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New Chiral Pool Approach to Anthracyclinones. The Stereoselective Synthesis of Idarubicinone

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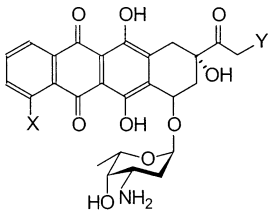
In the present work, a new chiral pool approach has been developed for the synthesis of anthracyclinones. Thus, enone **8**, readily available from L-rhamnose, has been converted via addition of 2,5-dimethoxybenzyllithium to the carbonyl group and a series of six reactions into a suitably protected aldehyde **21**. The $SnCl_4$-promoted stereospecific cyclization of the latter afforded enantiopure key intermediate **22**. Silylation of benzylic hydroxyl of **21** followed by anodic oxidation and selective hydrolysis gave ketoacetals **25** and **26** to which 3-cyano-1(3*H*)-isobenzofuranone **27** was annelated. Removal of the isopropylidene group in the resulting **28**, subsequent oxidation of the C_{13} hydroxyl and full deprotection led to idarubicinone (**4**).

Introduction

Anthracycline antibiotics[1] such as doxorubicin (**1**) and daunorubicin (**2**) are among the most potent antitumor agents, with proven clinical effectiveness against leukemias, lymphomas, breast carcinomas, and sarcomas.[2] Their importance in chemotherapy cytostatic activity has stimulated an ongoing interest in the exploration of this family of compounds.[3]

Their cardiotoxicity as well as intrinsic and acquired resistance[4] prompted continued search for analogues with improved therapeutical properties.[5] This has resulted in the synthesis of many (more then 2000) nonnatural anthracycline antibiotics, of which only a few reached the status of a drug used in clinical application. One of them, idarubicin (**3**),[6] a 4-demethoxy analogue of daunorubicin (**2**), exhibits lower toxicity and improved antineoplastic activity than its naturally occurring analogues **1** and **2** and is a registered drug for cancer chemotherapy.[7] Originally, idarubicin (**3**) was obtained by the demethoxylation of daunorubicin (**2**).[8] In a search for more efficient methods for its preparation, a considerable effort was expanded in total syntheses, which focused on the synthesis of the corresponding aglycone: idarubicinone (**4**).[9]



1 X = OMe, Y = OH
2 X = OMe, Y = H
3 X = H, Y = H

Several methodologies for the synthesis of the aglycone moiety of the anthracycline antibiotics have been developed.[9,10] Among the strategies for assembling the tetracyclic skeleton of the aglycone, a particularly effective and

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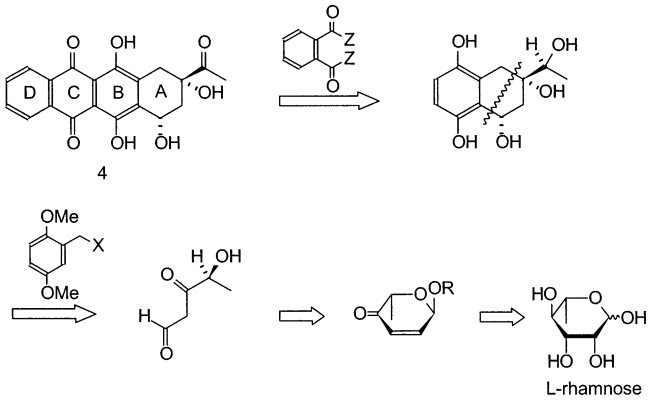
SCHEME 1



versatile approach is based on the coupling of its AB and CD ring segments.[11] Since the two stereogenic centers of an anthracycline are located in ring A, an enantiopure AB-ring building block with a defined configuration is required for the synthesis of the chiral target molecule. Use of this methodology has allowed several syntheses of daunomycinone and idarubicinone (**4**) to be accomplished. For this purpose, chiral AB fragments have been obtained by various methods, including resolution of a racemic precursor, asymmetric synthesis using a chiral auxiliary or a chiral catalyst, and a chiral pool approach. In the latter approach, substrates derived from α-amino[12] and α-hydroxy acids,[13] glycerol-related compounds[14] and sugars[15,16] were employed.

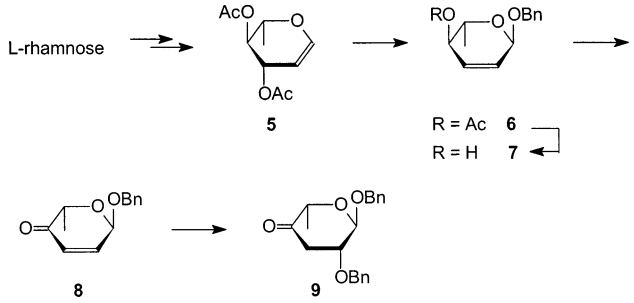
In this contribution, we describe the stereoselective synthesis of (+)-(7*S*,9*S*)-idarubicinone (**4**) using L-rhamnose as a chiral starting material. Our strategy is outlined in Scheme 1.

Results and Discussion

Ketone 9. Di-*O*-acetylrhamnal (**5**), obtained from L-rhamnose or commercial sources, was converted into the known benzyl glycoside **7**[17] according to the Ferrier procedure.[18] Oxidation of the C-4 hydroxy group in the latter with pyridinium dichromate gave enone **8** in 67% overall yield (Scheme 2).

In a previous study, we found that lithium reagents add to the carbonyl group of an enone, analogous to **8** but with a methyl instead of a benzyl aglycone, either with low stereoselectivity (butyllithium, benzyllithium)

SCHEME 2



or from the α-side of the pyranoside ring (2,5-dimethoxy-4-methylphenyllithium). Unexpectedly, in the case of 2,5-dimethoxybenzyllithium, the reagent required in our synthetic scheme, 1,4-addition decidedly prevailed over 1,2-addition to the carbonyl group.[19] Moreover, the product of both 1,4- and 1,2-addition resulted from the α-side attack on the molecule. The tertiary alcohol was produced not only in small yield but also with a (4*R*)-configuration, not suitable for our synthesis.

To alleviate the adverse course of the reaction, i.e., to eliminate the 1,4-addition of lithium reagent and reverse its stereochemistry, we decided first to protect the double bond in enone **8** by introduction of a benzyloxy substituent α to the C-2 position. Treatment of enone **8** with an excess of benzyl alcohol in the presence of potassium carbonate gave ketone **9**. The addition should occur on the face trans to the anomeric substituent.[20] The expected configuration at C-2 of the ketone **9** was consistent with ^{1}H NMR data and was unequivocally confirmed at the next step of the synthesis by single-crystal X-ray analysis (vide infra) of its derivative. The introduction of the benzyloxy substituent at C-2 served yet another purpose: activation of the C-1−C-2 bond for future scission.

Tetraline 22. Reaction of 2,5-dimethoxybenzyllithium, prepared by the reductive lithiation of 2,5-dimethoxybenzyl ethyl ether,[21] with ketone **9** in THF−toluene solution at −70 °C, resulted in a single adduct **10** isolated in 63% yield[1] (Scheme 3).

In the next step, the *O*-benzyl substituents at C-1 and C-2 of the alcohol **10** were removed by catalytic hydrogenation, yielding pyranose **11** and setting the stage for the oxidative cleavage of the C-1−C-2 bond. Since the stereochemistry of the newly formed stereogenic center at C-4 in alcohol **10** (or **11**) could not be assigned in a straightforward manner from the ^{1}H NMR spectrum, its configuration was established by single-crystal X-ray analysis. To this end, compound **11**, which like **10** could not be induced to crystallize, was reacted with 2,3-dimethoxypropane in the presence of *p*-toluenesulfonic acid. The resulting two-component mixture was separated to give a major (55%) product, crystalline 1,2-*O*-isopropylidene derivative **12**. The minor (14%) product was identified as the isomeric 1,2-*O*-isopropylidene derivative **13** with a furanose ring. The latter structural

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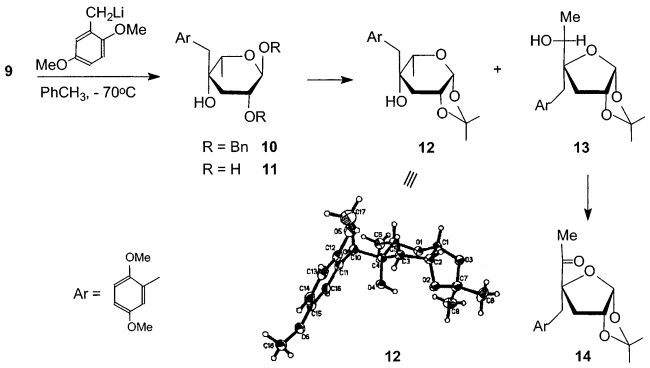
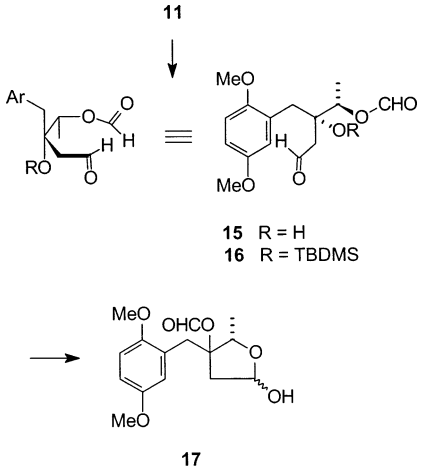
SCHEME 3[a]



[a] Side products 2,5-dimethoxytoluene and 1,2-bis(2,5-dimethoxyphenyl)ethane were identified in this reaction. They were readily separated from alcohol **10** by silica gel chromatography.

SCHEME 4



assignment is based on the ^{1}H NMR spectra of furanoside **13** and its oxidation product, ketone **14** (Scheme 3).

Recrystallization of compound **12** from ether−hexane afforded crystals suitable for X-ray analysis (see Supporting Information), which established the (2*S*,4*S*)-configuration and confirmed the expected steric course of the two additions: benzyl alcohol to the double bond in enone **8** and 2,5-dimethoxybenzyllithium to the carbonyl group in ketone **9**. It was gratifying to find that the stereogenic center at C-4 in **12** (or **11**) has the same configuration as the C-9 center in the idarubicinone (**4**) as well as in other anthracyclinones into which it shall be converted in the course of the synthesis.

Oxidative scission with sodium periodate of the C-1−C-2 bond in pyranose **11** furnished dihydroxyaldehyde **15**, an immediate precursor of the AB fragment of the target anthracyclinone. However, all our attempts to carry out cyclization of aldehyde **15** under Friedel−Crafts reaction conditions resulted in the migration of the formyl group to the tertiary hydroxyl with concomitant formation of the stable cyclic hemiacetal **17**, instead of formation of the carbocyclic ring A. An obvious possibility of suppressing the formation of the hemiacetal **17** was to use aldehyde **15** with a protected tertiary hydroxy group. The 4-*O*-TBDMS derivative of alcohol **10** was converted as above to silyl ether **16**. Unfortunately, all attempts to cyclize compound **16** failed.

No reaction was observed either at low temperature (between −70 and −40 °C) in the presence of tin tetrachloride or on prolonged (>12 h) standing at room temperature. The use of other Lewis acids ($TiCl_4$, BF_3, $AlCl_3$) led to the decomposition of the starting material. Since the search for appropriate conditions for the direct cyclization of aldehyde **15** or **16** did not look promising, we followed the example of Monneret et al.[16] and switched the protective groups of the tertiary and secondary hydroxyls from TBDMS and formyl, respectively, to an isopropylidene group. This could be achieved only in a stepwise fashion. Reduction of aldehyde **15** with sodium borohydride gave triol **18**, which on treatment with 2,3-dimethoxypropane under acidic conditions yielded isopropylidene derivative **19**. Mixed acetal **20** arising in the reaction as a side product could be easily converted without isolation into **19** by acidic methanolysis. Oxidation of **19** with iodoxybenzoic acid (IBX)[22] gave aldehyde **21**.

The isopropylidene derivative of dihydroxyaldehyde, structurally similar to **21** but lacking a methyl group in the side chain, was readily cyclized[16] with high stereoselectivity. In our case, the use of isopropylidene as a protecting group also facilitated cyclization. Treatment of aldehyde **21** with tin tetrachloride at −70 °C gave a high yield of bicyclic alcohol **22**, as a single isolated product. The (*S*)-configuration of the new stereogenic center, consistent with the rationale advanced by Monneret,[16] as well as the stereochemistry of remaining chiral centers present in tetraline **22** was firmly established by single-crystal X-ray analysis (see Supporting Information).

Idarubicinone (4). Having in hand the AB building block of an anthracyclinone with the correct absolute stereochemistry corresponding to the (7*S*,9*S*)-configuration of the target molecule **4**, we chose to assemble its tetracyclic skeleton by the Kraus addition cyclization method.[23] This procedure of CD-segment annelation, requiring mild conditions to preclude the loss of stereochemical integrity in the chiral AB segment, has been successfully used before for regiospecific anthracyclinone syntheses.[16,24]

Protection of the benzylic hydroxyl group of **23** wih TBDPS followed by anodic oxidation[25] in MeOH solution of the aromatic ring afforded the resulting bisketal **24**, which was regioselectively hydrolyzed yielding ketoacetals **25** and **26** in a ratio of approximately 10:1 (Scheme 6). For the synhesis of idarubicinone (**4**), where the problem of a substituent at C-4 does not exist, the presence of the minor regioisomer **26** is of no consequence. However, it could be easily removed by chromatography or crystallization.

The annelation of the 3-cyano-1(3*H*)-isobenzofuranone **27** to the ketoacetal **25** gave tetracyclic compound **28**.

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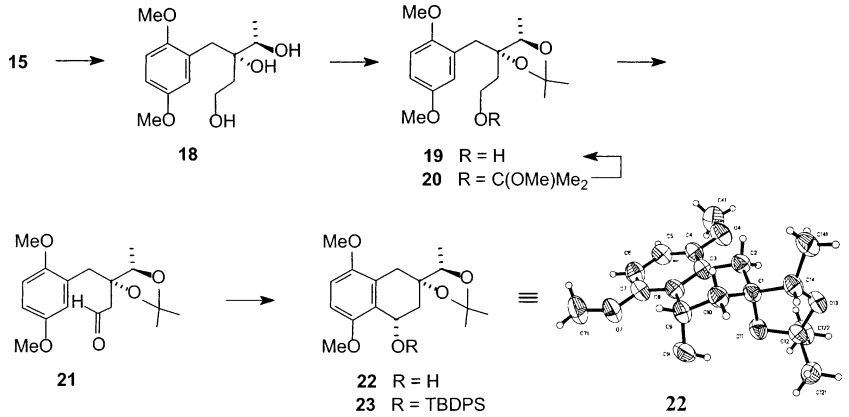
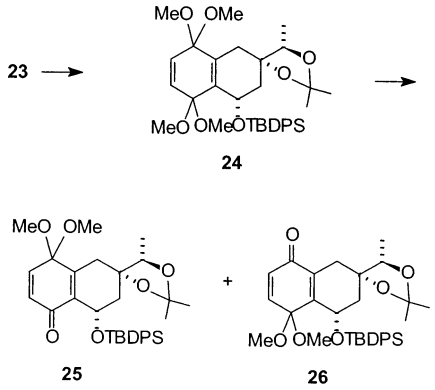
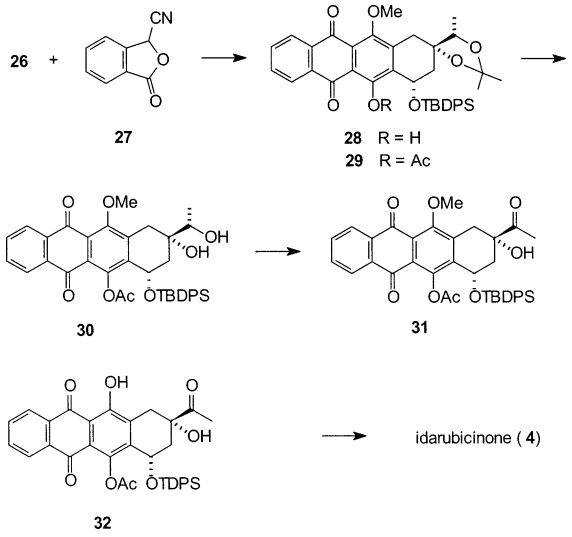
SCHEME 5



SCHEME 6



SCHEME 7



Selective hydrolysis of isopropylidene group in **28** followed by oxidation of the secondary hydroxyl group with IBX[22] gave protected idarubicinone (**4**). However, better yields were achieved when, prior to the hydrolysis and oxidation steps, the phenolic hydroxyl group was protected as its acetate **29**. Then, hydrolysis of the dioxolane ring and oxidation of triol **30** gave ketone **31** with all the functional groups of idarubicinone (**4**) in place (Scheme 7). It should be mentioned that the diol **30** has a structure, including the defined (13*S*)-configuration, identical with that assigned to the aglycon of the metabolite or microbial reduction product of idarubicine (**3**).[26]

Three protecting groups still present in ketone **31** were removed in two steps according to well-known procedures.[24] First, the C-12 methoxy group was cleaved with the aid of boron trichloride to give **32**, and then acetate and silyl groups were removed by acidic methanolysis. The order of these reactions could be reversed, but using boron trichloride cleavage as the last step causes purification problems due to complexation of idarubicinone (**4**) with boron.[24] Idarubicinone (**4**) of high (>99% by HPLC) purity was obtained in 72.5% yield (calculated on the annelation product **28**).

Experimental Section

General Procedures. Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz using TMS as an internal reference. IR spectra were recorded for $CHCl_3$ solutions with an FTIR spectrophotometer. MS and HRMS were obtained by EI or liquid secondary ionization mass spectrometry (LSIMS). Chromatography refers to column chromatography on Merck Kieselgel 60 (230−400 mesh). Thin-layer chromatography was performed using precoated aluminum plates (Merck Kieselgel 60 F_{254}) and visualized with UV light or acidic molybdate(IV)−cerium sulfate reagent.

Where appropriate, reactions were carried out in oven-dried glassware (120 °C, 3 h) under an Ar atmosphere. Dry solvents were prepared using standard procedures.

Benzyl 4-*O*-Acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (6). A solution of boron trifluoride etherate (11.5 g, 0.08 mol) in methylene dichloride (25 mL) was added dropwise to a cooled (5 °C) solution of 3,4-di-*O*-acetyl-L-rhamnal (**5**, 107 g, 0.5 mol) and benzyl alcohol (62.7 g, 60 mL, 0.58 mol) in benzene (500 mL) at a rate such that the temperature did not exceed 10 °C. After completion of addition, the reaction mixture was stirred for 1 h at 5−10 °C and then poured into a saturated solution of sodium bicarbonate (500 mL). The organic layer was washed with water and brine and dried. After evaporation of the solvent, the residue was distilled at 118 °C/0.05 Torr to give 116.5 g (88.8%) of product **6** as a pale yellow oil.

Benzyl 2,3,6-Trideoxy-α-L-hex-2-enopyranosid-4-ulose (8). To a solution of benzyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (**6**, 44.2 g, 0.17 mol) in methanol (300 mL) was added a small amount of sodium, and the solution was left at room temperature for 3 h. It was then neutralized with a few drops of acetic acid, evaporated to

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dryness, and coevaporated with toluene (2 × 100 mL). The residue was dissolved in DMF (450 mL) and pyridinium dichromate (122 g, mol), and powdered 4Å molecular sieves (40 g) were added; the reaction mixture was stirred overnight, diluted with ethyl acetate (300 mL), washed thoroughly with water and then with brine, and dried. After evaporation of the solvent the residue was distilled at 105−115 °C/0.05 Torr to give 28.1 g (76.5%) of product **8**, which contained (HPLC) 8% β-anomer.

An analytical sample was chromatographed to give pure **8**, bp 90 °C/0.02 Torr, $[\alpha]_D$ +29.16 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.4−7.3 (m, 5H); 6.83 (dd, *J* = 10.2, 3.5 Hz, 1H); 6.09 (d, *J* = 10.2 Hz, 1H); 5.28 (bd, *J* = 3.5 Hz, 1H); 4.85 (d, *J* = 11.7 Hz, 1H); 4.69 (d, *J* = 11.9 Hz, 1H); 4.56 (q, *J* = 6.8 Hz, 1H); 1.37 (d, *J* = 6.8 Hz, 3H). IR: ν_{max} 3028, 1699, 1454, 1026 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.50; H, 6.50. Found: C, 71.08; H, 6.51. HRMS: calcd for $C_{13}H_{14}O_3$ (M^+), 218.094294; found, 218.094166. *m/z*: 91, 105, 111, 145, 174, 218.

Benzyl 2,3,6-Trideoxy-β-L-hex-2-enopyranosid-4-ulose. ^{1}H NMR: δ 7.40−7.30 (m, 5H); 6.91 (dd, *J* = 10.3, 2.0 Hz, 1H); 6.13 (dd, *J* = 10.3, 1.6 Hz, 1H); 5.40 (m, 1H); 4.95 (d, *J* = 11.7 Hz, 1H); 4.68 (d, *J* = 11.7 Hz, 1H); 4.24 (qd, *J* = 7.0, 0.9 Hz, 1H); 1.46 (d, *J* = 7.0 Hz, 3H). IR: ν_{max} 3032, 1701, 1454, 1375, 1160, 1059 cm^{-1}.

Benzyl 2-*O*-Benzyl-3,6-dideoxy-α-L-*threo*-hexopyranosid-4-ulose (9). A mixture of unsaturated ketone **8** (28 g, 0.128 mole), benzyl alcohol (100 mL), and anhydrous potassium carbonate (5 g) was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water until neutral and then with brine, and dried. After removal of the solvent, the residue was distilled at reduced pressure to remove unreacted benzyl alcohol and unsaturated ketone. The residue was bulb-to-bulb distilled at 200 °C/10^{-3} Torr to give 26.5 g (63.3%) of product **9** containing 7% β-L-*erythro* isomer.

An analytical sample was chromatographed to give pure **9**, bp 200 °C/10^{-3} Torr, $[\alpha]_D$ −126.3 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.45−7.20 (m, 10 H); 5.03 (bd, $J_{1,2}$ = 2.6 Hz, 1H); 4.83 (d, *J* = 11.9 Hz, 1H); 4.65 (d, *J* = 11.9 Hz, 1H); 4.57 (s, 2H); 4.18 (q, *J* = 6.8 Hz, 1H); 3.91 (ddd, *J* = 5.9, 4.4, 2.6 Hz, 1H); 2.81 (dd, *J* = 15.6, 4.4 Hz, 1H); 2.67 (dd, *J* = 15.6, 5.9 Hz, 1H); 1.32 (d, *J* = 6.8 Hz, 3H). IR: ν_{max} 3031, 1730, 1074 cm^{-1}. HRMS: calcd for $C_{20}H_{22}O_4$ (M − Bn), 235.097034; found, 235.097402. *m/z*: 91, 105, 146, 182, 235.

Benzyl 2-*O*-Benzyl-3,6-dideoxy-β-L-*erythro*-hexopyranosid-4-ulose. ^{1}H NMR: δ 7.40−7.20 (m, 10 H); 4.95 (d, *J* = 10.9 Hz, 1H); 4.91 (d, *J* = 4.0 Hz, 1H); 4.65 (d, *J* = 10.9 Hz, 1H); 4.64 (d, *J* = 12.1 Hz, 1H); 4.58 (d, *J* = 12.1 Hz, 1H); 4.10 (q, *J* = 7.0 Hz, 1H); 3.94 (ddd, *J* = 5.9, 5.1, 4.2 Hz, 1H); 2.93 (dd, *J* = 16.2, 5.0 Hz, 1H); 2.56 (dd, *J* = 16.2, 5.9 Hz, 1H); 1.39 (d, *J* = 6.9 Hz, 3H).

Benzyl2-*O*-Benzyl-4-*C*-2,5-dimethoxybenzyl-3,6-dideoxy-α-L-*ribo*-hexopyranoside (10). To an energetically stirred suspension of 3 g of finely cut lithium in THF (30 mL), cooled to −20 °C, under Ar, was slowly added a solution of 2,5-dimethoxybenzyl ethyl ether (14.7 g, 75 mmol) in ether (15 mL). After adding ca. 1/4 of the ether solution, an exothermic reaction started and the rate of addition was adjusted so as to keep the temperature between −15 and −20 °C. After completion of the addition (1.5 h), the reaction mixture was stirred for an additional 1 h at the same temperature, and then toluene (50 mL) was added and the solution transferred by double-ended needle to a flask containing toluene (100 mL) cooled to −70 °C. To this solution was added dropwise ketone **9** (14.7 g, 45 mmol) in toluene (100 mL) over a period of 2 h. After the addition was finished, the reaction mixture was stirred for an additional 1 h at −70 °C and then allowed to warm to −30 °C and poured into saturated ammonium chloride solution (300 mL). The reaction mixture was washed with saturated ammonium chloride (2 × 100 mL) and then with water until neutral and with brine and dried. After removal of the solvents under reduced pressure, the residue was chromatographed to give product **10** (13.5 g, 62.6%) as a thick yellowish oil. $[\alpha]_D$ −66.3 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.40−7.20 (m, 10 H); 6.95 (bs, 1H); 6.77 (bs, 2H); 4.87 (bs, 1H); 4.74 (d, *J* = 11.9 Hz, 1H); 4.50 (d, *J* = 12.1 Hz, 1H); 4.49 (s, 2H); 3.94 (q, *J* = 6.5 Hz, 1H); 3.92 (s, 1H); 3.77 (2, 3H); 3.74 (s, 3H); 3.52 (m, 1H); 2.81 (dd, *J* = 13.4, 1.4 Hz, 1H); 2.57 (d, *J* = 13.7, 1H); 1.84 (dd, *J* = 15.0, 3.2 Hz, 1H); 1.68 (dm, *J* = 15 Hz, 1H); 1.32 (d, *J* = 6.4 Hz, 3H). IR: ν_{max} 3500, 1500, 1425, 1124, 1012 cm^{-1}. HRMS: calcd for $C_{29}H_{34}O_6$ (M^+), 478.235539; found, 478.235613. *m/z* 91, 152, 241, 313, 328, 370, 478.

4-*C*-2,5-Dimethoxybenzyl-3,6-dideoxy-α- and β-L-*ribo*-Hexopyranose (11). Adduct **10** (12 g, 25 mmol) in 2:1 ethyl acetate−ethanol (150 mL) was hydrogenated in the presence of 2 g of 5% Pd/C. After 4 h, the catalyst was filtered off and washed with ethyl acetate and the solvent evaporated yielding **11** as a thick oil (7.2 g, 96.3%) that existed as a mixture of anomers α and β in a ratio of approximately 3:2.

α-Anomer. ^{1}H NMR (after D_2O exchange): δ 6.90−6.60 (m, 3H); 4.63 (bs, 1H); 3.84 (s, 3H); 3.77 (s, 3H); 3.62 (m, 1H); 3.57 (q, *J* = 6.4 Hz, 1H); 3.02 (d, *J* = 14.1 Hz, 1H); 2.28 (d, *J* = 14.1 Hz, 1H); 1.82 (dd, *J* = 14.8, 3.1 Hz, 1H); 1.52 (dd, *J* = 14.8, 3.3 Hz, 1H); 1.37 (d, *J* = 6.4 Hz, 3H).

β-Anomer. ^{1}H NMR (after D_2O exchange, partial spectrum): δ 5.14 (bs, 1H); 4.09 (q, *J* = 6.4 Hz, 1H); 3.05 (d, *J* = 14.1 Hz, 1H); 2.33 (d, *J* = 14.0 Hz, 1H); 1.79 (dd, *J* = 14.8, 3.5 Hz, 1H); 1.31 (d, *J* = 6.4 Hz, 3H). IR: ν_{max} 3452, 1500, 1460, 1045 cm^{-1}.

4-*C*-(2,5-Dimethoxybenzyl)-1,2-*O*-isopropylidene-3,6-dideoxy-β-L-*ribo*-hexopyranose (12). To a solution of compound **11** (500 mg, 1.67 mmol) in acetone (3 mL) and 2,2-dimethoxypropane (3 mL) was added a small amount of *p*-TsOH, and the reaction mixture was left at room temperature for 20 h. After neutralization with one drop of triethylamine, the solvents were removed on a rotary evaporator, and the residue was dissolved in ethyl acetate, washed with water and brine, and dried. Removal of the solvent left an oil that was flash-chromatographed to give **12** (307 mg, 55%). After crystallization from ether/hexane, mp = 120.5−122 °C and $[\alpha]_D$ 0.54 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 6.97−6.64 (m, 3H); 5.10 (bd, *J* = 2.0 Hz, 1H); 3.99 (m, 1H); 3.76 (s, 3H); 3.75 (s, 3H); 3.53 (q, *J* = 6.2 Hz, 1H); 3.25 (bd, *J* = 1.7 Hz, 1H); 2.76 (dd, *J* = 13.6, 1.8 Hz, 1H); 2.53 (d, *J* = 13.6 Hz, 1H); 1.94 (dd, *J* = 16.0, 2.2 Hz, 1H); 1.79 (dd, *J* = 16.1, 3.8 Hz, 1H); 1.59 (s, 3H); 1.32 (d, *J* = 6.3 Hz, 3H); 1.30 (s, 3H). IR: ν_{max} 3540, 1499, 1465, 1161, 1113, 1015 cm^{-1}. HRMS: calcd for $C_{18}H_{26}O_6$ (M^+), 338.17294; found, 338.17460.

(3*S*,4*S*)-3-(2,5-Dimethoxybenzyl)-4-formyloxy-3-hydroxypentanal (15). A solution of sodium periodate (8.0 g, 37.4 mmol) in water (100 mL) was added dropwise to a stirred solution of aldose **11** (7.0 g, 23.5 mmol) in methanol (150 mL). After complete addition (1 h), the reaction was stirred for an additional 1 h, and then ethylene glycol (5 mL) was added and stirring continued for 15 min. The formed precipitate was filtered off and washed with methanol and the organic phase concentrated to about 100 mL. The residue was extracted with ethyl acetate, and the organic layer was washed with water until neutral and then dried. Evaporation of the solvent gave aldehyde **15** as an oil (6.5 g) that was used without purification in the next step. ^{1}H NMR: δ 9.75 (t, *J* = 2.5 Hz, 1H); 8.07 (s, 1H); 6.90−6.60 (m, 3H); 4.97 (qd, *J* = 6.4, 0.7 Hz, 1H); 4.17 (s, 1H); 3.81 (s, 3H); 3.75 (s, 23H); 3.06 (d, *J* = 13.9 Hz, 1H); 2.88 (d, *J* = 13.9 Hz, 1H); 2.59 (dd, *J* = 16.0, 2.4 Hz, 1H); 2.49 (dd, *J* = 16.0, 2.6 Hz, 1H); 1.36 (d, *J* = 6.4 Hz, 3H). IR: ν_{max} 3482, 2837, 1719, 1500, 1465 cm^{-1}. HRMS: calcd for $C_{15}H_{20}O_6$ (M^+), 296.12599; found, 296.12422.

(3*S*,4*S*)-3-(2,5-Dimethoxybenzyl)pentane-1,3,4-triol (18). To a solution of sodium borohydride (2 g) in 1:1 water−2-propanol (40 mL) was added dropwise a solution of aldehyde **15** (6.5 g, 21.9 mmol) in THF (50 mL). After stirring for 1 h, the reaction mixture was neutralized with acetic acid and concentrated. The residue was dissolved in ethyl acetate, washed with water and brine, and dried. Evaporation of the

solvent gave 5.9 g (100%) of triol **18** as a thick oil. The analytical sample was chromatographed to give pure **18**. $[\alpha]_D$ +7.1 (*c* 1, $CHCl_3$). ^1H NMR: δ 6.90−6.75 (m, 3H); 3.82 (s, 3H); 3.76 (s, 3H); 3.81−3.72 (m, 2H); 3.64 (q, J = 6.4 Hz, 1H); 3.19 (d, J = 14.1 Hz, 1H); 2.51 (d, J = 13.9 Hz, 1H); 1.93−1.64 (m, 2H); 1.21 (d, J = 6.4 Hz, 3H). IR: ν_{max} 3432, 1592, 1500, 1285, 1179, 1117, 1068 cm^{-1}. HRMS: calcd for $C_{14}H_{22}O_5$ (M^+), 270.14673; found, 270.14601. *m*/*z*: 43, 121, 137, 152, 175, 207, 225, 252, 270.

(3*S*,4*S*)-3-(2,5-Dimethoxybenzyl)-3,4-*O*-isopropylidene-pentane-1,3,4-triol (19). To a solution of triol **18** (5.5 g, 20.3 mmol) in acetone (25 mL) and dimethoxypropane (10 mL) was added *p*-toluenesulfonic acid (50 mg), and the reaction mixture was stirred for 3 h, evaporated to dryness, and coevaporated with 100 mL toluene. The residue, consisting of an approximately 1:1 mixture of **19** and **20**, was redissolved in 25:1 acetone−water (40 mL). Pyridinium *p*-toluenesulfonate (1 g) was added and the mixture stirred for 2 h. Solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed with water until neutral, dried, and evaporated to dryness to give crude **19** (5.7 g, 90%), which was used in the next step.

The analytical samples were obtained by flash chromatography of a 1:1 mixture of **19** and **20**.

19: $[\alpha]_D$ +102.8 (*c* 1, $CHCl_3$). ^1H NMR: δ 7.00 (m, 1 H); 6.80−6.70 (m, 2H); 4.28 (q, J = 6.4 Hz, 1H); 3.75 (s, 3H); 3.74 (s, 3H); 3.82−3.47 (m, 2H); 2.96 (d, J = 13.7 Hz, 1H); 2.55 (J = 13.7 Hz, 1H); 1.80 (ddd, J = 15.0, 8.2, 4.6 Hz, 1H); 1.59 (ddd, J = 15.0, 6.0, 4.2 Hz, 1H); 1.66 (s, 3H); 1.42 (s, 3H); 1.35 (d, J = 6.4 Hz, 3H). IR: ν_{max} 3510, 2836, 1590, 1497, 1466 cm^{-1}. HRMS: calcd for $C_{17}H_{26}O_5$ (M^+), 310.17801; found, 310.17464. *m*/*z*: 59, 101, 151, 159, 205, 235, 295, 310.

(3*S*,4*S*)-3-(2,5-Dimethoxybenzyl)-3,4-*O*-isopropylidene-1-*O*-(1-methoxy-1-methylethyl)-pentane-1,3,4-triol (20). $[\alpha]_D$ +54.4 (*c* 1, $CHCl_3$). ^1H NMR: δ 7.05 (m, 1H); 6.80−6.68 (m, 2H); 4.32 (q, J = 6.2 Hz, 1H); 3.75 (s, 3H); 3.74 (s, 3H); 3.53−3.30 (m, 2H); 3.13 (s, 3H); 2.95 (d, J = 13.8 Hz, 1H); 2.57 (d, J = 13.7 Hz); 1.81−1.60 (m, 2H); 1.63 (s, 3H); 1.38 (s, 23H); 1.34 (d, J = 6.2 Hz, 3H); 1.29 (s, 6H). IR: ν_{max} 1499, 1465, 1380, 1160, 1090 cm^{-1}. HRMS: calcd for $C_{21}H_{34}O_6$ (M^+), 382.23554; found, 382.23940.

(3*S*,4*S*)-3-(2,5-Dimethoxybenzyl)-3,4-*O*-isopropylidene-3,4-dihydroxypentanal (21). Alcohol **19** (5.7 g, 18.3 mmol) and IBX (6.1 g, 22 mmol) in DMSO (35 mL) were stirred for 3 h. Water (50 mL) was added, and the precipitated iodozobenzoic acid was filtered off; the filtrate was washed thoroughly with ether. The ether solution was washed with water until neutral, dried, and evaporated. The residue was crystallized from ether−hexane to give aldehyde **21** (4.85 g, 86%), mp 55.5−56.5 °C, $[\alpha]_D$ +98.6 (*c* 1, $CHCl_3$). ^1H NMR: δ 9.51 (t, J = 2.5 Hz, 1H); 6.96−6.93 (m, 1H); 6.77−6.74 (m, 2H); 4.15 (q, J = 6.2 Hz, 1H); 3.76 (s, 3H); 3.72 (s, 3H); 3.03 (d, J = 13.6 Hz, 1H); 2.56 (d, J = 13.9 Hz, 1H); 2.52 (dd, J = 15.9, 1.9 Hz, 1H); 2.39 (dd, J = 15.9, 2.9 Hz, 1H); 1.66 (s, 3H); 1.40 (d, J = 6.2 Hz, 3H); 1.35 (s, 3H). IR: ν_{max} 2837, 2746, 1716, 1593, 1500, 1180, 1049 cm^{-1}. HRMS: calcd for $C_{17}H_{24}O_5$ (M^+), 308.16238; found, 308.16058.

(4*S*,5*S*,4′*S*)-5′,8′-Dimethoxy- 4′-hydroxy-2,2,5-trimethylspiro[1,3-dioxolane-4,2′-1′,2′,3′,4′-tetrahydronaphthalene] (22). A solution of tin tetrachloride (3.31 g, 12.7 mmol) in methylene chloride (5 mL) was added dropwise to a cooled (−70 °C) solution of aldehyde **21** (3.9 g, 12.6 mmol) in methylene chloride (90 mL). Stirring was continued for 1 h, and then the reaction mixture was poured into a 1.5 M NaOH solution (100 mL) that was energetically stirred and cooled in an ice−water bath. The organic phase was separated, washed with water and brine, and dried. After evaporation of solvent, the residue was triturated with ether to induce crystallization. Filtration afforded **22** (3.31 g, 85%). Chromatography of the mother liquor and crystallization from ether−hexane gave additionally 0.26 g (6.7%) of **22**. Mp 108.5−109.5 °C, $[\alpha]_D$ +37.3 (*c* 1, $CHCl_3$). ^1H NMR: δ 6.74 (s, 2H); 5.07 (ddd, J = 8.8, 5.1, 3.2 Hz, 1H); 4.14 (d, J = 8.8 Hz, 1H); 4.08 (q, J = 6.4 Hz, 1H); 3.86 (s, 3H); 3.78 (s, 3H); 2.98 (dd, J = 17.6, 1.8 Hz, 1H); 2.46 (d, J = 17.6 Hz, 1H); 2.13 (ddd, J = 13.9, 3.3, 2.0 Hz, 1H); 1.95 (dd, J = 13.7, 5.1 Hz, 1H); 1.41 (s, 3H); 1.39 (s, 3H); 1.26 (d, J = 6.4 Hz, 3H). IR: ν_{max} 3511, 1602, 1483, 1263, 1099 cm^{-1}. HRMS: calcd for $C_{17}H_{24}O_5$ (M^+), 308.16237; found, 308.16243.

(4*S*,5*S*,4′*S*)-4′-*tert*-Butyldiphenylsilyloxy-5′,8′-dimethoxy-2,2,5-trimethylspiro[1,3-dioxolane-4,2′-1′,2′,3′,4′-tetrahydronaphthalene] (23). A solution of bicyclic alcohol **22** (3.1 g, 10 mmol), *tert*-butyldiphenylsilyl chloride (4.1 g, 15 mmol), and imidazole (1.5 g, 22 mmol) in DMF (20 mL) was kept, with stirring, at 70−75 °C (oil bath) for 15 h. After the mixture was cooled, ethyl acetate was added and the mixture washed thoroughly with water and brine and dried. Evaporation of the solvent gave a thick oil that was diluted with ether (10 mL) and left to crystallize. Filtration afforded silyl derivative **23** (4.2 g, 72.4%), mp 109−111 °C, $[\alpha]_D$ −2.74 (*c* 1, $CHCl_3$). Flash chromatography of the residue gave additionally 0.76 g (13%) of **23**. ^1H NMR: δ 7.90−7.80 (m, 2H); 7.50−7.20 (m, 8H); 6.68 (d, J = 8.92 Hz, 1H); 6.44 (d, J = 8.79 Hz, 1H); 5.33 (t, J = 3.57 Hz, 1H); 3.79 (s, 3H); 3.73 (q, J = 6.2 Hz, 1H); 3.36 (d, J = 15.6 Hz, 1H); 3.26 (s, 3H); 2.90 (d, J = 15.6 Hz, 1H); 2.41 (dd, J = 14.7, 3.5 Hz, 1H); 1.55 (dd, J = 14.8, 3.7 Hz, 1H); 1.54 (s, 3H); 1.40 (s, 3H); 0.99 (s, 9H); 0.91 (d, J = 6.2 Hz, 3H). IR: ν_{max} 2934, 2858, 1489, 1280, 1104 cm^{-1}. HRMS: calcd for $C_{32}H_{39}O_5Si$ (M − CH_3) 531.25665; found, 531.25896. Calcd for $C_{29}H_{33}O_5Si$ (M − *t*-Bu), 489.20972; found, 489.20681.

(4*S*,5*S*,4′*S*)-4′-*tert*-Butyldiphenylsilyloxy-5′,5′,8′,8′-tetramethoxy-2,2,5-trimethylspiro[1,3-dioxolane-4,2′-1′,2′,3′,4′,5′,8′-hexahydronaphthalene] (24). A suspension of silyl derivative **23** (4.2 g, 7.46 mmol) in a solution of KOH in methanol (1%, 180 mL), cooled to − 5 °C, was oxidized anodically using a Pt cathode and a Pt-net cylinder as an anode (0.8−0.95 A, 1.15 V). After 4 h, the electrolysis was terminated, and the reaction mixture was neutralized with solid CO_2 and evaporated from a cold bath. The resulting oil was dissolved in methylene chloride, washed with water and brine, and dried. Removal of the solvent gave tetramethoxy compound **24** (4.3 g, 92.1%) as a thick oil that was used immediately for the next step. ^1H NMR: δ 7.85 − 7.25 (m, 10 H); 6.20 (d, J = 10.6 Hz, 1H); 6.12 (d, J = 10.6 Hz, 1H); 4.78−4.73 (m, 1H); 3.37 (q, J = 6.41 Hz, 1H); 3.24 (s, 3H); 3.22 (s, 3H); 3.16 (s, 3H); 3.07 (s, 3H); 2.57 (d, J = 17.2 Hz, 1H); 2.25 (d, J = 17.6 Hz, 1H); 1.87 (dd, J = 13.9, 5.7 Hz, 1H); 1.39 (s, 3H); 1.27 (dd, J = 14.0, 4.5 Hz, 1H); 1.19 (s, 3H); 1.09 (s, 9H); 1.02 (d, J = 6.2 Hz, 3H).

(4*S*,5*S*,4′*S*)-4′-*tert*-Butyldiphenylsilyloxy-8′,8′-dimethoxy-5′-oxo-2,2,5-trimethylspiro[1,3-dioxolane-4,2′-1′,2′,3′,4′,5′,8′-hexahydronaphthalene] (25). To a solution of tetramethoxy compound **24** (4.2 g, 6.9 mmol) in acetone (25 mL) was added aqueous acetic acid (8%, 8 mL), and the mixture was stirred at rt for 2 h. After neutralization with saturated sodium bicarbonate solution, acetone was evaporated from a cold bath and the residue extracted with methylene chloride. The organic layer was washed with saturated sodium bicarbonate solution, water, and brine and dried. Removal of solvent gave a ca. 9:1 mixture of **25** and its isomer **26** (3.65 g, 94%). A sample of this mixture was chromatographed to give as the main product **25**: $[\alpha]_D$ −4.75 (*c* 1, $CHCl_3$); ^1H NMR: δ 7.88−7.83 (m, 2H); 7.69−7.64 (m, 2H); 7.42−7.25 (m, 6H); 6.71 (d, J = 10.4 Hz, 1H); 6.29 (d, J = 10.4 Hz, 1H); 4.88−4.84 (m, 1H); 3.79 (q, J = 6.2 Hz, 1H); 3.33 (s, 3H); 3.20 (s, 3H); 2.59 (dd, J = 18.9, 1.3 Hz, 1H); 2.18 (dd, J = 19.2, 0.5 Hz, 1H); 1.95 (dm, J = 14.1 Hz, 1H); 1.51 (dd, J = 14.3, 5.31 Hz, 1H); 1.48 (s, 3H); 1.35 (s, 3H); 1.15 (d, J = 6.2 Hz, 3H); 1.00 (s, 9H). IR: ν_{max} 3073, 1677, 1651, 1103 cm^{-1}. HRMS: calcd for $C_{32}H_{39}O_6Si$ (M^+ − CH_3), 547.25159; found, 547.24989. Calcd for $C_{29}H_{33}O_6Si$ (M^+ − $C(CH_3)_3$), 505.20456; found, 505.20648.

Minor Product: (4*S*,5*S*,4′*S*)-4′-*tert*-Butyldiphenylsilyloxy-5′,5′-dimethoxy-8′-oxo-2,2,5-trimethylspiro[1,3-dioxolane-4,2′-1′,2′,3′,4′,5′,8′-hexahydronaphthalene] (26). $[\alpha]_D$

+21.1 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 7.82−7.76 (m, 4H); 7.47−7.31 (m, 6H); 6.73 (d, J = 10.3 Hz, 1H); 6.43 (d, J = 10.4 Hz, 1H); 4.83−4.78 (m, 1H); 3.35 (q, J = 6.2 Hz, 1H); 3.19 (s, 3H); 3.17 (s, 3H); 2.84 (d, J = 17.4 Hz, 1H); 2.39 (dd, J = 17.2, 1.5 Hz, 1H); 2.00 (dd, J = 13.9, 6.4, 1H); 1.39 (s, 3H); 1.33 (dd, J = 13.9, 4.4 Hz, 1H); 1.19 (s, 3H); 1.09 (s, 9H); 0.85 (d, J = 6.2, 3H). IR: ν_{max} 3073, 1711, 1673, 1645, 1111 cm^{-1}.

(7′*S*,9′*S*,4*S*)-7′-*tert*-Butyldiphenylsilyloxy-6′-hydroxy-11′-methoxy-2,2,5-trimethylspiro[1,3-dioxolane-4,9′-7′,8′,9′,10′-tetrahydrotetracene]-5′,12′-dione (28). To a cooled (−15 °C) solution of potassium *t*-butoxide (970 mg, 8.6 mmol) in THF (30 mL) was added dropwise a solution of cyanophthalide **27** (1.27 g, 8 mmol) in THF (5 mL) followed, after few minutes, by a solution of monoketals **25** and **26** (3.8 g, 6.7 mmol) in THF (15 mL). The reaction mixture, which turned black, was stirred at −10 °C for 30 min; then, 10% HCl (40 mL) was added, and the red solution was stirred at room temperature for 40 min. Most of the THF was evaporated; the residue was extracted with ethyl acetate, and the organic layer was washed with water and brine and dried. Evaporation of solvents furnished product **28** (4.4 g, 98.3%) as a red foam. ^{1}H NMR: δ 13.09 (s, 1H); 8.29−7.16 (m, 14H);; 5.57 (t, J = 3.6 Hz, 1H); 3.92 (s, 3H); 3.79 (q, J = 6.4 Hz, 1H); 3.50 (d, J = 16.1 Hz, 1H); 3.04 (d, J = 16.1 Hz); 2.37 (dd, J = 15.0, 3.2 Hz, 1H); 1.58 (dd, J = 15.0, 3.5 Hz, 1H); 1.57 (s, 3H); 1.42 (s, 3H); 1.04 (s, 9H); 0.95 (d, J = 6.4 Hz, 3H). IR: ν_{max} 1799, 1668, 1631, 1594, 1359, 1106, 987 cm^{-1}. HRMS: calcd for $C_{40}H_{43}O_7Si$ (M + H$^+$), 663.27781; found, 663.277776.

(7′*S*,9′*S*,4*S*)-6′-Acetoxy-7′-*tert*-butyldiphenylsilyloxy-11′-methoxy-2,2,5-trimethylspiro[1,3-dioxolane-4,9′-7′,8′,9′,10′-tetrahydrotetracene]-5′,12′-dione (29). A solution of compound **28** (4.2 g, 6.33 mmol) in pyridine (5 mL) and acetic anhydride (5 mL) with a catalytic amount of DMAP was kept at 45−50 °C for 3 h and then poured into ice−water. The organic layer was washed with saturated potassium bicarbonate solution, 10% HCl, water, and brine. After drying and removal of the solvent, **29** was obtained as a bright yellow solid (4.4 g, 98.5%). ^{1}H NMR: δ 8.23−7.14 (m, 14H); 5.14 (bs, 1H); 3.98 (s, 3H); 3.76 (q, J = 6.2 Hz, 1H); 3.72 (d, J = 15.9 Hz, 1H); 3.07 (d, J = 15.9 Hz, 1H); 2.37 (dd, J = 15.0, 3.3 Hz, 1H); 1.92 (s, 3H); 1.58 (s, 3H); 1.52 (bd, 1H); 1.42 (s, 3H); 0.99 (s, 9H); 0.93 (d, J = 6.0 Hz, 3H). IR: ν_{max} 1763, 1674, 1578, 1332, 1097 cm^{-1}. HRMS: calcd for $C_{42}H_{45}O_8Si$ (M + H$^+$), 705.28837; found, 705.28562.

(7*S*,9*S*,1′*S*)-6-Acetoxy-7-(*tert*-butyldiphenylsilyloxy)-9-hydroxy-9-(1′-hydroxyethyl)-11-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (30). Compound **29** (4.4 g, 6.24 mmol) was dissolved in 80% acetic acid (90 mL) and THF (15 mL), and the reaction mixture was kept at 80 °C for 5 h. After the mixture was cooled, most of the THF was removed on a rotary evaporator, and the residue was poured into water (50 mL) and extracted with ethyl acetate. The organic layer was washed with saturated potassium bicarbonate solution, water, and brine and dried. Removal of the solvent gave diol **30** as an orange solid (4.15 g, 100%). ^{1}H NMR: δ 8.23−6.77 (m, 14H); 5.44 (t, J = 2.9 Hz, 1H); 5.20 (s, 1H); 3.95 (s, 3H); 3.76−3.65 (m, 1H); 3.70 (q, J = 6.5 Hz, 1H); 3.44 (dd, J = 19.0, 1.0 Hz, 1H); 2.81 (d, J = 18.9 Hz, 1H); 2.73 (dm, J = 14.7 Hz, 1H); 1.76 (dd, J = 14.7, 3.4 Hz, 1H); 1.46 (s, 3H); 1.33 (d, J = 6.4 Hz, 3H); 0.89 (s, 9H). IR: ν_{max} 3477, 1763, 1675, 1339, 1113 cm^{-1}.

(7*S*,9*S*,1′*S*)-6-Acetoxy-9-acetyl-9-hydroxy-7-(*tert*-butyldiphenylsilyloxy)-11-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (31). To a solution of diol **30** (4.10 g, 6.17 mmol) in DMSO (20 mL) was added IBX (2.8 g, 10 mmol), and the reaction mixture was stirred at room temperature for 18 h and then poured into water (50 mL). Precipitated iodosobenzoic acid was filtered off and washed thoroughly with *tert*-butyl methyl ether. After separation of the water layer, the solution was extracted with *tert*-butyl methyl ether. The ethereal solution was washed with water, 10% sodium bicarbonate, water, and brine and then dried. Evaporation of the solvent gave **31** (3.56 g, 87%) as a yellow solid. ^{1}H NMR: δ 8.23−6.82 (m, 14H); 5.48 (bs, 1H); 5.43 (t, J = 2.9 Hz, 1H); 3.93 (s, 3H); 3.49 (dd, J = 18.5, 0.9 Hz, 1H); 3.21 (d, J = 18.5 Hz, 1H); 2.51 (dm, 1H); 2.44 (s, 3H); 2.05 (dd, J = 14.7, 3.1 Hz, 1H); 1.54 (s, 3H); 0.92 (s, 9H). IR: ν_{max} 3477, 1765, 1715, 1676, 1340, 1114 cm^{-1}. HRMS: calcd for $C_{39}H_{38}O_8SiNa$ (M$^+$ + Na), 685.22337; found, 685.22645.

(7*S*,9*S*,1′*S*)-6-Acetoxy-9-acetyl-9,11-dihydroxy-7-(*tert*-butyldiphenylsilyloxy)-7,8,9,10-tetrahydronaphthacene-5,12-dione (32). Boron trichloride (1 M in CH_2Cl_2, 20 mL) was added in one portion to a solution of tetracyclic ketone **31** (2 g, 3 mmol) in methylene chloride (100 mL), cooled to −70 °C, and the reaction mixture was stirred at that temperature for 1 h. Methanol (30 mL) was added, and after rt was reached, the solvents were partially removed on a rotary evaporator. The crystallizing residue was dissolved in ethyl acetate, washed with water until neutral, and dried. Evaporation left 2 g (100%) of **33** as an orange solid. ^{1}H NMR: δ 13.46 (s, 1H); 8.33−6.98 (m, 14 H); 5.52 (s, 1H); 5.38 (t, J = 2.9 Hz, 1H); 3.44 (dd, J = 19.0, 1.3 Hz, 1H); 3.12 (d, J = 19.0 Hz, 1H); 2.50 (dm, 1H); 2.45 (s, 3H); 2.07 (dd, J = 15.0, 3.1 Hz, 1H); 1.54 (s, 3H); 0.94 (s, 9H). IR: ν_{max} 3476, 1768, 1717, 1672, 1634, 1595, 1355 cm^{-1}. HRMS: calcd for $C_{38}H_{36}O_8SiNa$ (M$^+$ + Na), 671.20772; found, 671. 21026.

Idarubicinone (4). Compound **32** (2 g, 3 mmol) was dissolved in a solution of hydrogen chloride in methanol (3%, 100 mL) and the mixture left at room temperature for 48 h. Solid ammonium acetate was added for neutralization, and the precipitate was filtered off and washed with methanol. After evaporation to dryness, the residue was extracted with hot methanol (3 × 20 mL). Crystallization started upon cooling of the mixture, and after 24 h, the precipitate was filtered, washed with methanol, and dried, yielding 956 mg (86.5%) of idarubicinone (**4**) of 98% purity (HPLC). Enantiomeric homogeneity was confirmed by HPLC on a chiral column (Chiralcel OD-R, 65:35 MeCN/0.5 M $HClO_4$). Trituration of the crude product with hot methanol (10 mL) gave **4** (940 mg, 98.3%) of purity >99% (HPLC). ^{1}H NMR: δ 13.52 (s, 1H); 13.23 (s, 1H); 8.35−8.27 (m, 2H); 7.88−7.80 (m, 2H); 5.32−5.26 (m, 1H); 4.59 (s, 1H); 3.86 (d, J = 5.9 Hz, 1H); 3.18 (dd, J = 18.9, 2.0 Hz, 1H); 2.94 (d, J 18.9 Hz, 1H); 2.44 (s, 3H); 2.36 (dt, J = 14.6, 2.1 Hz, 1H); 2.17 (dd, J = 14.6, 4.6 Hz, 1H).

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Supporting Information Available: Figure S1 and Figure S2 showing ORTEP drawings of **12** and **22**, respectively, and Tables S1−S15 listing crystallographic details, fractional coordinates for non-hydrogen and hydrogen atoms, interatomic bond distances and bond angles, torsion angles, and anisotropic and isotropic displacement parameters of **12** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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