Anthracyclinones. 3.[1] Chiral Pool Synthesis of Anthracyclinones via Tetralin Intermediates

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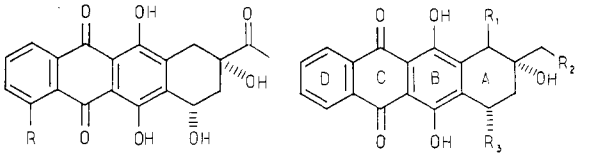
The synthesis of AB ring segments **14**, **15**, and **28** of anthracyclinones involves in a key step an ortho-alkylation of bromodimethoxybenzene **5** (X = Br) with chiral aldehydes **6** or **19**, which are themselves prepared from the isopropylidene derivative of α-D-isosaccharinolactone **16**. After suitable transformations of the adduct **7** or **20**, A ring closure was stereospecifically performed with $SnCl_4$ at −78 °C in dry dichloromethane, giving **14** and **28**, respectively. Protection of the benzylic alcohol of **28** and anodic oxidation followed by selective hydrolysis afforded the tetralin-type quinone monoketals **31** and **32**, which were condensed with the anion of cyanophthalide **33**. Complete deprotection of anthracyclinones **34** and **35** led to 4-demethoxy-9-deacetyl-9-(hydroxymethyl)daunomycinone (**3**).

Introduction

Considerable effort over the last ten years has been focused on the synthesis of the aglycon moiety of anthracyclines and in particular toward daunomycinone **1** and its 4-demethoxy analogue **2**.[2] Except for the Farmitalia route to **1**,[3a] it is only recently that much effort have been expanded on the synthesis of enantiomerically pure aglycons **1** or **2**[2b,d,f,g,3] AB ring segments[4] or analogues.[5] The availability of such compounds would avoid the complex separation of diastereoisomeric products in the final glycosidation step since only the cis (7*S*,9*S*) glycoside derivatives of **1** or **2** are biologically active.[2a]

On the other hand, the coupling of AB + CD fragments is more versatile than the alternative A + BCD approach for the preparation of anthracyclinone analogues. For example the addition cyclization techniques of Kraus[6] and Hauser[7] for anthraquinone synthesis have already been widely adapted to regiospecific anthracyclinone syntheses by condensation of phthalide anions with either 1(4*H*)-naphthalenone derivatives[8] or tetralin-type quinone monoketals.[2d,9] This mild method has been shown compatible with a fully functionalized ring A in a proper cis (7*S*,9*S*) configuration and adaptable on a large scale. Moreover it occurs without loss of chiral integrity.[2d,10]

According to the foregoing remarks, our objectives were to prepare optically active aglycons from sugar derivatives. In previous papers,[11,12] we have shown that 4-demethoxy-9-deacetyl-9-(hydroxymethyl)daunomycinone (**3**) and (−)-4-deoxyrhodomycinone (**4**) can be synthesized by using isosaccharinic acid[13] as a chiral precursor of ring A and leucoquinizarin as a BCD component.



1 R=OMe
2 R=H

3 R_1=H R_2=R_3=OH
4 R_1=OH R_2=Me R_3=H

In this paper, we would like to describe as an alternative, the synthesis of an AB ring segment which contained functionalities closely related to daunomycinone but also possessed a cis 7*S*,9*S* configuration. We would like also to describe the subsequent access to **3** using the cyanophthalide annelation procedure.[2d]

This new and highly convergent approach to the AB ring segment involves in the key step an ortho-alkylation of bromodimethoxybenzene[14] a with chiral aldehydes b giving

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(2) See, for example: (a) Arcamone, F. In *Doxorubicin*; Academic: New York, 1981; p 259. (b) Broadhurst, M. J.; Hassal, C. H.; Thomas, G. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2249. (c) Dominguez, D.; Ardecky, R. J.; Cava, M. P. *J. Am. Chem. Soc.* **1983**, *105*, 1608. (d) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625. (e) Rama Rao, A. V.; Yadav, J. S.; Bal Reddy, K.; Mehendale, A. R. *Ibid.* **1984**, 4643. (f) Gupta, R. C.; Harland, P. A.; Stoodley, R. J. *Ibid.* **1984**, 4657. (g) Tamoto, K.; Sugimori, M.; Terashima, S. *Ibid.* **1984**, 4617. (h) Gupta, R. C.; Jackson, D. A.; Stoodley, R. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 525.

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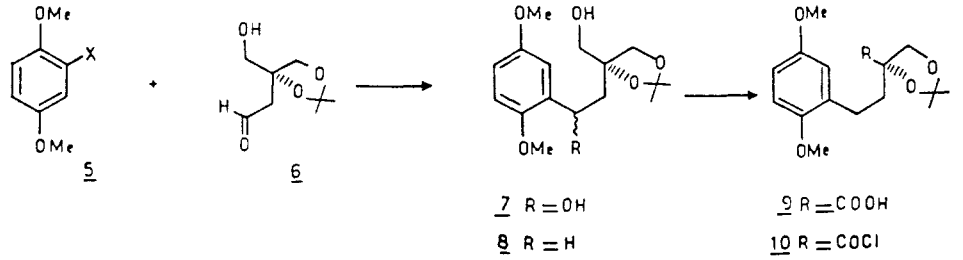
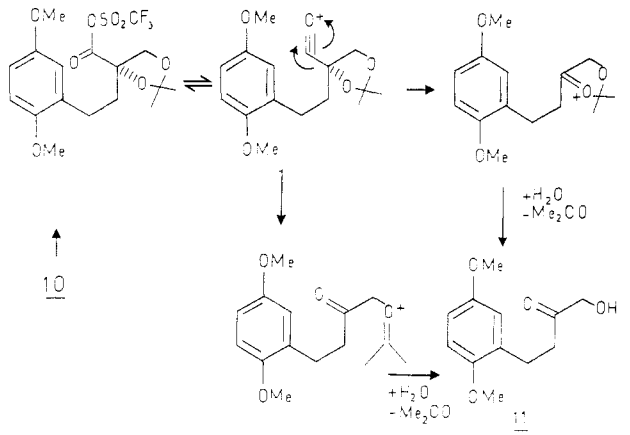
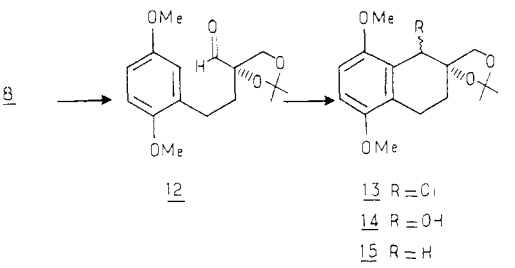
Scheme I



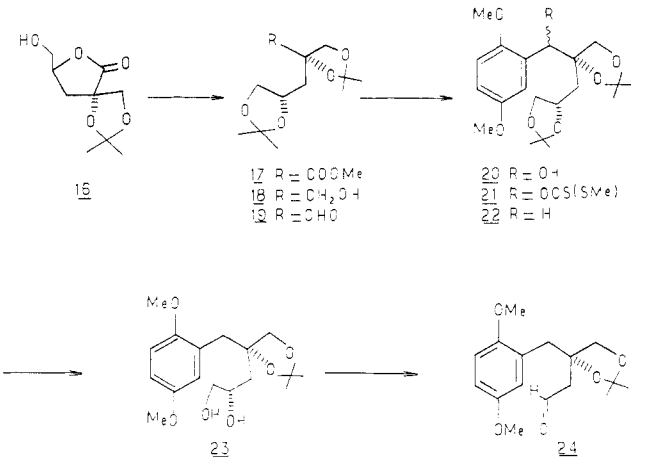
Scheme II



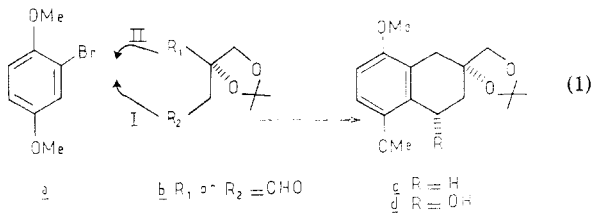
Scheme III



Scheme IV



the tetralins c or d (eq 1) after suitable transformations and ring closure. According to either R_1 or R_2 is the aldehyde function, two routes (I and II) have been followed.



(1)

Results and Discussion

Synthesis of AB Ring Segment Following Route I. The aldehyde **6** (Scheme I), which was obtained in three steps from α-D-isosaccharino-1,4 lactone,[11] was condensed at −78 °C with either the lithio or Grignard derivative of **5** to afford **7** as a mixture of diastereoisomers in 40% and 70% isolated yields, respectively.

Attempts to remove selectively the benzylic alcohol of **7** or its trifluoroacetyl derivative by hydrogenolysis under neutral conditions (H_2 over Pd–$BaSO_4$, or Pd/C or Raney-Ni...) so as to avoid elimination and then aromatization during the subsequent ring closure resulted in recovery of the starting material or in its complete degradation. More drastic conditions such as hydrogenolysis in acidic medium could not be employed as ring opening of acetal would occur, giving a triol derivative.

Eventually it was found that cleavage of the benzylic alcohol to give **8** (40% yield) could be achieved by reaction of an alcoholate solution of **7** with Na in liquid ammonia.

Oxidation of **8** with pyridinium dichromate in DMF solution[15] led to the corresponding carboxylic acid **9** in 40% yield. Cyclization of alkanoic acids such as **9** to the corresponding cyclic ketones (1-tetralone analogues) can be achieved under mild conditions. Triflate activation of the carboxyl group through the formation of a mixed anhydride, which has been shown particularly efficient in both inter-[16] and intramolecular[17] Friedel–Crafts acylation of aromatic compounds, was thus attempted. At first **9** was treated with trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butylpyridine.[18] However this led to numerous compounds that were not analyzed in detail. On the other hand when carboxylic–triflic anhydride was generated in situ from the acid chloride **10** with the silver salt of trifluoromethanesulfonic acid, exclusive formation of **11** was observed. Structural assignment of **11** was fully supported by IR, NMR, and DCI/NH_3 mass spectrometry.

The formation of **11** (Scheme II) can be explained in terms of a dissociation equilibrium of the anhydride. The acylium cation so formed may lose CO,[16a] yielding an oxonium ion which can rearrange in either a concerted or nonconcerted manner giving the ketol **11** with loss of acetone after hydrolysis.

Difficulties encountered during attempts to cyclize the acid derivative led us to turn our attention toward the corresponding aldehyde **12** readily obtained (90% yield) by pyridinium oxidation of **8** in dichloromethane[15] (Scheme III). Treatment of **12** with $AlCl_3$ at −78 °C in CH_2Cl_2 afforded the chloro derivative **13** in 25% yield with nu-

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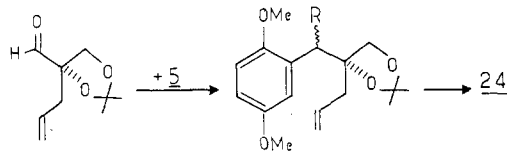
Scheme V



25 26 R = OH 27 R = H

merous side products and starting material (recovered in 30% yield), while with $SnCl_4$ at −78 °C the hydroxytetralin derivative **14** was obtained in 85% yield after crystallization. Interestingly only a single product was formed during the later ring closure; however, the configuration at C-1 could not be assigned by classical means. In a next step **14** was converted to the tetralin derivative **15** by radical deoxygenation via the methyl dithiocarbonate with Bu_3SnH.[19]

Synthesis of AB Ring Segment Following Route II. Acidic ring opening[20] of α-D-isosaccharino-1,4-lactone **16** in the presence of 2,2-dimethoxypropane afforded the ester **17** (75% yield), which was reduced to the alcohol **18** with LAH in THF. Oxidation of **18** with pyridinium dichromate in dichloromethane produced the aldehyde **19**[11] in nearly quantitative yield (Scheme IV).

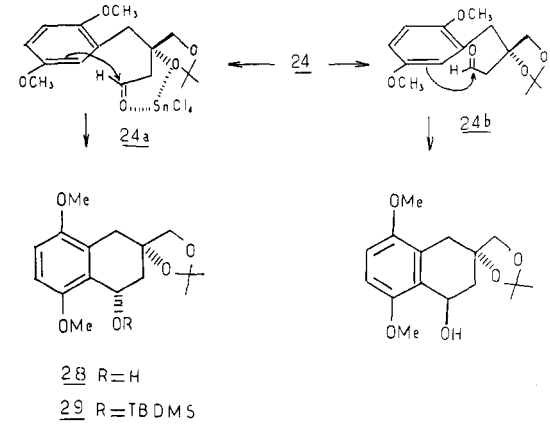
Coupling of aldehyde **19** with the lithio derivative of **5** afforded the adduct **20** in 70% yield. Radical deoxygenation[19] with Bu_3SnH of the methyl dithiocarbonate **21** led to **22** in 42% overall yield for the three steps. However, when the same sequence of reactions (**19** → **22**) was done without isolation of intermediates, the overall yield **19** → **22** was increased from 30% to 64%. Regioselective hydrolysis of terminal isopropylidene gave the monoacetonide **23** in 50% yield along with **22** (45% recovered). Cleavage of the glycol component of **23** with sodium periodate gave **24** in almost quantitative yield. Owing to difficulties encountered when scaling-up the selective acid hydrolysis of **22**, an alternative route was developed. Aldehyde **25**, which was easily prepared from **16** in several steps,[12] was condensed with the lithio derivative of **5** (Scheme V) to afford the adduct **26** in 75% yield. After removal of the benzylic alcohol (75% yield) by radical deoxygenation (Bu_3SnH and AIBN) of the corresponding methyl dithiocarbonate, ozonolysis of **27** gave the aldehyde **24** in 50% yield.

Since the ring closure of **12** in the presence of $SnCl_4$ was previously successful (vide supra) the same catalyst was used to cyclize **24**. This afforded in good yield (80%) and stereospecifically the tetralin derivative **28** as a crystalline compound. The cis configuration (1*S*,3*S*) was unambigously established from ^1H NMR data at 270 MHz in $CDCl_3$.

Kinetic aldol condensations are generally pictured in terms of transition states in which the C=O component approaches the α-carbon atom perpendicular to the plane of the enolate.[21] Transition state **24a** (Scheme VI), which leads to the cis tetralin **28**, should be favored compared to the transition state **24b**, giving the trans tetralin, since in the former, chelation can occur with $SnCl_4$ between aldehyde and oxygen of the tertiary alcoxy group.[22]

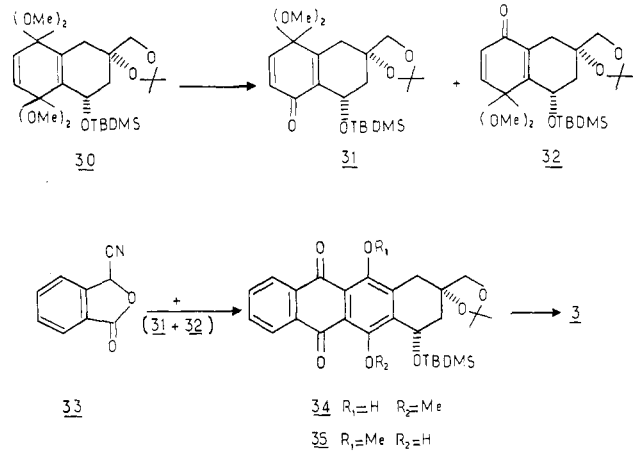
Coupling of the AB and CD Segments: Synthesis of Anthracyclinones. To access to the tetracyclic

Scheme VI



28 R=H
29 R=TBDMS

Scheme VII



skeleton of anthracyclinones, the next step requires the coupling of CD segment with fully protected AB segment under conditions as previously described. Thus the benzylic OH of **28** was protected (87% yield) with *tert*-butyldimethylsilyl chloride,[23] and the tetralin **29** was subjected to anodic oxidation[24] to afford the quinone bisketal **30** in excellent yield (98%) (Scheme VII).

Selective hydrolysis of **30** in aqueous acetic acid[25] afforded a 3:1 ratio of monoketals **31** and **32**. Better selectivity was found in this case when the crude material resulting from anodic oxidation was stirred overnight in dichloromethane solution in the presence of silica gel. This gave 8:2 ratio of **31** and **32**.

The coupling reaction of **31** and **32** with the anion of 3-cyano-1(3*H*)-isobenzofuranone (**33**) by the known procedure[2d] afforded the mixture of regioisomeric anthracyclinones **34** and **35** in a 90% yield. These compounds were readily separated by chromatography on silica gel. In fact it is not necessary to separate intermediates **34** and **35** since desilylation (Bu_4NF) followed by boron trichloride demethylation converted both regioisomers to the desired aglycon **3** in a nearly quantitative yield.

Following route II, tetralin **28** functionalized with the proper absolute configuration of anthracyclinone of the daunorubicin type was thus obtained in seven steps and in 20% overall yield from the readily available *O*-isopropylidene derivative of isosaccharino-1,4-lactone. After suitable protection of the benzylic OH group and acetal

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cleavage, transformation of the sidechain into $COCH_3$ or $COCH_2OH$ will afford the AB ring segment of daunomycinone and adriamycinone. On the other hand, synthesis of AB ring segment of rhodomycins following route I is now under investigation.

Experimental Section

For general methods see ref 12.

(2*R*,4*R*)- and (2*R*,4*S*)-4-(2,5-Dimethoxyphenyl)-2-(hydroxymethyl)-2,2′-*O*-isopropylidenebutane-1,2,4-triol (7). 1. Via Lithio Derivative. To a solution of 1-bromo-2,5-dimethoxybenzene (11 g; 50.5 mmol) in dry tetrahydrofuran (100 mL), cooled at −78 °C under argon, was added dropwise 53 mL of *n*-butyllithium 50.5 mmol). After the mixture was stirred for 50 min, a solution of 4.39 g of aldehyde **6** (25.2 mmol) in dry THF was added, and stirring was continued for an additional period of 18 h. Then, a saturated solution of ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic solution was dried (Na_2SO_4) and evaporated under reduced pressure to give an oil, which was purified by chromatography on silica gel with hexane–acetone (2:1) as eluent, affording 45 g (57%) of **7**.

2. Via Grignard Reagent. To a three-necked flask containing a magnetic stirring bar and argon inlet was added dry ether (150 mL), 5.8 g (241.5 mmol) of activated magnesium turnings (by successive washing with dry ether and heating at 100 °C under reduced pressure), and one iodine crystal. Then, was added a solution of 1-bromo-2,4-dimethoxybenzene (37.5 g; 172.5 mmol) in dry ether (150 mL), the first 15 mL without stirring and then the remaining volume as soon as the reaction started. The mixture was vigorously stirred under reflux overnight and cooled to room temperature, and a solution of aldehyde **6** (6 g, 34.5 mmol) in dry ether (50 mL) was added. After 6 h, the reaction was quenched by addition of crushed ice, water (30 mL) and 30% aqueous sulfuric acid (30 mL). The mixture was extracted with ether, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo to give a crude product, which was purified as above. The resulting oil (677 mg; 70%) was a mixture of diastereoisomers as shown by its ^1H NMR spectrum: ^1H NMR δ 7.04 (m, 1 H), 6.77 (s, 1 H), and 6.71 (s, 1 H) (Ar H), 5.21 (q, 1 H, J = 4 Hz, J' = 7.5 Hz, 4-H), 5.10 (d, 1 H, J = 9.5 Hz, 4-H), 4.03 (d, 1 H, J = 9 Hz) and 3.92 (d, 1 H, J = 9 Hz) (AB, 2′-H), 3.76 (s, 3 H) and 3.72 (s, 3 H) (OMe), 3.65 (d, 1 H, J = 11 Hz) and 3.56 (d, 1 H, J = 11 Hz) (AB, 1-H), 3.14 (s, 2 H, 1-OH and 4-OH), 2.00 (m, 2 H, 3-H), 1.40 (s, 6 H, CMe_2); DCI/NH_3, m/z (relative intensity) 312 (M^+, 100), 295 ($M^+ - 17$, 88), 254 ($M^+ - 58$, <5), 174 (5), 167 (12), 131 (40).

(+)-(2*R*)-4-(2,5-Dimethoxyphenyl)-2-(hydroxymethyl)-2,2′-*O*-isopropylidenebutane-1,2-diol (8). To a solution of **7** (4.24 g, 13.6 mmol) in dry THF (20 mL) at 0 °C was added 816 mg (27.2 mmol) of sodium hydride (80%) in the course of 20 min. The mixture was stirred for 1 h at 0 °C and then cooled to −50 °C. Approximately 100 mL of liquid ammonia was added, followed by addition of small pieces of sodium until an homogeneous persistent blue color was observed.

After the mixture has been stirred under reflux for 1 h, the excess of Na was consumed by the rather rapid addition of a saturated solution of ammonium chloride, and the ammonia was allowed to evaporate overnight. The residue was partitioned between ether and brine. The ether solution was dried (Na_2SO_4), and the solvent was removed under reduced pressure. Flash chromatography on silica gel with hexane–acetone (3:1) as eluent provided 1.63 g (40%) of **8**: $[\alpha]^{20}_D$ +5° (*c* 1.2, $CHCl_3$); ^1H NMR δ 6.80–6.60 (m, 3 H, Ar H), 3.92 (d, 1 H, J = 9 Hz) and 3.81 (d, 1 H, J = 9 Hz) (AB, 2′-H), 3.75 (s, 3 H) and 3.73 (s, 3 H) (OMe), 3.62 (d, 1 H, J = 11 Hz) and 3.54 (d, 1 H, J = 11 Hz) (AB, 1-H), 3.60 (s, 1 H, OH), 2.72–2.48 (m, 2 H, 4-H), 2.02–1.77 (m, 2 H, 3-H), 1.44 (s, 3 H) and 1.43 (s, 3 H) (CMe_2); DCI/NH_3, m/z (relative intensity) 296 (M^+, 30), 281 ($M^+ - 15$, <5), 265 ($M^+ - 31$, <5) 238 ($M^+ - 58$, <5), 207 (24), 181 (21), 164 (42.5), 151 (100), 131 (18), 121 (30), 105 (54.5), 91 (54.5), 77 (48.5). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16; O, 26.99. Found: C, 64.92; H, 8.07; O, 26.69.

(+)-(2*S*)-4-(2,5-Dimethoxyphenyl)-2-(hydroxymethyl)-2-hydroxy-2,2′-*O*-isopropylidenebutanoic Acid (9). To a solution of alcohol **8** (250 mg, 0.85 mmol) in DMF (10 mL) was added 1.6 g (4.25 mmol) of pyridinium dichromate. The mixture was stirred at room temperature for 17 h, and then after addition of water (50 mL) the mixture was acidified by the addition of 1 N aqueous HCl and extracted with ether. The organic layer was concentrated under reduced pressure to afford 107 mg (41%) of acid **9**: $[\alpha]^{20}_D$ +62° (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) 3600 (OH), 1725 cm^{-1} (C=O); ^1H NMR δ 6.75–6.67 (m, 3 H, Ar H), 4.37 (d, 1 H, J = 9 Hz) and 3.96 (d, 1 H, J = 9 Hz) (AB, 2′-H), 3.75 (s, 3 H) and 3.73 (s, 3 H) (OMe), 2.82 (sext, 1 H, J = 11 Hz, J' = 12 Hz, J'' = 5 Hz) and 2.59 (sext, 1 H, J = 5 Hz, J' = 11 Hz, J'' = 12 Hz) (ABXY, 4-H), 2.22 (sext, 1 H, J = 5 Hz, J' = 11 Hz, J'' = 12 Hz), and 2.02 (sext, 1 H, J = 5 Hz, J' = 11 Hz, J'' = 12 Hz) (ABXY, 3-H), 1.51 (s, 3 H) and 1.47 (s, 3 H) (CMe_2); MS/EI, m/z (relative intensity) 310 ($M^{\bullet+}$, <5), 284 (<5), 279 ($M^{\bullet+} - 31$, <5), 270 (100), 164 (27), 151 (83), 121 (27). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.85; H, 7.12.

(2*S*)-4-(2,5-Dimethoxyphenyl)-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-2-hydroxybutanoyl Chloride (10). To a solution of acid **9** (130.5 mg, 0.421 mmol) in dry dichloromethane (25 mL) was added 0.1 mL of pyridine and 0.11 mL (1.26 mmol) of oxalyl chloride. The mixture was stirred at room temperature for 3 h and then concentrated. The residue was dissolved into dichloromethane, and the organic solution was filtered and concentrated under reduced pressure to obtain **10** (125 mg, 90%) as a colorless oil: IR film 1775 cm^{-1} (C=O); ^1H NMR (80 MHz) δ 6.60 (s, 3 H, Ar H), 4.41 (d, 1 H) and 3.85 (d, 1 H) (AB, 2′-H), 3.68 (s, 3 H) and 3.67 (s, 3 H) (2 OMe), 2.69 (m, 2 H, 4-H), 2.17 (m, 2 H, 3-H), 1.45 (s, 3 H) and 1.42 (s, 3 H) (CMe_2).

4-(2,5-Dimethoxyphenyl)-2-oxobutanol (11). To a solution of **10** (125.2 mg, 0.38 mmol) in dry dichloromethane, which was cooled at −78 °C under argon, were added 196 mg (0.76 mmol) of silver trifluoromethanesulfonate and 73 mg (0.38 mmol) of 2,6-di-*tert*-butylpyridine. The mixture was stirred for 2.5 h and then allowed to reach room temperature and stirred for 3 h. The mixture was then poured into crushed ice, and aqueous solution of $NaHCO_3$ was added. After extraction with ether, the aqueous layer was acidified with a 1 N aqueous HCl solution and then extracted with ethyl acetate. The organic layer was concentrated to give 25 mg (30%) of **11** as a syrup: IR film 3425 (OH), 1725 cm^{-1} (C=O); ^1H NMR δ 6.72–6.90 (m, 3 H, Ar H), 4.16 (s, 2 H, 1-H), 3.71 (s, 3 H) and 3.69 (s, 3 H) (2 OMe), 3.08 (s, 1 H, OH), 2.88 (t, 2 H, J = 7 Hz, J' = 7 Hz, 4-H) and 2.66 (t, 2 *H*, J = 7 Hz, J' = 7 Hz, 3-H) (A_2X_2), DCI/NH_3, m/z (relative intensity 242 ($M + NH_4^+$, 100), 224 (M^+, 18), 207 (7), 168 (<5), 151 (18), 105 (<5). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.40; H, 7.36, O, 28.39.

(−)-(2*S*)-4-(2,5-Dimethoxyphenyl)-2-(hydroxymethyl)-2,2′-*O*-isopropylidenebutanal (12). To a solution of alcohol **8** (1.44 g, 4.86 mmol) in dry dichloromethane (50 mL) were added successively pyridinium dichromate (2.75 g, 7.3 mmol), freshly activated molecular sieves powder (4 g, 3 Å, heated for 5 h at 320 °C), and then anhydrous acetic acid (500 μL). After being stirred for 1 h at room temperature, the crude mixture was diluted with ether and filtered on Celite, and the ether layer was evaporated under reduced pressure. The residue was dissolved into ether (50 mL) filtered through a short pad of silica gel and evaporated under reduced pressure to give **12** as a pure product (1.30 g, 90%): $[\alpha]^{20}_D$ −4° (*c* 2.2, $CHCl_3$); ^1H NMR δ 9.60 (s, 1 H, H ald), 6.75–6.62 (m, 3 H, Ar H), 4.20 (d, 1 H, J = 9 Hz) and 3.80 (d, 1 H, J = 9 Hz) (AB, 2′-H), 3.74 (s, 3 H) and 3.72 (s, 3 H) (OMe), 2.72 (m, 1 H, J = 12.5 Hz, J' = 12 Hz, J'' = 5 Hz) and 2.51 (m, 1 H, J = 12.5 Hz, J' = 12 Hz, J'' = 5 Hz) (ABXY, 4-H), 2.07 (m, 1 H, J = 12.5 Hz, J' = 12 Hz, J'' = 5 Hz) and 1.92 (m, 1 H, J = 12 Hz, J' = 12 Hz, J'' = 5 Hz) (ABXY, 3-H), 1.47 (s, 3 H) and 1.43 (s, 3 H) (CMe_2); EIMS, m/z (relative intensity) 294 ($M^{\bullet+}$, 35), 279 ($M^{\bullet+} - 15$, <5), 265 ($M^{\bullet+} - 29$, 9), 207 (37), 151 (100), HRMS, m/e calcd for $C_{16}H_{22}O_5$ 294.3492, found 294.3482.

(1*R*,- or (1*S*,2*S*)-1-Chloro-2-hydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (13). To a stirred solution of aldehyde **12** (200 mg, 0.68 mmol) in dry dichloromethane (10 mL) at −78 °C was slowly added 13.3 mg (0.1 mmol) of aluminum chloride. The suspension was stirred for 2 h, and then the addition of ≃10 mL of aqueous saturated solution of $NaHCO_3$ was followed by extraction with dichloromethane. After purification of the crude extract by flash chromatography with hexane–ethyl acetate (95:5) as eluent 35 mg of **13** was obtained: ^1H NMR δ 6.67 (d, 1 H, J

= 9 Hz) and 6.62 (d, 1 H, J = 9 Hz) (Ar H) 5.11 (d, 1 H, 1-H), 4.23 (d, 1 H, J = 9 Hz) and 3.96 (d, 1 H, J = 9 Hz) (AB, 2'-H), 3.80 (s, 3 H) and 3.73 (s, 3 H) (2 OMe), 2.94 (dd, 1 H, J = 19 Hz, J' = 7 Hz) and 2.74 (m, 1 H, J = 19 Hz, J' = 12 Hz, J'' = 7 Hz) (ABXY, 4-H), 2.33 (m, 1 H, J = 13 Hz, J' = 12 Hz, J'' = 7 Hz) and 1.93 (dd, 1 H, J = 13 Hz, J' = 7 Hz) (ABXY, 3-H), 1.41 (s, 3 H) and 1.36 (s, 3 H) (CMe_2); DCI/NH_3, m/z (relative intensity) 312 (M^+, 48), 297 (M^+ - 15, 7), 237 (M^+ - CH_3COOH, 7), 219 (30), 198 (RDA, 27), 177 (52), 43 (100).

Anal. Calcd for $C_{16}H_{21}O_4Cl$: C, 61.43; H, 6.76; Cl, 11.33. Found: C, 61.55; H, 6.70; Cl, 11.40.

(1*R*,- or (1*S*,2*R*)-1,2-Dihydroxy-2-(hydroxymethyl)-2,2'-*O*-isopropylidene-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (14). To a solution of aldehyde **12** (1.1 g, 3.74 mmol) in dry dichloromethane (50 mL) cooled to -78 °C under argon, was added dropwise $SnCl_4$ (0.75 mL, 5.61 mmol). After complete addition and after the mixture was stirred for 2 h, addition of Et_3N (1 mL) was followed by dilution with dichloromethane (100 mL). The organic solution was washed with 1 N aqueous NaOH solution and with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 990 mg of crude **14**. Recrystallization from ether–hexane gave 920 mg (85%) of **14**: mp 125 °C; $[\alpha]^{20}_D$ -60° (c 1.3, $CHCl_3$); ^1H NMR δ 6.47 (s, 2 H, Ar H), 4.57 (s, 1 H, 1-H), 4.16 (d, 1 H, J = 9 Hz) and 3.78 (d, 1 H, J = 9 Hz) (AB, 2'-H), 3.56 (s, 3 H) and 3.52 (s, 3 H) (OMe), 2.81–2.46 (m, 3 H, 4-H and OH), 1.80 (m, 2 H, 3-H), 1.21 (s, 3 H) and 1.14 (s, 3 H) (CMe_2); DCI/NH_3, m/z (relative intensity) 312 ($M + NH_4^+$, 20), 295 ($M + H^+$, 20) 294 ($M + NH_4^+ - H_2O$, 100), 277 ($M + H^+ - H_2O$, 5), 254 ($M + NH_4^+ - CH_3COCH_3$, <5), 236 and 219 (<5). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.14; H, 7.67.

(2*R*)-2-Hydroxy-2-(hydroxymethyl)-2,2'-*O*-isopropylidene-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (15). 1. Route A. To a solution of the alcohol **14** (150 mg, 0.51 mmol) in dry THF (20 mL) at 0 °C under argon was added slowly 23 mg (0.765 mmol) of sodium hydride (80%). After the mixture was stirred for 0.5 h, carbon sulfur (0.1 mL, 1.66 mmol) was added, and stirring was continued for an additional period of 1 h at 0 °C. After addition of methyl iodide (0.1 mL, 1.60 mmol), the mixture was allowed to warm slowly to room temperature and stirred overnight. Solvent was removed in vacuo and the residue dissolved in toluene (25 mL). After addition of tributyltin hydride (0.2 mL, 0.51 mmol) and of AIBN (10 mg), the mixture was maintained under reflux for 5 h. Solvent removal afforded an oil, which was chromatographed on silica gel with hexane–dichloromethane (1:1) as eluent to give 100 mg (70%) of **15**.

2. Route B. A solution of crude **28** (prepared from 74 mg of **24** according the procedure described below) in THF (3 mL) was cooled to -60 °C. Approximately 15 mL of liquid ammonia were added followed by small pieces of sodium until obtention of an homogenous persistent blue solution. The mixture was stirred for 2 h and then quenched by addition of an aqueous saturated solution of ammonium chloride (1 mL). The ammonia was allowed to evaporate at room temperature overnight. The residue was extracted with ether, dried (Na_2SO_4), and evaporated to leave an oil. Purification by chromatography on silica gel with hexane–dichloromethane (1:1) as eluent gave 30 mg (52%) of **15**: $[\alpha]^{20}_D$ +1° (c 0.7, $CHCl_3$); ^1H NMR δ 6.55 (s, 2 H, Ar H), 3.81 (d, 1 H, J = 9 Hz) and 3.80 (d, 1 H, J = 9 Hz) (AB, 2'-H), 3.74 (s, 6 H, OMe), 2.87 (m, 1 H, J = 17 Hz, J' = 7 Hz, J'' = 6 Hz) and 2.66 (m, 1 H, J = 17 Hz, J' = 7 Hz, J'' = 6 Hz) (ABXY, 4-H), 2.86 (d, 1 H, J = 15 Hz) and 2.75 (d, 1 H, J = 15 Hz) (AB, 1-H), 2.01 (m, 1 H, J = 13 Hz, J' = 7 Hz, J'' = 6 Hz) and 1.78 (m, 1 H, J = 13 Hz, J' = 7 Hz, J'' = 6 Hz) (ABXY, 3-H), 1.43 (s, 6 H, CMe_2); EIMS, m/z (relative intensity) 278 ($M^{\cdot+}$, 62.5), 263 ($M^{\cdot+}$ - 15, <5), 220 ($M^{\cdot+}$ - 58, 12.5), 203 (61), 189 (23), 164 (40), 149 (32), 91 (28.5), 72 (53.5), 43 (100); HRMS, m/e calcd for $C_{16}H_{22}O_4$ 278.3474, found 278.3468.

(-)-(2*S*,4*S*)-Methyl 2,4,5-Trihydroxy-2-(hydroxymethyl)-2,2':4,5-di-*O*-isopropylidenepentanoate (17). To a solution of lactone **16**[11] (28.6 g, 140 mmol) in methanol (60 mL) were added α,α-dimethoxypropane (200 mL) and 10 g of Amberlyst 15 ion-exchange resin. The mixture was stirred for 75 h at room temperature, then filtered on Celite, and evaporated. Chromatography on silica gel with hexane and then hexane–acetone (4:1) as eluent provided 31.5 g (82%) of **17**: $[\alpha]^{20}_D$ -17° (c 2, $CHCl_3$); IR (film) 1750 (C=O), 1220 cm^{-1} (C-O); ^1H NMR δ 4.25 (d, 1 H, J = 9 Hz) and 3.85 (d, 1 H, J = 9 Hz) (AB, 2'-H), 4.16 (m, 1 H, 4-H), 4.10 (dd, 1 H, J = 8 Hz, J' = 6.6 Hz) and 3.54 (dd, 1 H, J = 8 Hz, J' = 7 Hz) (ABX, 5-H), 3.74 (s, 3 H, COOMe), 2.27 (dd, 1 H, J = 13 Hz, J' = 7 Hz) and 1.87 (dd, 1 H, J = 13 Hz, J' = 5 Hz) (ABX, 3-H), 1.43 (s, 6 H), 1.34 (s, 3 H) and 1.30 (s, 3 H) (2 CMe_2). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 57.05; H, 8.10.

(-)-(2*R*)-3-Deoxy-2-*C*-(hydroxymethyl)-2,2':4,5-di-*O*-isopropylidene-D-glyceropentitol (18). To a solution of ester **17** (19 g, 69 mmol) in dry ether (300 mL) was slowly added 2.8 g (73 mmol) of lithium aluminum hydride. The mixture was heated at reflux under argon overnight. The reaction was quenched by successive addition of water (2.8 mL), 15% aqueous NaOH solution (2.8 mL), and water (8.4 mL). The suspension was filtered through Celite and the filtrate concentrated under reduced pressure to leave 16.5 g (97%) of **18**. Spectroscopic data were similar to those previously reported.[11]

3-Deoxy-2-*C*-(hydroxymethyl)-2,2':4,5-di-*O*-isopropylidene-D-ribose (19). A solution of **18** (21.5 g, 87 mmol) was treated as previously described for the preparation of **12** from **8**. This gave after purification by flash chromatography (hexane–acetone, 9:1) 19.95 g of **19** (93.5%). Spectroscopic data were identical in all respects with those previously reported.[11]

(1*R*,- and (1*S*,2*S*,4*S*)-1-(2,5-Dimethoxyphenyl)-1,2,4,5-tetrahydroxy-3-deoxy-2-(hydroxymethyl)-2,2':4,5-di-*O*-isopropylidenepentitol (20). To a solution of 1-bromo-2,4-dimethoxybenzene (12.9 g, 59.4 mmol), in dry THF (300 mL) cooled to -78 °C under an argon atmosphere, was added dropwise 53 mL of 1.13 M solution of n-butyllithium in hexane (59.4 mmol). After the solution was stirred for 1 h, aldehyde **19** (12.1 g, 49.5 mmol) in solution in dry THF (300 mL) was slowly added. The resulting mixture was stirred for 1 h at -78 °C and quenched with aqueous saturated solution of ammonium chloride, and then diluted with ether. The ethereal extracts were dried (Na_2SO_4), and the solvents were removed in vacuo. The resulting syrup was chromatographed on silica gel with hexane–acetone (20:1) as eluent to afford 15.8 g (70%) of **20**: ^1H NMR δ 7.08 (s, 1 H) and 6.71 (s, 2 H) (Ar H), 5.18 (s, 1 H, 1-H), 4.32 (m, 1 H, 4-H), 4.23 (d, 1 H, J = 8.5 Hz) and 3.69 (d, 1 H, J = 8.5 Hz) (AB, 2'-H), 3.97 (dd, 1 H, J = 8 Hz, J' = 6 Hz) and 3.40 (dd, 1 H, J = 8 Hz, J' = 8 Hz) (ABX, 5-H), 3.74 (s, 3 H) and 3.72 (s, 3 H) (OMe), 2.09 (dd, 1 H, J = 15 Hz, J' = 7 Hz) and 1.66 (dd, 1 H, J = 15 Hz, J' = 4.5 Hz) (ABX, 3-H), 1.40 (s, 6 H) and 1.34 (s, 3 H) and 1.30 (s, 3 H) (2 CMe_2); EIMS, m/z (relative intensity) 382 ($M^{\cdot+}$, <5), 367 ($M^{\cdot+}$ - 15, <5), 249 (6), 215 (57), 167 (14), 166 (22), 157 (18), 101 (100).

(1*R*,- and (1*S*,2*S*,4*S*)-1-(2,5-Dimethoxyphenyl)-1,2,4,5-tetrahydroxy-3-deoxy-1-*O*-[(methylthio)thiocarbonyl]-2-(hydroxymethyl)-2,2':4,5-di-*O*-isopropylidenepentitol (21). To a solution of alcohol **20** (18.2 g, 47.7 mmol) in dry THF (300 mL) cooled to 0 °C was added 1.7 g of sodium hydride (80%). After 30 min, 8.6 mL (143 mmol) of carbon sulfur were added dropwise. The resulting mixture was stirred for 1.5 h at 0 °C before methyl iodide (9 mL, 143 mmol) was added. The mixture was allowed to reach room temperature and stirred overnight. Solvent was removed in vacuo, and the remaining residue was chromatographed on silica gel with hexane–ethyl acetate (5:1) as eluent to give 17.4 g (77%) of **21**: IR (film) 1220 cm^{-1}; ^1H NMR δ 7.02–6.65 (m, 3 H, Ar H), 4.40–4.29 (m, 1 H, 4-H), 4.20 (d, 1 H, J = 9 Hz) and 3.90 (d, 1 H, J = 9 Hz) (AB, 2'-H), 4.11–3.94 (m, 1 H) and 3.48–3.36 (m, 1 H) (5-H), 3.79 and 3.77 (2 s, total 3 H) and 3.71 and 3.70 (2 s, total 3 H) (2 OMe), 2.50 and 2.49 (2 s, total 3 H, SMe), 2.12–1.96 (m, 1 H), 1.81–1.65 (m, 1 H), 1.45–1.03 (m, 6 H, 2 CMe_2).

1-(2,5-Dimethoxyphenyl)-1,3-dideoxy-2-*C*-(hydroxymethyl)-2,2':4,5-di-*O*-isopropylidene-D-ribitol (22). 1. From 21. To a solution of 17.4 g (36.75 mmol) of the isomeric mixture of **21** in toluene (500 mL) were added 12 mL (45 mmol) of tributyltin hydride and 300 mg of AIBN. The mixture was heated to reflux under argon for 2 h. After cooling and filtration, the resulting solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel (hexane and then an increasing ratio of dichloromethane) to give 11.6 g (86%) of **22**: $[\alpha]^{20}_D$ +5° (c 2.4, $CHCl_3$); ^1H NMR δ 6.8 (s, 1 H) and 6.7 (s, 2 H) (Ar H) 4.34 (m, 1 H, 4-H), 4.05 (dd, 1 H, J = 8 Hz, J' = 5.5

Hz) and 3.44 (dd, 1 H, J = 8 Hz, J' = 8 Hz) (ABX, 5-H), 3.82 (d, 1 H, J = 9 Hz) and 3.74 (d, 1 H, J = 9 Hz) (AB, 2'-H), 3.73 (s, 3 H) and 3.72 (s, 3 H) (2 OMe), 2.98 (s, 2 H, 1-H), 1.89 (dd, 1 H, J = 13.5 Hz, J' = 6.5 Hz) and 1.77 (dd, 1 H, J = 13.5 Hz, J' = 5.5 Hz) (ABX, 3-H), 1.39 (s, 3 H), 1.36 (s, 6 H), and 1.17 (s, 3 H) (2 CMe_2); HRMS, m/e calcd for $C_{20}H_{30}O_6$ 366.4534, found 366.4527.

2. From 5 + 19. To a solution of 26.5 g (122.1 mmol) of 1-bromo-2,4-dimethoxybenzene in dry THF (500 mL), which was cooled to −78 °C under argon was added dropwise 56 mL (122.1 mmol) of *n*-butyllithium. The mixture was stirred for 1 h at −78 °C. Then a solution of aldehyde **19** (19.95 g; 81.4 mmol) in THF was slowly added. The solution was stirred for 1 h after which time TLC analysis (hexane–ethyl acetate, 1:1) showed no starting aldehyde. Then 25 mL (366.5 mmol) of carbon sulfur was added, and the mixture was allowed to reach 0 °C.

The mixture was stirred for 1 h, and then 30 mL of methyl iodide was added and the solution stirred overnight at room temperature. Solvent was removed in vacuo, and the remaining residue was diluted with toluene and filtered. To the filtrate were added 17 mL of tributyltin hydride and 115.6 mg of AIBN. The mixture was warmed under reflux for 2 h, then cooled to room temperature, filtered, and concentrated. The crude residue was chromatographed on silica gel with hexane–ethyl acetate (4:1) as eluent to give 19 g (64%) of **22**.

(+)-1-(2,5-Dimethoxyphenyl)-1,3-dideoxy-2-*C*-(hydroxymethyl)-2,2'-*O*-isopropylidene-D-ribitol (23). A solution of **22** (2.45 g, 6.7 mmol) in methanol (30 mL), water (15 mL), and acetic acid (30 mL) was stirred at 25 °C for 48 h. After neutralization by dropwise addition of 1 N aqueous solution of NaOH, the crude mixture was extracted with ethyl acetate. The organic layer was separated and dried (Na_2SO_4), and ethyl acetate was removed under reduced pressure. This gave 2.3 g of crude material as a syrup. Purification by chromatography on silica gel (hexane–dichloromethane, 4:1, then increasing ratio of dichloromethane) gave successively starting material **22** (1.1 g, 45%) and monoisopropylidene derivative **23** (1.15 g, 52.7%): $[\alpha]^{20}_D$ +13° (*c* 2.4; $CHCl_3$); ^1H NMR δ 6.86 (m, 1 H) and 6.60 (m, 2 H) (Ar H), 3.98 (m, 1 H, 4-H), 3.94 (d, 1 H, J = 9 Hz) and 3.80 (d, 1 H, J = 9 Hz) (AB, 2'-H), 3.75 (s, 3 H) and 3.74 (s, 3 H) (2 OMe), 3.50 (dd, 1 H, J = 11 Hz, J' = 3 Hz), and 3.37 (dd, 1 H, J = 11 Hz, J' = 7 Hz) (ABX, 5-H), 3.30 (s, 1 H, OH), 3.03 (d, 1 H, J = 14 Hz) and 2.91 (d, 1 H, J = 14 Hz) (AB, 1-H), 2.44 (s, 1 H, OH), 1.79 (dd, 1 H, J = 15 Hz, J' = 9 Hz) and 1.56 (dd, 1 H, J = 15 Hz, J' = 3 Hz) (ABX, 3-H) 1.40 (s, 3 H) and 1.32 (s, 3 H) (CMe_2).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 40.75; H, 12.70. Found: C, 40.82; H, 12.65.

(+)-(3*S*)-4-(2,5-Dimethoxyphenyl)-3-hydroxy-3-(hydroxymethyl)-3,3'-*O*-isopropylidenebutanal (24). 1. From 23. To the mixture of 8.74 g (26.8 mmol) of diol **23** in aqueous methanol (150 mL) was added 6.3 g (29.5 mmol) of sodium metaperiodate in 75 mL of water. The mixture was stirred for 1 h at room temperature then filtered and extracted with dichloromethane. The organic solution was dried (Na_2SO_4) and evaporated under reduced pressure to give an oil (7.64 g, 97%): $[\alpha]^{20}_D$ +4° (*c* 3.2, $CHCl_3$); IR (film) 2820 and 2720 (aldehyde), 1720 cm^{-1} (C=O); ^1H NMR δ 9.66 (d, 1 H, J = 2 Hz, H ald), 6.77 (s, 1 H) and 6.69 (s, 2 H) (Ar H), 4.00 (d, 1 H, J = 9 Hz) and 3.82 (d, 1 H, J = 9 Hz) (AB, 3'-H), 3.73 (s, 3 H) and 3.70 (s, 3 H) (2 OMe), 3.03 (d, 1 H, J = 14 Hz) and 2.94 (d, 1 H, J = 14 Hz) (AB, 4-H), 2.64 (dd, 1 H, J = 18 Hz, J' = 2 Hz) and 2.48 (dd, 1 H, J = 18 Hz, J' = 2 Hz) (ABX, 2-H), 1.37 (s, 3 H) and 1.35 (s, 3 H) (CMe_2).

2. From 27. A solution of **27** (200 mg, 0.68 mmol) in a mixture of dichloromethane (30 mL) and methanol (3 mL) was cooled to −78 °C, and ozone was introduced through the liquid until TLC (hexane–acetone, 2:1) showed the complete disappearance of the starting material (20 min). Nitrogen was passed through the solution (10 min) and after the mixture warmed to −10 °C, dimethyl sulfide was added (3 mL). The solution was allowed to reach room temperature, stirred overnight, and concentrated under reduced pressure to give a crude residue. Flash chromatography with hexane–acetone (5:1) as eluent led to 100 mg of pure **24** (50%).

(1*R*,- and (1*S*,2*S*)-1-(2,5-Dimethoxyphenyl)-1,2-dihydroxy-2-(hydroxymethyl)-2,2'-*O*-isopropylidene-4-pentene (26). To a solution of 1-bromo-2,4-dimethoxybenzene (9.13 mmol, 2 g) in dry THF (30 mL) under argon and cooled at −78 °C was added dropwise *n*-butyllithium (6.7 mL, 9.13 mmol). The mixture was stirred for 1 h before addition of a solution of **25**[12] (1.41 g, 8.3 mmol) in dry THF (20 mL). Stirring at −78 °C was continued for an additional period of 2 h. After addition of a saturated solution of NH_4Cl (20 mL), extraction with ether afforded 3.5 g of crude material, which was chromatographed on silica gel with hexane–acetone (5:1) as eluent. This gave 1.92 g (75%) of **26**: ^1H NMR δ 7.04 (s, 1 H) and 6.68 (s, 2 H) (Ar H), 5.96–5.63 (m, 1 H, 4-H), 5.17–4.97 (m, 2 H, 5-H), 4.93 (s, 1 H, 1-H), 4.18 (d, 1 H) and 3.69 (d, 1 H) (AB, J = 9 Hz, 2'-H), 3.74 (s, 3 H) and 3.72 (s, 3 H) (2 OMe), 3.10 (s, 1 H, exchangeable in D_2O, OH), 2.59–2.46 (q, 1 H) and 2.13–2.02 (q, 1 H) (ABX, J = 16 Hz, J' = 8 Hz, 3-H), 1.38 (s, 3 H) and 1.36 (s, 3 H) (CMe_2); DCI/NH_3 m/z (relative intensity) 326 (M + NH_4^+, <5), 308 (M^+, 9), 292 (17), 291 (M + H^+ − H_2O; 100), 268 (24), 251 (23), 141 (18); HRMS, m/e calcd for $C_{17}H_{24}O_5$ 308.2746, found 308.2765.

(−)-(2*R*)-1-(2,5-Dimethoxyphenyl)-1,2-dihydroxy-2-(hydroxymethyl)-2,2'-*O*-isopropylidene-4-pentene (27). To a stirred solution of **26** (1.2 g, 3.9 mmol) in dry THF (100 mL) at 0 °C and under argon was added slowly (180 mg, 5.8 mmol) of sodium hydride (80%). After 30 min, 1.2 mL (11.7 mmol) of carbon sulfur was added. The solution was stirred for 1 h at 0 °C, and then 2 mL of methyl iodide was added. The mixture was allowed to reach room temperature overnight. Solvent was removed in vacuo, and the remaining residue was dissolved in toluene. After addition of 2 mL of tributyltin hydride and 100 mg of AIBN, the mixture was heated under reflux for 3 h. Solvent removal afforded an oil, which was chromatographed on silica gel with hexane–acetone (6:1) as eluent to give 854 mg (75%) of **27**: $[\alpha]^{20}_D$ −3° (*c* 1.1, $CHCl_3$); ^1H NMR δ 6.80 (s, 1 H) and 6.68 (s, 2 H) (Ar H), 5.98–5.79 (m, 1 H, 4-H), 5.17–5.01 (m, 2 H, 5-H), 3.74 (br s, 8 H, 2 OMe and 2'-H), 2.90–2.86 (m, 2 H, 1-H), 2.37–2.31 (m, 2 H, 3-H), 1.38 (s, 3 H) and 1.16 (s, 3 H) (CMe_2); DCI/NH_3, m/z (relative intensity) 310 (M + NH_4^+, 50), 293 (M + H^+, 100), 252 (41), 235 (30), 141 (14); HRMS, m/e calcd for $C_{17}H_{24}O_4$ 292.3742, found 292.3755.

(+)-(1*S*,3*S*)-1,3-Dihydroxy-3,3'-*O*-isopropylidene-3-(hydroxymethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (28). To a cooled solution at −78 °C of aldehyde **24** (5.5 g, 18.7 mmol) in dry dichloromethane (150 mL) was added dropwise under argon 2.2 mL (18.7 mmol) of $SnCl_4$. The mixture was stirred for 2.5 h, quenched by addition of triethylamine (2 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 filtered and the solvent removed under reduced pressure to give 4.94 g of crude tetralin. Recrystallization from acetone–hexane gave 4.62 g (84%) of **28**: mp 148 °C; $[\alpha]^{20}_D$ +31° (*c* 0.73, $CHCl_3$); ^1H NMR δ 6.64 (s, 2 H, Ar H), 5.06 (m, 1 H, J = 9 Hz, J' = 6 Hz, J'' = 4 Hz, 1-H), 4.16 (d, 1 H, J = 9 Hz, OH), 3.85 (s, 2 H, 3'-H), 3.78 (s, 3 H) and 3.72 (s, 3 H) (2 OMe), 3.03 (d, 1 H, J = 18 Hz) and 2.66 (d, 1 H, J = 18 Hz) (AB, 4-H), 2.35 (dd, 1 H, J = 14 Hz, J' = 4 Hz) and 1.98 (dd, 1 H, J = 14 Hz, J' = 6 Hz) (ABX, 2-H), 1.43 (s, 3 H) and 1.36 (s, 3 H) (CMe_2); DCI/NH_3, m/z (relative intensity) 312 (M + NH_4^+, <5), 295 (M + H^+, 18), 294 (M^+, 100), 277 (M + H^+ − 18, 35).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.34; H, 7.63.

(+)-(1*S*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4-tetrahydro-3-hydroxy-3-(hydroxymethyl)-3,3'-*O*-isopropylidene-5,8-dimethoxynaphthalene (29). To a solution of tetralin derivative **28** (790 mg, 2.7 mmol) in dry DMF (20 mL) were added successively imidazole (2.03 g, 13.5 mmol) and *tert*-butyldimethylsilyl chloride (1.9 g, 27 mmol). The mixture was heated at 100 °C under argon overnight. After cooling, the mixture was extracted with ether. The organic layer was washed, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in dichloromethane and filtered on a short pad of silica gel. Evaporation of the solvent gave **29** as crystalline compound (960 mg, 87%): mp 59 °C; $[\alpha]^{20}_D$ +30° (*c* 1, $CHCl_3$); ^1H NMR δ 6.76–6.62 (m, 2 H, Ar H), 5.21 (t, 1 H, J = J' = 6 Hz, 1-H), 3.76 (s, 6 H, 2 OMe), 3.67 (s, 2 H, 3-H), 3.06 (d, 1 H, J = 16 Hz) and 2.95 (d, 1 H, J = 16 Hz) (AB, 4-H), 2.25 (d, 2 H, J = 6 Hz, 2-H), 1.51 (s, 3 H) and 1.46 (s, 3 H) (CMe_2), 0.91 (s, 3 H, Me), 0.20 (s, 3 H) and 0.08 (s, 3 H) (2 Me); DCI/NH_3, m/z (relative intensity) 294 (M + H^+ − 115, 100), 277 (32), 201 (7),

92 (9). Anal. Calcd for $C_{22}H_{36}O_5Si$: C, 64.50; H, 8.81. Found: C, 64.66; H, 8.88.

(1*S*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,5,8-hexahydro-3-hydroxy-3-(hydroxymethyl)-3,3′-*O*-isopropylidene-5,5-dimethoxynaphthalen-8-one (31) and Its 8,8-Dimethoxy 5-One Isomer (32). Anodic oxidation of **29** was carried out with a TACUSSEL PRT 20-02 potentiostat in a two compartments cell (anode and cathode compartments separated by a medium porosity fritted disk). The cathode compartment contained 1% KOH in MeOH (50 mL), while the anode compartment contained **29** (500 mg, 1.2 mmol) dissolved in 100 mL of the same solution. The oxidation was carried out at a constant potential of 1.3 V vs. a Pt reference electrode (20 V applied) at 0 °C. The progress of the reaction was monitored by following the decrease in intensity of the UV maximum at 290 nm (in **29**) to about 1% of its original value (2 h). The methanol was removed in vacuo and the oil extracted into ether to leave 590 mg of a yellow oil (bis(ketal) **30**).

(1) Half of the crude bis(ketal) **30** (300 mg) was dissolved in acetone (5 mL) and stirred for 5 min in the presence of aqueous 10% AcOH solution (2.5 mL). Neutralization with saturated $NaHCO_3$ solution followed by extraction with ether, provided 235 mg of a mixture of monoketals **31** and **32** in a 3:1 ratio.

(2) The remaining crude bis(ketal) (≃290 mg) was dissolved in CH_2Cl_2 (50 mL) and stirred for 24 h in the presence of silica gel (1.5 g). Filtration and evaporation of the filtrate under reduced pressure gave 230 mg (88%) of a mixture of **31** and **32** in a 8:2 ratio. A sample of pure **31** was obtained by chromatography on silica gel with hexane–acetone (6:1) as eluent **31**: IR (film) 1675, 1650, 1625 cm^{-1}; ^1H NMR δ 6.72 (d, 1 H, J = 10 Hz, 7-H), 6.38 (d, 1 H, J = 10 Hz, 6-H), 4.84 (m, 1 H, 1-H), 3.74 (m, 2 H, 3-H), 3.30 (s, 3 H) and 3.25 (s, 3 H) (2 OMe), 2.57 (m, 2 H, 4-H), 1.47 (s, 3 H) and 1.43 (s, 3 H) (CMe_2), 0.90 (s, 9 H, 3 Me), 0.22 (s, 3 H), and 0.17 (s, 3 H) (2 Me); DCI/NH_3, m/z (relative intensity) 442 (M + NH_4^+, 18), 425 (M + H^+, 100), 410 (71), 393 (10), 367 (14), 310 (9), 293 (15).

(7*S*,9*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-7,8,9,10-tetrahydro-6-methoxy-9-hydroxy-9-(hydroxymethyl)-11-hydroxy-5,12-naphthalenedione (34) and Its 11-Methoxy-6-Hydroxy Isomer (35). A three-necked flask containing anhydrous THF (25 mL) and diisopropylamine (0.17 mL, 1.24 mmol) was cooled to −78 °C and *n*-BuLi (0.95 mL of 1.3 M solution, 1.24 mmol) added slowly. After stirring at 0 °C for 10 min, the solution was again cooled to −78 °C and HMPT (0.3 mL) added slowly. Cyanophthalide **33**[26] (197.2 mg, 1.24 mmol) in tetrahydrofuran (25 mL) was added 5 min later, and the solution turned orange. The solution was warmed to −23 °C, maintained at this temperature for 10 min, and cooled to −78 °C before the ketal mixture **31** + **32** (350 mg, 0.82 mmol) in THF (25 mL) was added slowly. The mixture was allowed to warm to room temperature over 2 h, aqueous AcOH (20%, 5 mL) added, and the solution stirred overnight. The solution was neutralized with aqueous $NaHCO_3$ and the THF removed in vacuo. The aqueous residue was extracted with ether. The organic solvent was dried (Na_2SO_4) and evaporated under reduced pressure. This afforded a crude residue (650 mg), which was chromatographed on silica gel with hexane–dichloromethane (1:3) as solvent. Elution afforded successively **34** (50 mg, 11.5%) and **35** (340 mg, 78.5%).

Compound **34**: mp 200 °C (hexane); $[\alpha]^{20}_D$ −37° (c 0.093, $CHCl_3$); IR (KBr) 1670, 1630, 1595 cm^{-1}; ^1H NMR δ 13.60 (s, 1 H, OH), 8.31–8.23 (m, 2 H, Ar H), and 7.85–7.72 (m, 2 H, Ar H) (AA′, BB′), 5.39–5.31 (t, 1 H, J = J' = 4 Hz, 7-H), 3.94 (s, 3 H, OMe), 3.80 (d, 1 H, J = 8 Hz) and 3.69 (d, 1 H, J = 8 Hz) (AB, 13-H), 3.30 (d, 1 H, J = 20 Hz) and 3.17 (d, 1 H, J = 20 Hz) (AB, 10-H), 2.46–2.37 (dd, 1 H, J = 14 Hz, J' = 4 Hz) and 2.13–2.02 (dd, 1 H, J = 14 Hz, J' = 4 Hz) (ABX, 8-H), 1.58 (s, 3 H) and 1.52 (s, 3 H) (CMe_2), 0.97 (s, 9 H, *t*-Bu), 0.31 (s, 3 H) and 0.17 (s, 3 H) (2 Me); DCI/NH_3; m/z (relative intensity) 525 (23), 411 (32), 410 (100), 393 (14). Anal. Calcd for $C_{29}H_{36}O_7Si$: C, 66.38; H, 6.91. Found: C, 66.18; H, 6.80.

Compound **35**: mp 150 °C (hexane); $[\alpha]^{20}_D$ +77° (c 0.05, $CHCl_3$); IR (KBr) 1675, 1625, 1590 cm^{-1}; ^1H NMR δ 13.76 (s, 1 H, OH), 8.30–8.18 (m, 2 H, Ar H) and 7.81–7.72 (m, 2 H, Ar H) (AA′, BB′), 5.35–5.28 (m, 1 H, 7-H), 3.96 (s, 3 H, OMe), 3.75 (s, 2 H, 13-H), 3.21 (d, 1 H, J = 18 Hz) and 3.11 (d, 1 H, J = 18 Hz) (AB, 10-H), 2.32–2.26 (m, 2 H, 8-H), 1.60 (s, 3 H) and 1.54 (s, 3 H) (CMe_2), 1.01 (s, 9 H, *t*-Bu), 0.33 (s, 3 H) and 0.23 (s, 3 H) (2 Me); DCI/NH_3, m/z (relative intensity) 525 (M + H^+, 14), 467 (16), 425 (14), 410 (100), 395 (16). Anal. Calcd for $C_{29}H_{36}O_7Si$: C, 66.38; H, 6.91. Found: C, 66.04, H, 6.88.

(+)-9-Deacetyl-9-(hydroxymethyl)-4-demethoxydaunomycinone (3). To a stirred solution of **34** and **35** (100 mg, 0.19 mmol) in THF (15 mL) was added, all at once, tetrabutylammonium fluoride (1 M solution in THF, 0.4 mL). The reaction became intense blue and was stirred for 30 min at room temperature. Neutralization with a few drops of 1 N aqueous HCl gave a red solution, and THF was removed under reduced pressure by evaporation. The residue was taken up in CH_2Cl_2 (150 mL) and the organic layer was washed with water, dried (Na_2SO_4), and evaporated. The crude product was taken up in dry CH_2Cl_2 (15 mL), and the solution was cooled at −78 °C under argon. BCl_3 (1 M solution in CH_2Cl_2, 2 mL, 1.9 mmol) was added over a period of 2 min. After being stirred for 30 min at −78 °C and addition of methanol (3 mL), the solution was concentrated under reduced pressure. Extraction with ethyl acetate of the residue afforded **3** (66 mg, 98%) as a crystalline orange material. Recrystallization from ethyl acetate gave a sample whose characteristics were identical with those previously described.[11]

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