketal mixture **25** + **26** (650 mg) under the conditions previously described (see ref 19) afforded, after chromatography on silica gel with toluene–acetone (98:2), 600 mg of **28** + **29** (75%).

Compound 28: syrup; $[\alpha]^{20}_D$ +67° (*c* 0.03, chloroform); IR ($CHCl_3$) 1650 and 1625 cm^{-1}; ^{1}H NMR δ 13.44 (s, OH, phenol), 8.33 (m, 2 H, Ar) and 7.82 (m, 2 H, Ar), 5.62 (d, 1 H, 7-H), 3.97 (d, 1 H, J = 4, 8-H), 3.87 (s, 3 H, OMe), 3.42 (d, J = 14) and 3.27 (d, J = 14) (AB, 10-CH_2), 1.58 (s, 3 H) and 1.51 (s, 3 H) (CMe_2), 1.24 (s, 3 H, Me), 0.81 (s, 9 H, *tert*-butyl), 0.09 (s, 3 H) and −0.02 (s, 3 H) ($SiMe_2$); DCI/NH_3 m/z 525 (M + H^+), 409, 395, 394, 336.

Compound 29: syrup; $[\alpha]^{20}_D$ −6° (*c* 0.14, chloroform); IR (film) cf. **26**; ^{1}H NMR δ 13.44 (s, OH, phenol), 8.30 (m, 2 H, Ar) and 7.82 (m, 2 H, Ar), 5.42 (d, 1 H, J = 4, 7-H), 3.97 (d, 1 H, J = 4, 8-H), 3.87 (s, 3 H, OMe), 3.43 (d, J = 14) and 3.23 (d, J = 14) (AB, 10-CH_2), 1.55 (s, 3 H) and 1.51 (s, 3 H) (CMe_2), 0.81 (s, 9 H, *tert*-butyl), 0.10 (s, 3 H) and −0.04 (s, 3 H) ($SiMe_2$); DCI/NH_3 m/z 525 (M + H^+), 409, and 391. Anal. Calcd for $C_{29}H_{36}O_7Si$: C, 66.38; H, 6.91. Found: C, 66.43; H, 7.12.

(−)-(7*R*,8*R*,9*S*)-7,8,9,10-Tetrahydro-6,7,8,9,11-pentahydroxy-8,9-*O*-isopropylidene-9-methyl-11-methoxy-5,12-naphthacenequinone (30). To a solution of **28** + **29** (300 mg, 0.57 mmol) in dry THF (30 mL) was added tetrabutylammonium fluoride (1 M solution in THF, 1.15 mL). After being stirred for 3 h, the blue mixture was neutralized by addition of some drops of 1 N HCl until the color became red. Extraction with ether gave a crude mixture (280 mg), and flash chromatography on silica gel (hexane–EtOAc, 3:1) allowed isolation of **30** (168 mg) and unreacted **29** (60 mg). For compound **30**: $[\alpha]^{20}_D$ −5° (*c* 0.11, chloroform); IR ($CHCl_3$) 1650, 1625 cm^{-1}; ^{1}H NMR δ 13.9 (s, OH, phenol), 8.28 (m, 2 H, Ar), 7.81 (m, 2 H, Ar), 5.31 (d, 1 H, J = 4, 7-H), 4.35 (d, 1 H, 8-H), 3.94 (s, 3 H, OMe), 3.42 (d, 1 H, J = 16) and 2.73 (d, 1 H, J = 16) (AB, 10-CH_2), 1.58 (s, 3 H), 1.47 (s, 3 H), 1.27 (s, 3 H) (Me and CMe_2). Anal. Calcd for $C_{23}H_{22}O_7$:

C, 67.30; H, 5.40. Found: C, 67.35; H, 5.42.

(+)-(8*R*)-9-Deacetyl-8-hydroxy-9-methyl-4-demethoxydaunomycinone (6). To a solution of **30** (100 mg, 0.19 mmol) in dry dichloromethane (30 mL) cooled at −78 °C were added 10 equiv of BCl_3 (2.5 mL of 1 M solution in dichloromethane). The mixture was stirred for 30 min, quenched with 30 mL of MeOH, and allowed to reach room temperature. Evaporation under reduced pressure followed by crystallization from ethyl acetate afforded **6** (60 mg, 0.17 mmol, 89%) as red crystals: mp 268 °C; $[\alpha]^{20}_D$ +152° (*c* 0.02, dioxane); IR ($CHCl_3$) 3640, 1660, and 1625 cm^{-1}; ^1H NMR δ 8.32 (m, 2 H, Ar), 7.69 (m, 2 H, Ar), 4.10 (d, 1 H, *J* = 4, 8-H), 5.55 (d, 1 H, 7-H), 3.68 (d, 1 H, *J* = 20) and 2.91 (d, 1 H, *J* = 20) (AB, 10-CH_2), 1.73 (s, 3 H, Me); DCI/NH_3 *m/z* 374 (M + NH_4^+), 357 (M + H^+). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.91; H, 9.29.

(1*R*- and 1*S*,2*R*,3*S*)-1-(1,4-Dihydroxy-5,10-anthraquinonyl)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-ene (32). To a solution of leucoquinizarin **31** (1.4 g, 5.78 mmol) in THF (100 mL), under an argon atmosphere, were added DBU (1 mL) and then a solution of the aldehyde **14** (500 mg, 2.94 mmol) in THF (10 mL). After being stirred for 0.5 h at room temperature, the reaction mixture was reoxidized by bubbling air through the solution, diluted with CH_2Cl_2, and acidified by addition of 1 N HCl. Separation of the organic layer followed by usual workup afforded a residue (860 mg), and chromatography on silica gel (toluene–acetone, 97:3) led to isolation of 400 mg of **32** as a mixture of stereoisomers: syrup, IR ($CHCl_3$) 3600, 1620, and 1580 cm^{-1}; ^1H NMR δ 13.70, 13.47, 12.82 and 12.80 (4 s, OH, phenol), 8.29 (m, 2 H, Ar-H), 7.83 (m, 2 H, Ar-H), 7.62 and 7.46 (2 s, 1 H, Ar-H), 6.31–6.15 (m, 1 H, 4-H), 5.66 and 5.62 (2 d, 1 H, *J* = 17), 5.55 and 5.42 (d, 1 H, *J* = 10) (5-CH_2), 5.23–5.17 (2 d, 1 H, *J* = 4, 1-H), 4.51–4.46 (2 d, 1 H, *J* = 7, 3-H), 3.04 and 2.84 (d, 1 H, *J* = 4, OH), 1.48, 1.44, 1.37, and 1.18 (4 s, total 9 H, Me and CMe_2); EIMS (relative intensity) *m/z* 395 ($M^{\bullet+}$ − 15, 30), 294 (25), 141 (80).

(+)-2,3-*O*-Isopropylidene-2-*C*-methyl-L-erythrofuranose (34). It was prepared by oxidation of **13**, as indicated for **20**, in 80% yield and isolated as a colorless syrup: $[\alpha]^{20}_D$ +59° (*c* 2.7, chloroform); ^1H NMR δ 5.39 (s, 1 H, 1-H), 4.22 (s, 1 H, 2-H), 3.97 (d, 1 H, *J* = 9, 4a-H), 3.88 (d, 1 H, *J* = 9, 4b-H), 2.84 (s, 1 H, OH), 1.39, 1.46, and 1.55 (3 s, 9 H, Me and CMe_2); DIC/NH_3 *m/z* 192 (M + NH_4^+), 174, 159 ((M − 15)$^+$). Anal. Calc for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.40; H, 8.02.

(−)-(2*S*,3*R*)-1-*O*-Benzoyl-2,3-dihydroxy-2,3-*O*-isopropylidene-2-methylpent-4-ene (36). A solution of **13** (1 g, 5.8 mmol) in anhydrous pyridine (30 mL) was stirred at room temperature for 1 h in the presence of benzoyl chloride (0.9 mL, 7.56 mmol). After cooling at 0 °C, addition of H_2O (30 mL), and stirring for 30 min, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with 5% H_2SO_4 solution, and H_2O, and with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–acetone (8:1) as eluent and afforded **36** (1.55 g, 95%) as a colorless syrup: $[\alpha]^{20}_D$ −3.8° (*c* 2.6, chloroform); IR ($CHCl_3$) 1720, 1600 cm^{-1}; ^1H NMR δ 8.17–7.42 (m, 5 H, Ar-H), 5.95 (m, 1 H, 4-H), 5.51 (d, 1 H, *J* = 18, 5a-H), 5.31 (d, 1 H, *J* = 10, 5b-H), 4.39 (d, 1 H, *J* = 8, 3-H), 4.26 (d, 1 H, *J* = 11, 1a-H), 4.15 (d, 1 H, *J* = 11, 1b-H), 1.51 and 1.41 (2 s, 9 H, Me and CMe_2); DIC/NH_3 *m/z* 294 (M + NH_4^+), 277 (M + H^+), 219. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.56; H, 7.29. Found: C, 69.81; H, 7.18.

(−)-(2*S*,3*S*)-4-*O*-Benzoyl-2,3-dihydroxy-2,3-*O*-isopropylidene-2-methylbutanal (37). Compound **36** (1.4 g, 5 mmol) was treated as indicated previously for the preparation of **20** with OsO_4 (2.54 mL, 0.25 mmol) and $NaIO_4$ (10.85 g, 50 mmol). Purification of the crude residue over silica gel column with hexane–acetone (3:1) as eluent gave 1.2 g (86%) of **34** as a colorless syrup: $[\alpha]^{20}_D$ −30° (*c* 2, chloroform); IR (film) 1780, 1715, 1380 cm^{-1}; ^1H NMR δ 9.84 (s, 1 H, CHO), 8.24–7.97 (m, 2 H, Ar-H), 7.62–7.39 (m, 3 H, Ar-H), 4.37 (d, 1 H, *J* = 12, 4a-H), 4.27 (s, 1 H, 2-H), 4.11 (d, 1 H, *J* = 12, 4b-H), 1.55 (s, 6 H, CMe_2), 1.45 (s, 3 H, CH_3); DIC/NH_3 *m/z* 296 (M + NH_4^+), 279 (M + H^+). No satisfactory analysis could be obtained for this compound.

(+)-(2*R*,3*S*)-2-[2,3,4-Trihydroxy-2,3-*O*-isopropylidene-3-methylbutyl]-1,4-dihydroxy-9,10-anthraquinone (35). A solution of **37** (1.45 g, 5.21 mmol) and leucoquinizarin **31** (1.4 g, 5.73 mmol) in dry DMF (100 mL) was stirred under argon, and DBU (3.45 mL, 22.9 mmol) was added dropwise. After stirring for 5 min at room temperature and addition of sodium dithionite, the reaction mixture was heated at 80 °C for 0.5 h. The solution was allowed to reach room temperature, 1 N NaOH (15 mL) was added, and stirring was maintained for 1 h. Water was added, and the mixture was extracted with EtOAc (150 mL), washed with 1 N HCl and H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the residue on silica gel with toluene–acetone (85:15) as eluent gave **35** (1.25 g, 60%) as a red crystalline compound: mp 200 °C (MeOH); $[\alpha]^{20}_D$ +153° (*c* 0.2, chloroform); IR 3600, 1625, 1590 cm^{-1}; ^1H-NMR δ 13.24 (s, 1 H, phenol), 12.75 (s, 1 H, phenol), 8.22 (m, 2 H, Ar-H), 7.71 (m, 2 H, Ar-H), 7.15 (s, 1 H, Ar-H), 4.19 (dd, 1 H, *J* = 2, *J'* = 10, 2-H), 3.58 (d, 1 H, *J* = 10) and 3.45 (d, 1 H, *J* = 10, 4-CH_2), 3.11 (dd, 1 H, *J* = 15, *J'* = 2) and 2.79 (dd, 1 H, *J'* = 10, 1-CH_2), 1.55, 1.44, and 1.34 (3 s, 9 H, Me and CMe_2); DIC/NH_3 *m/z* 416 (M + NH_4^+), 399 (M + H^+), 340, 158. Anal. Calcd for $C_{22}H_{28}O_7$: C, 66.38; H, 5.56. Found: C, 66.45; H, 5.65.

(2*R*,3*R*)-4-(1,4-Dihydroxy-9,10-anthraquinon-2-yl)-2,3-dihydroxy-2,3-*O*-isopropylidene-2-methylbutanal (38). A solution of *N*-chlorosuccinimide (100 mg, 0.25 mmol) in toluene (15 mL) was stirred at 0 °C for 15 min before addition of dimethyl sulfide (0.11 mL, 1.5 mmol). A white precipitate appeared while the mixture was cooled to −25 °C before a solution of **35** (100 mg, 0.25 mmol) in toluene (5 mL) was added. After 2 h, triethylamine (0.5 mL) was added, and the mixture was allowed to reach room temperature and stirred overnight. After dilution with H_2O, the mixture was extracted with CH_2Cl_2 and the organic layer was washed with 1 N HCl, and with water, dried (Na_2SO_4), and concentrated under reduced pressure. This afforded **38** (90 mg, >90%) pure enough for the next step but too unstable to be purified: IR (chloroform) 1730, 1625, 1590, and 1380 cm^{-1}; ^1H NMR δ 13.26 and 12.68 (2 s, 2 PhOH), 9.66 (s, 1 H, CHO), 8.19 (m, 2 H, Ar-H), 7.77 (m, 2 H, Ar-H), 7.15 (s, 1 H, Ar-H), 4.24 (dd, 1 H, *J* = 10, *J'* = 2, 3-H), 3.14 (dd, 1 H, *J* = 14, *J'* = 2, 4a-H), 2.88–2.55 (dd, 1 H, *J* = 14, *J'* = 10, 4b-H), 1.37, 1.42, and 1.57 (3 s, 9 H, Me and CMe_2); DIC/NH_3 *m/z* 414 (M + NH_4^+), 3.97 (M + H^+). No satisfactory analysis could be obtained for this compound.

(+)-(8*S*,9*R*)-7,8,9,10-Tetrahydro-6,8,9,11-tetrahydroxy-8-methyl-5,12-naphthalenequinone (39). Aqueous solutions of KOH (70 mg in 4 mL) and sodium dithionite (75 mg, 0.43 mmol, in 4 mL) were added to a cold (0 °C) solution of crude aldehyde **38** (150 mg, 0.38 mmol) in MeOH and THF (1:1, 30 mL), and the mixture was stirred under an argon atmosphere for 0.5 h. Then, after oxidation by bubbling air through it, the reaction mixture was neutralized by dropwise addition of 1 N HCl and extracted with dichloromethane. Usual workup gave a residue which was dissolved in DMF (30 mL), and, after addition of sodium dithionite (220 mg) and water (15 mL), the mixture was heated at 80 °C for 0.5 h. After cooling and dilution with H_2O, extraction with ether followed by washings, drying (Na_2SO_4), and evaporation under reduced pressure afforded a crude residue (110 mg). Chromatography on silica gel using toluene–acetone (95:5) as eluent gave **39** (90 mg, 60% overall yield from **38**) as red crystals: mp 210–213 °C (MeOH); $[\alpha]^{20}_D$ +89° (*c* 0.25, chloroform); ^1H NMR δ 13.38 and 13.37 (2 s, PhOH), 8.24 (m, 2 H, Ar-H), 7.73 (m, 2 H, Ar-H), 4.37 (t, 1 H, *J* = 4, 9-H), 3.53 (dd, 1 H, *J* = 16, *J'* = 4, 10a-H), 3.36 (d, 1 H, *J* = 16, 7a-H), 2.57 (dd, 1 H, *J* = 16, *J'* = 4, 10b-H), 2.37 (d, 1 H, *J* = 16, 7b-H), 1.51, 1.33, and 1.03 (3 s, 9 H, Me and CMe_2), DIC/NH_3 *m/z* 398 (M + NH_4^+), 381 (M + H^+), 176, 159. Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.31; H, 5.48.

(−)-(8*S*,9*R*)-7,8,9,10-Tetrahydro-6,8,9,11-tetrahydroxy-8-methyl-5,12-naphthacenequinone (7). A solution of compound **39** (50 mg, 0.13 mmol) in a mixture acetic acid–water (15 mL, 8:2) was stirred at 90 °C for 3 h. After cooling, the mixture was diluted with toluene and evaporated. This operation was repeated twice to remove the excess of acetic acid. The residue was crystallized from acetone: mp 255–257 °C; $[\alpha]^{20}_D$ −27° (*c* 0.14, dioxane); ^1H NMR δ 8.23 (m, 2 H, Ar-H), 7.81 (m, 2 H, Ar-H), 4.84 (d, 1 H, *J* = 6, 8-H), 3.2–4.45 (m, 4 H, 7-H, 10-H), 1.22 (s, 3 H, Me); DIC/NH_3 *m/z* 358 (M + NH_4^+), 341 (M + H^+), 180 (100). Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74. Found: C, 67.12; H, 4.82.

Registry No. **3**, 492-30-8; **6**, 130353-08-1; **7**, 130353-09-2; **8**, 40519-00-4; **9**, 130464-15-2; **10**, 130353-10-5; **11**, 85963-85-5; **12**, 130353-11-6; **13**, 130353-12-7; **14**, 130353-13-8; **15**, 130353-14-9; **16**, 150-78-7; (*R*)-**17**, 130353-05-8; (*S*)-**17**, 130353-15-0; (*R*)-**18**, 130353-06-9; (*S*)-**18**, 130353-16-1; **19**, 130353-07-0; **20**, 130353-17-2; **21**, 130353-18-3; **22**, 130353-19-4; **24**, 130353-20-7; **25**, 130377-87-6; **26**, 130353-21-8; **27**, 27613-27-0; **28**, 130353-22-9; **29**, 130353-23-0; **30**, 130353-24-1; **31**, 476-60-8; (*R*)-**32**, 130353-25-2; (*S*)-**32**, 130353-31-0; **33**, 130377-88-7; **34**, 130548-07-1; **35**, 130353-26-3; **36**, 130353-27-4; **37**, 130353-28-5; **38**, 130353-29-6; **39**, 130353-30-9.

Solvent Effects in the Thermal Decomposition Reactions of Cyclic Ketone Diperoxides

L. F. R. Cafferata,* G. N. Eyler, E. L. Svartman, A. I. Cañizo, and E. Alvarez

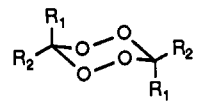
Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Casilla de Correo 16, Sucursal 4, (1900) La Plata, República Argentina

Received April 6, 1990

The kinetics of the thermal decomposition reactions of acetone, pinacolone, and cyclohexanone cyclic diperoxides were investigated in various solvents at different temperatures. Linear relationships were observed between the enthalpy and entropy of activation of the unimolecular reactions of those diperoxides. The acetone cyclic diperoxide (ACDP) reaction is relatively more sensitive to solvent changes, behavior attributed to a reduced steric hindrance of the methyl groups of its molecule. Qualitatively different ground or transition states for the corresponding unimolecular reactions of the ACDP may be postulated according to the strong solvent dependence.

Introduction

In a previous work[1] a significant substituent effect was demonstrated in the kinetics of the unimolecular decomposition reactions in benzene solution of cyclic diperoxides with a tetroxacyclohexane ring in their molecules, behavior attributed to steric hindrance.



ACDP: $R_1 = R_2 = CH_3$
APDP: $R_1 = CH_3$; $R_2 = C_6H_5$
BKDP: $R_1 = R_2 = C_6H_5CH_2$
BPDP: $R_1 = R_2 = C_6H_5$
CHDP: R_1–R_2 = –$(CH_2)_5$–
PDP: $R_1 = CH_3$; R_2 = *tert*-C_4H_9

On the other hand, the unimolecular thermolysis of some open chain diacyl peroxides exhibit solvent effects because their transition states have some polar character.[2] In the case of diaroyl peroxides such as benzoyl peroxide that effect is very important even though the products derive from benzoyloxy radicals rather than ion pairs.[3] Furthermore, the reaction of that peroxide on silica clearly shows the importance of ion-pair structures in the rate-determining transition state.[4] The kinetics of the thermal decomposition reactions of cyclic diperoxides as acetone cyclic diperoxide (3,3,6,6-tetramethyl-1,2,4,5-tetroxane, ACDP), pinacolone cyclic diperoxide (3,6-di-*tert*-butyl-3,6-dimethyl-1,2,4,5-tetroxane, PDP), and cyclohexanone cyclic diperoxide, (7,8,15,16-tetroxadispiro[5.2.5.2]hexadecane, CHDP) provide an interesting means to learn about the nature of solvent effects on the thermolysis of this type of molecules, which is the aim of the present study.

Results and Discussion

Rate measurements were made on the thermal decomposition of ACDP, PDP, and CHDP in a variety of solvents with different physicochemical characteristics (Table I). At each temperature the observed rate constant values, k, are practically independent of the initial diperoxide concentrations, and in our work the thermolyses follow first-order kinetic laws up to at least ca. 50% conversions. However, many runs showed that type of behavior for more higher decomposition of the diperoxides.

The effect of the temperature on the k values according to the Arrhenius method gives the activation parameters for the ACDP, PDP, and CHDP unimolecular reactions (Table II).

In general, a significant variation is evident in the observed values of the activation parameters. These parameters are associated with the corresponding unimolecular reactions, since induced decomposition pathways in the thermolyses of those substances were not detected. Activation enthalpies near 33 kcal mol^{-1} correspond to the peroxidic O–O bond strength for homolytic types of ruptures[5] although lower activation parameters for the decomposition of peroxides were attributed to ionic reactions in solution.[6]

The values of the activation parameters for the thermolysis of the diperoxides (Table II) show linear correlations ($\Delta H^{\ddagger} = \Delta H^{\circ} + \beta \Delta S^{\ddagger}$) according to Leffler's treatment[7] for the postulate of an isokinetic relationship, going from *n*-octane or toluene to acetic acid or acetophenone as reaction solvents. In the ACDP reaction the corresponding plot (Figure 1, $r = 0.998$) gives an isokinetic temperature of 217 °C, which is well outside the temperature range where the kinetic measurements were performed (90–166.6 °C). That relationship is consistent with the proposed[8,9] Exner correlation between the logarithm

(1) Cafferata, L. F. R; Eyler, G. N.; Svartman, E. L.; Cañizo, A. I.; Borkowski, E. J. *J. Org. Chem.* **1990**, *55*, 1058.
(2) Walling, C.; Waits, H. P.; Milovanovic, J.; Pappiaonnou, C. G. *J. Am. Chem. Soc.* **1970**, *92*, 4927.
(3) Mirifico, M. V.; Cafferata, L. F. R. *An. Asoc. Quim. Argent.* **1982**, *70*, 29.
(4) Flowers, G. C.; Leffler, J. E. *J. Org. Chem.* **1989**, *54*, 3995.
(5) Hiatt, R. *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1971; p 849.
(6) Bartlett, P. D.; Leffler, J. E. *J. Am. Chem. Soc.* **1950**, *72*, 3030.
(7) Leffler, J. E. *J. Org. Chem.* **1955**, *20*, 1202.
(8) Exner, O. *Nature* **1964**, *201*, 488.

0022-3263/91/1956-0411$02.50/0