analysis and Maureen Martin for help with the preparation of the ketals.

Registry No. 1, 98540-71-7; 2, 98540-72-8; 2-phenyl-1,3-dihydroxypropane, 1570-95-2; *p*-chloroacetophenone, 99-91-2.

Supplementary Material Available: Tables of positional parameters, anisotropic temperatures factors, bond angles, and interatomic distances for *cis*-1,3-dioxane (1) and *trans*-1,3-dioxane (2) (8 pages). Ordering information is given on any current masthead page.

Synthetic Opportunities Offered by Anti α-Methylene-β-hydroxy-γ-alkoxy Esters: Stereoselective Reactions at the Double Bond[1]

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Addition of *tert*-butyl β-(dimethylamino)propionate to (*S*)-*O*-[(benzyloxy)methyl]lactaldehyde and (*R*)-2,3-*O*-isopropylideneglyceraldehyde gave, after N-methylation and elimination, α-methylene-β-hydroxy-γ-alkoxy esters in fairly good yield (40–60%) and a high anti–syn ratio (7–12:1). These esters were easily lactonized, by acidic treatment, to the corresponding α-methylene-β-hydroxy-γ-butyrolactones. The double bond of these compounds was submitted to various reactions (cuprate addition, reduction, dihydroxylation). The stereoselectivity of these reactions was studied and ranged from poor to good depending on the specific substrate and reaction used. Acyclic substrates proved to be more selective than the corresponding γ-lactones. The stereoconfiguration of the products was assigned by comparison to known compounds (blastmycinolactol-*a*, *epi*-D-hamamelose).

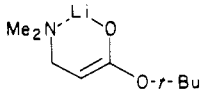
The aldol condensation is one of the most straightforward methods for generating C–C bonds in a stereoselective manner.[2] We recently reported that *tert*-butyl (β-(dimethylamino)propionate (1), a synthetic equivalent of *tert*-butyl acrylate, readily reacts with α-alkoxy aldehydes to give α-methylene-β-hydroxy-γ-alkoxy esters 2 with anti–syn selectivity up to 24:1[3] (Chart I).

We wish to report here additional examples of this anti-selective reaction and the transformation of 2 to various γ-lactones using stereoselective reactions at the double bond.

Results and Discussion

Optically pure (*S*)-*O*-[(benzyloxy)methyl]lactaldehyde (3)[3b] and (R)-2,3-*O*-isopropylideneglyceraldehyde (4)[4] were reacted, under previously described conditions,[3b] with *tert*-butyl β-(dimethylamino)propionate (1). The corresponding adducts were treated with K_2CO_3 and MeI in methanol[5] to give α-methylene-β-hydroxy-γ-alkoxy esters in fairly good yield (40–60%) and high anti–syn ratio (7–12:1) (Scheme I).

The condensation between 1 and lactaldehyde 3 was conducted in ethyl ether, after generating the enolate with LDA in ether at 0 °C in order to obtain the more stable and more anti-selective (*E*)-enolate 7.[3b] In the case of



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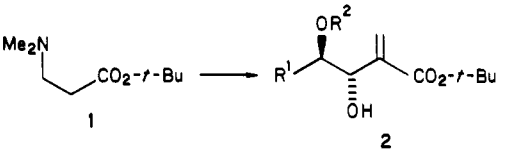
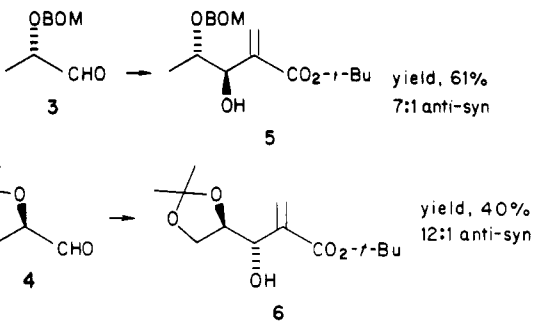
glyceraldehyde 4, on the contrary, after generating the enolate at 0 °C in ethyl ether, THF was added at −78 °C (THF–ether 5:1) in order to increase the reactivity toward the aldehyde. When the reaction was conducted in pure diethyl ether a slightly improved ratio was observed (13:1), accompanied by a much lower yield (15%). The one-pot N-methylation–elimination procedure used here (MeI–

Chart I



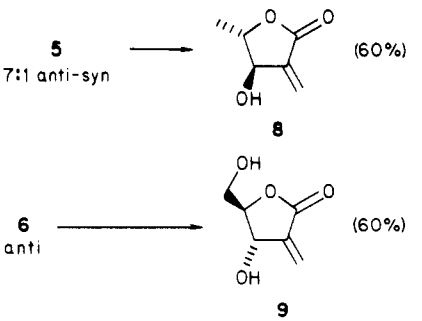
1 2

Scheme I[a]



[a] BOM = CH_2OCH_2Ph.

Scheme II



(1) We respectfully dedicate this work to the memory of Professor L. Canonica, untimely deceased in Aug, 1984. Part of this work has been preliminarily presented at the Fifth International Conference on Organic Synthesis, Freiburg, Aug 27–30, 1984, Abstract T24, p 108.

(2) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**,*13*, 1. Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212.

(3) (a) Banfi, L.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1112. (b) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, 3784.

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(5) Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* **1977**, *22*, 224.

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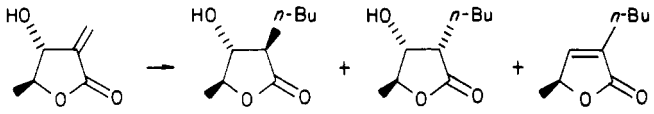
Scheme III



	8	10	11	12
(a) *n*-Pr_2CuLi/Et_2O/-78 °C AcOH/Et_2O/-78 °C		1	1	1
(b) *n*-Pr_2CuLi/Et_2O/-78 °C NH_4Cl/H_2O/0 °C		8	1	16

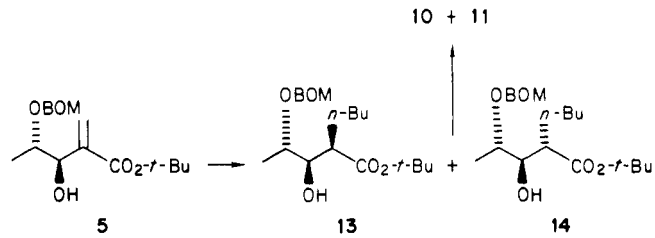
K_2CO_3–MeOH) gave better yields in comparison to the previously used[3] two-step (MeI, DBU) procedure.

The anti configuration of the compounds obtained (**5** and **6**) was assumed by analogy to the known examples[3] (Felkin–Anh-type addition)[6] and confirmed by ^{13}C NMR spectroscopy[7] and correlation to known compounds (vide infra).

α-Methylene-β-hydroxy-γ-butyrolactones. The hydroxy esters **5** and **6** were lactonized with 0.7 N HCl in AcOH–H_2O (Scheme II). In the case of the lactic derivatives, the small amount of syn isomer was separated at the lactone level by flash chromatography, whereas the syn isomer of **6** was easily removed at the hydroxy ester level.

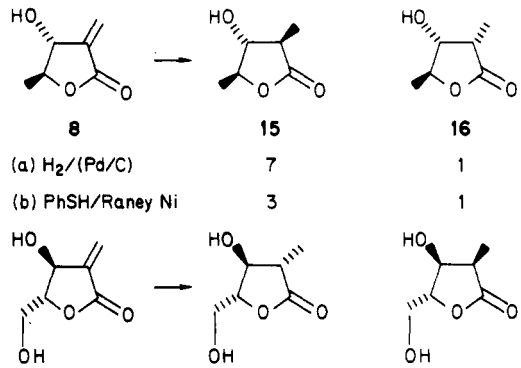
α-Methylene-β-hydroxy-γ-butyrolactones are very interesting compounds for their cytotoxic and antitumor activities[8] and for their skin-sensitizing properties.[9] A few syntheses of such racemic lactones have been reported recently:[9] Our synthesis is therefore the first general method to obtain these compounds optically pure, without starting from sugar precursors.[8a,10]

Scheme IV



	5	13	14
(a) *n*-Pr_2CuLi/Et_2O/-25 °C AcOH/Et_2O/-78 °C		2	1
(b) *n*-Pr_2CuLi/Et_2O/-25 °C NH_4Cl/H_2O/0 °C		6	1

Scheme V



	8	15	16
(a) H_2/(Pd/C)		7	1
(b) PhSH/Raney Ni		3	1
	9	17	18
(a) H_2/(Pd/C)		1	1
(b) PhSH/Raney Ni		3	1

Cuprate Addition to the Double Bond. Lithium dipropyl cuprate was added to the α-methylene lactone **8** in diethyl ether at −78 °C. The selectivity of the addition is dependent on the type of quenching procedure (Scheme III). When the reaction was quenched at −78 °C with AcOH (kinetic quench) a 1:1:1 mixture of the compounds **10**, **11**, and **12** was obtained, with 85% overall yield. When the reaction was quenched at 0 °C with NH_4Cl–H_2O an enhanced **10**–**11** ratio was obtained (8:1), accompanied by a larger amount of **12** with 85% overall yield.

The lack of selectivity in the kinetic protonation of this system is somehow unexpected, compared to the high ratio (5–9:1) obtained in lactones with similar functionality.[11] The facile elimination to butenolide **12** is not surprising, considering the well-known stability of this class of compounds.[12]

Adding the cuprate to the acyclic hydroxy ester **5** reduced the extent of elimination (10% at any temperature), and compounds **13** and **14** were obtained in 80% overall yield (Scheme IV). Quenching the reaction at 0 °C resulted in a 6:1 ratio favoring the arabino isomer **13**. The 6:1 mixture of esters **13** and **14** was lactonized as described above, and lactone **10** was isolated by flash chromatography in 69% yield. Lactone **10** is blastmycinolactol-*a*, an intermediate in the total synthesis of the antifungal antibiotic antimycin A_3 (blastmycin).[13]

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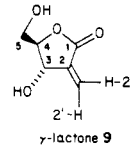
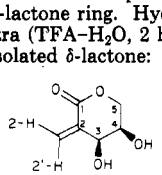
(9) Barbier, P.; Benezra, C. *J. Org. Chem.* **1983**, *48*, 2705 and references therein.
(10) Recently C. Papageorgiu and C. Benezra (Pâpageorgiu, C.; Benezra, C. *J. Org. Chem.* **1985**, *50*, 157) published data on lactone **9** which are not consistent with our data. Evidence that our compound is the actual γ-lactone, while the compound described by Benezra is the δ-lactone is reported below. The IR ($CHCl_3$), ^1H NMR (D_2O and Me_2SO-d_6),



γ-lactone **9**

and ^{13}C NMR spectra are reported in the Experimental Section. The ^1H NMR spectrum in Me_2SO-d_6 gives added support to our conclusions: the primary and secondary hydroxy protons are a triplet and a doublet [δ 5.04 (t, J = 5.5 Hz), 5.87 (d, J = 5.7 Hz)]. This indicates the presence of a γ-lactone. The trans relationship between 3-H and 4-H is apparent from the $J_{3,4}$ value (3.9 Hz). In the ^{13}C NMR spectrum the C4 chemical shift is 86.8 ppm, typical of a γ-lactone ring. Hydrolyzing ester **6** with the method reported by Benezra (TFA–H_2O, 2 h), resulted in a 1:4 γ-lactone/δ-lactone mixture. Isolated δ-lactone: IR (KBr) ν_{max} 1715, 1635



δ-lactone

cm^{-1}; $[\alpha]^{20}_D$ −90° (c 0.28, MeOH); ^1H NMR (D_2O) δ 4.24 (1 H, m, 4-H), 4.47 (2 H, AB part of an ABX system, 5,5′-H), 4.72 (1 H, m, 3-H), 6.16 (1 H, dd, 2′-H), 6.62 (1 H, m, 2-H), (Me_2SO-d_6) 3.90 (1 H, m, 4-H, $J_{4,3}$ = 2.3 Hz), 4.23 (2 H, AB part of an ABX system, 5,5′-H), 4.44 (1 H, m, 3-H, $J_{2,3} = J_{2',3}$ = 2.3 Hz), 5.17 (1 H, d, HOC4, J = 3.8 Hz, exchangeable), 5.45 (1 H, d, HOC3, J = 6.3 Hz, exchangeable), 5.88 (1 H, dd, 2′-H, $J_{2,2'} = J_{2,3}$ = 2.3 Hz), 6.30 (1 H, m, 2-H). Anal. Found: C, 49.67; H, 5.65. Calcd for $C_6H_8O_4$: C, 50.0; H, 5.59.

(11) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733. Takano, S.; Hatakeyama, S.; Numata, H. *Tetrahedron Lett.* **1984**, 3617.
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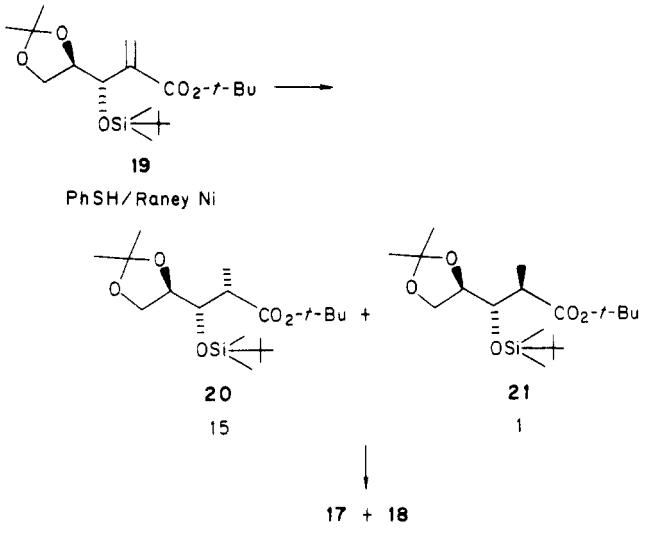
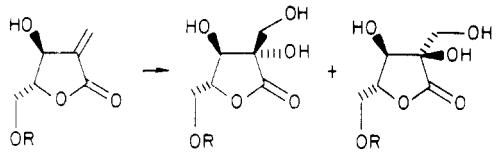
(13) Aburaki, S.; Konishi, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1254.

Scheme VI



Scheme VII

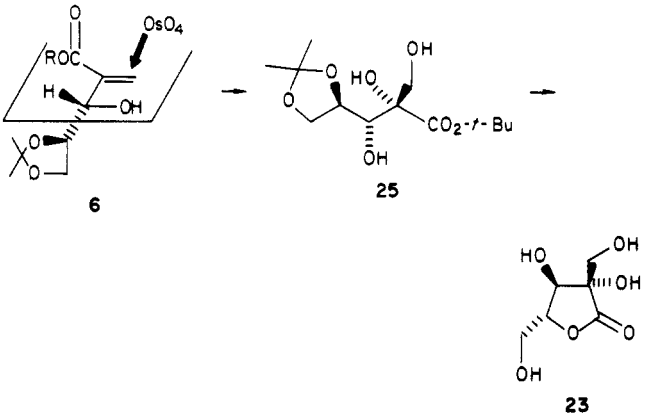


This example clearly shows that yields and stereoselectivity are often better with acyclic substrates than with the corresponding cyclic ones. Further examples of this type are reported in the following paragraphs.

Reduction of the Double Bond. The double bond of lactones **8** and **9** was reduced with H_2/Pd–C or by adding thiophenol and desulfurizing with Raney Ni (Scheme V). The catalytic hydrogenation is quite selective for **8** (7:1) but not for **9** (1:1). The addition of thiophenol is clearly thermodynamically controlled and furnishes in both cases, after Raney Ni reduction, a 3:1 ratio in favor of the isomer with arabino configuration. The major stability of the arabino vs. ribo isomer of these 2-methyl lactones is well-known and is due to the fact that only in the arabino isomer are all the substituents pseudoequatorial.[14] Also in this case the addition onto the acyclic substrate proved to be more selective. Adding thiophenol to ester **19** and then reducing with Raney Ni resulted in the formation of compounds **20** and **21** in high yield and in high ratio (15:1) favoring the arabino isomer. The mixture was then transformed into the lactones **17** and **18** by simple acidic treatment (Scheme VI).

Dihydroxylation of the Double Bond. The double bond of lactone **9** was dihydroxylated with osmium tetraoxide in catalytic conditions.[15] Two epimeric lactones were obtained (3:1) in quantitative yield, and the major isomer was assigned as **23** (R = H), a known compound named *epi*-D-hamamelolactone.[16] In order to improve this ratio we checked several protecting groups, and we found that the *O*-trityl-protected lactone **22** gives, after osmylation and deprotection, a **23**–**24** ratio 8:1 (Scheme VII).

Scheme VIII



The change in the ratio using the *O*-trityl lactone is probably due to a conformational change on the lactone ring induced by the trityl group. In order to further improve the ratio we submitted the acyclic compound **6** to osmylation. This compound actually follows the Stork's and Kishi's rule for osmylation[17] and gives the hydroxy ester **25** as a single isomer in quantitative yield (Scheme VIII). Also the reaction with $KMnO_4$ in CH_2Cl_2 in the presence of dicyclohexyl-18-crown-6[20] gave the compound **25** as the major isomer (9:1) in quite good yield (60%).

The hydroxy ester **25** was then cyclized to *epi*-D-hamamelolactone (**23**), which was in turn reduced to *epi*-D-hamamelose,[18] by using $NaBH_4$ at pH 4.[19] The dihydroxylation of **6** is an additional case where acyclic stereoselection is much more effective than cyclic (five-membered) stereoselection.

Experimental Section

^1H NMR spectra were recorded with a Varian XL-200 or Bruker WP-80 instrument and ^{13}C NMR spectra with a Varian XL-100 instrument, in the FT mode, using tetramethylsilane as internal standard. IR spectra were recorded with a Perkin-Elmer 457 spectrophotometer. Optical rotations were measured in 1-dm cells of 1-mL capacity using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel 60 F_{254} plates (Merck) were used for analytic TLC; 270–400 mesh silica gel (Merck) was used for flash chromatography.[21] GLC analyses were performed on a Dani 3900 instrument with a capillary OV-1 column using a Hewlett-Packard 3390 A integrator. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. "Dry" solvents were distilled under dry N_2 just before use: Diethyl ether and tetrahydrofuran (THF) were distilled from sodium metal in the presence of benzophenone as indicator; *n*-pentane was distilled from sodium metal; methanol was distilled from magnesium methoxide; CH_2Cl_2, diisopropylamine, and triethylamine were distilled from CaH_2; acetone was distilled from K_2CO_3. All reactions employing dry solvents were run under a nitrogen (from liquid N_2) atmosphere.

***tert*-Butyl 2-Methylene-3-hydroxy-4-[(benzyloxy)methoxy]pentanoate (5).** To a solution of LDA (1.5 mmol) in anhydrous ether (0.5 mL) was added the ester **1**[22] (1.5 mmol) at 0 °C. The solution was stirred for 3 h at this temperature and then cooled to −78 °C. A solution of 2-[(benzyloxy)methoxy]propanal[3b] (1 mmol) in ether (0.2 mL) was added, and after 10 min, the reaction was quenched with a solution of AcOH in the same

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solvent. After the usual workup the crude product was dissolved in dry methanol (2.5 mL), powdered K_2CO_3 (0.7g) was added, and the mixture, cooled to 0 °C, was treated with methyl iodide (0.5 mL) under stirring. The reaction was stirred at room temperature for 2 hr and then filtered, and the filtrate, diluted with ether, was washed twice with water. The organic extracts were evaporated to give a crude oil, which was analyzed by GLC (7:1 anti–syn). Purification by flash chromatography furnished the pure diastereoisomeric mixture in 75% yield: IR ($CHCl_3$) ν_{max} 3680, 3560, 1715, 1630, 1165, 1130, 1095 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (3 H, d, J = 6.4 Hz, Me anti), 1.22 (3 H, d, J = 6.4 Hz, Me syn), 1.47 (9 H, s, t-Bu), 3.91 (1 H, dq, J = 6.4 Hz, J = 4.8 Hz, MeCH syn), 4.06 (1 H, dq, J = 6.7 Hz, J = 4.2 Hz, MeC*H* anti), 4.37 (1 H, m, C*H*OH syn), 4.58 (1 H, m, C*H*OH anti), 4.62 (2 H, s, OCH_2Ph), 4.81 (2 H, s, OCH_2O), 5.83 (1 H, t, J = 1.5 Hz, trans HC=CCO syn), 5.86 (1 H, t, J = 1.5 Hz, trans HC=CCO anti), 6.25 (1 H, t, J = 1.5 Hz, cis HC=CCO), 7.33 (5 H, s, Ph); ^{13}C NMR (25.14 MHz, $CDCl_3$) [selected data] δ 142.0 (syn), 140.5 (anti), 125.7 (anti), 125.5 (syn), 93.8 (syn), 93.1 (anti), 74.3 (syn), 73.1 (anti), 76.6 (syn), 74.9 (anti), 17.3 (syn), 14.1 (anti). Anal. Found: C, 67.13; H, 8.10. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13.

***tert*-Butyl 2-Methylene-3-hydroxy-4,5-(isopropylidenedioxy)pentanoate (6).** To a solution of LDA (1.5 mmol) in dry ether (0.5 mL) was added ester 1[22] (1.5 mmol) at 0 °C. The solution was stirred at this temperature for 3 h, then cooled to −78 °C, and diluted with THF (2.5 mL). A solution of 2,3-*O*,*O*-isopropylidene-D-glyceraldehyde (4)[23] (1.5 mmol) in THF (0.2 mL) was added, and after 10 min the reaction was quenched with water. After the usual workup the crude product was dissolved in dry methanol (2.5 mL), powdered K_2CO_3 (0.7 g) was added, and the mixture, cooled to 0 °C, was treated with MeI (0.5 mL) under stirring. The reaction was stirred at room temperature for 2 h, then the salts were filtered off, and the filtrate, diluted with brine, was extracted with ether. The combined organic layers were evaporated under reduced pressure to give an oil, which was analyzed by GLC (12:1 anti–syn). Purification by flash chromatography (75:25 n-hexane–AcOEt) afforded pure *anti*-**6** in 40% yield: IR ($CHCl_3$) ν_{max} 3680, 1695, 1625, 1150, 1060 cm^{-1}. Anal. Found: C, 60.51; H, 8.52. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58.

anti-**6**: $[\alpha]^{20}_D$ +3.93° (*c* 1.22, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 1.36 (3 H, s, Me), 1.46 (3 H, s, Me), 1.51 (9H, s, t-Bu), 3.06 (1 H, d, J = 5.3 Hz, OH), 3.86–4.62 (4 H, m, CHO), 5.92 (1 H, t, J = 1.5 Hz, trans *H*C=C CO_2-t-Bu), 6.29 (1 H, t, J = 1.5 Hz, cis *H*C=CCO_2-t-Bu); ^{13}C NMR (25.14 MHz, $CDCl_3$) δ 165.35, 139.78, 129.57, 126.07, 81.55, 76.85, 71.29, 65.35, 28.10, 26.62, 25.24.

syn-**6**: $[\alpha]^{20}_D$ −9.55 (*c* 1.35, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 1.3 (3 H, s, Me), 1.4 (3 H, s, Me), 1.47 (9 H, s, t-Bu), 2.85 (1 H, d, J = 6.7 Hz, OH), 3.5–4.6 (4 H, m, CHO), 5.8 (1 H, t, J = 1 Hz, trans *H*C=CCO_2-t-Bu), 6.2 (1 H, t, J = 1 Hz, cis *H*C=CCO_2-t-Bu); ^{13}C NMR (25.14 MHz, $CDCl_3$) δ 165.28, 141.02, 125.75, 109.67, 81.43, 78.21, 71.00 66.30, 28.10, 26.54, 25.35.

(3*R*,4*S*)-2-Methylene-3-hydroxy-4-methyl-γ-butyrolactone (8). To a solution of **5** (7:1 anti–syn, 400 mg, 1.24 mmol) in 4:1 AcOH–H_2O (9.2 mL) was added 12 N HCl (0.6 mL, 7.2 mmol). The reaction was stirred overnight at room temperature, then AcONa (1.7 g, 21.6 mmol) was added, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (55:45 AcOEt–n-hexane) to give lactone **8** as a white solid (95 mg, 60%): mp 140 °C; $[\alpha]^{20}_D$ −11.07° (*c* 1.02, MeOH); IR (neat) ν_{max} 3200–3600, 1760, 1675 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3/D_2O$) δ 1.3 (3 H, d, J = 6.7 Hz, Me), 4.40 (1 H, q, J = 6.7 Hz, C*H*Me), 4.45 (1 H, s, CHOD), 5.98 (1 H, d, J = 2 Hz, trans HC=CCO), 6.42 (1 H, d, J = 2 Hz, cis HC=CCO); ^{13}C NMR (25.14 MHz, $CDCl_3$) δ 169.22, 138.83, 125.84, 82.10, 74.17, 19.02; MS, m/z 128 (M^+). Anal. Found: C, 56.18; H, 6.32. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29.

(3*S*,4*R*)-2-Methylene-3-hydroxy-4-(hydroxymethyl)-γ-butyrolactone (9). A solution of **6** (465 mg, 1.8 mmol) in 70% aqueous AcOH (10 mL) was stirred at 40 °C for 1 h. The solution was then cooled to room temperature, 12 N HCl (0.3 mL) was added, and the reaction was stirred overnight at this temperature. A second portion of 12 N HCl (0.3 mL) was then added, and the reaction was stirred for 4 h more and eventually quenched with AcONa (1.6 g). The solvent was evaporated and the crude product purified by flash chromatography (10:1 CH_2Cl_2–MeOH) to give pure **9** (156 mg, 60%): $[\alpha]^{20}_D$ −8.1° (*c* 0.355, MeOH); IR ($CHCl_3$) ν_{max} 3600, 1765, 1710 cm^{-1}; ^1H NMR (80 MHz, D_2O) δ 3.65–4.15 (2 H, m, CH_2OD), 4.55 (1 H, m, C*H*CH_2OD), 4.9 (1 H, ddd, J = 2 Hz, J = 2 Hz, J = 3.8 Hz, CHOD), 6.2 (1 H, d, J = 2 Hz, trans HC=CCO), 6.5 (1 H, d, J = 2 Hz, cis HC=CCO), (80 MHz, Me_2SO-d_6) 3.65 (2 H, AB part of an ABX system, H-5 and H-5′), 4.19 (1 H, dt, H-4, $J_{3,4}$ = $J_{4,5}$ = $J_{4,5'}$ = 3.9 Hz), 4.59 (1 H, m, H-3, $J_{2,3}$ = $J_{2',3}$ = 2 Hz), 5.04 (1 H, t, HOC-5, J = 5.5 Hz, exchangeable), 5.87 (1 H, d, HOC-3, J = 5.7 Hz, exchangeable), 5.89 (1 H, d, H-2′, $J_{2',3}$ = 2 Hz), 6.17 (1 H, d, H-2, $J_{2,3}$ = 2 Hz); ^{13}C NMR (25 MHz, D_2O) δ 172.10, 138.16, 128.59, 86.79, 68.95, 61.66. Anal. Found: C, 49.91, H 5.62. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59.

Cuprate Addition to 8. To a suspension of CuI (67 mg, 0.35 mmol) in dry ether (1.5 mL) was added a solution of 0.7 M PrLi in pentane[24] (975 μL, 0.7 mmol) dropwise at 0 °C. After 2 min the solution was cooled at −78 °C, and a solution of lactone **8** (18 mg, 0.14 mmol) in dry ether (100 μl) was added. The reaction was quenched after 30 min at −78 °C.

Quenching a. A 1 N solution of AcOH in ether (1.8 mL) was added at −78 °C. The mixture was allowed to warm to room temperature and then partitioned between ether and an aqueous solution (pH 8) of ammonia and ammonium chloride. The organic extracts were dried with Na_2SO_4, and the solvent was evaporated.

Quenching b. The reaction was kept at 0 °C for 2 min and then quenched with aqueous NH_4Cl. The mixture was allowed to warm to room temperature and worked up as described in a.

The crude reaction mixture was analyzed by GLC (see Scheme III). Lactones **10** and **11** and butenolide **12** were isolated by flash chromatography (7:3 n-hexane–AcOEt) in 85% overall yield.

(2*R*,3*R*,4*S*)-2-Butyl-3,4-dihydroxypentanoic acid 1,4-lactone (natural (−)-blastmycinolactol) (10): mp 49–50 °C; (lit.[13] mp 49.5–50.5 °C); $[\alpha]^{20}_D$ −17° (*c* 1.05, MeOH) (lit.[13] $[\alpha]^{20}_D$ −18° (*c* 1.09, MeOH); IR ν_{max} (CCl_4) 3635, 1785 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.9 (3 H, m, CH_3CH_2), 1.12–1.95 (6 H, m), 1.42 (3 H, d, J = 6.0 Hz, *Me*CH), 2.20 (1 H, br s, OH), 2.50 (1 H, m, CHC=O), 3.82 (1 H, dd, J = 8 Hz, J = 7 Hz, CHOH), 4.2 (1 H, dq, J = 6 Hz, J = 7 Hz, C*H*Me). Anal. Found: C, 62.60; H, 9.22. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36.

(2*S*,3*R*,4*S*)-2-Butyl-3,4-dihydroxypentanoic acid 1,4-lactone (11): $[\alpha]^{20}_D$ +68° (*c* 0.3, MeOH); IR ν_{max} (CCl_4) 3620, 1780 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.9 (3 H, m, *Me*CH_2), 1.33 (3 H, d, J = 7 Hz, *Me*CH), 1.2–1.9 (6 H, m), 2.05 (1 H, br s, OH), 2.55 (1 H, m, CHC=O) 4.18 (1 H, dd, J = 5.6 Hz, J = 1.1 Hz, CHOH), 4.5 (1 H, dq, J = 1.1 Hz, J = 7 Hz, CHMe). Anal. Found: C, 62.53; H, 9.41. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36.

(5*S*)-3-Butyl-5-methyl-2(5*H*)-furanone (12): $[\alpha]^{20}_D$ +11.7° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1745, 1270 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.9 (3 H, m, *Me*CH_2), 1.35 (3 H, d, J = 6.7 Hz, *Me*CH), 1.12–1.8 (4 H, m, 2 CH_2), 2.3 (2 H, m, CH_2C=), 4.95 (1 H, m, C*H*Me), 6.95 (1 H, m, HC=). Anal. Found: C, 69.98; H, 9.22. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15.

Cuprate Addition to 5. Ester **5** was reacted with Pr_2LiCu as described for lactone **8**, except that the reaction was allowed to warm to −25 °C and kept at this temperature overnight before quenching.

The diastereomeric ratio (see Scheme IV) was determined by 200-MHz ^1H NMR on the crude reaction mixture, which was subjected to lactonization without purification.

***tert*-Butyl 2-butyl-4-[(benzyloxy)methyl]-3-hydroxypentanoate (13 and 14):** ^1H NMR (200 MHz, $CDCl_3$) δ 0.9 (3 H, m, *Me*CH_2), 1.42 (9 H, s, t-Bu, arabino isomer), 1.44 (9 H, s, t-Bu, ribo isomer), 1.1–1.75 (6 H, m, 3 CH_2), 2.25–2.65 (1 H, m, CHC=O), 3.4–3.9 (2 H, m, C*H*OH and C*H*OR), 4.61 (2 H, s, CH_2Ph, arabino isomer), 4.62 (2 H, s, CH_2Ph, ribo isomer), 4.79 (2 H, s, OCH_2O, arabino isomer), 4.81 (2 H, s, OCH_2O, ribo isomer), 7.34 (5 H, s, Ph).

Lactonization of 13 and 14. Synthesis of Natural (−)-Blastmycinolactol (10). A 6:1 mixture of hydroxy esters **13** and **14** (30 mg, 0.08 mmol) was dissolved in 4:1 AcOH–H_2O (350 μL), and 12 N HCl (22 μL) was added. The reaction was stirred overnight, then AcONa (100 mg) was added, and the solvent was

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evaporated under reduced pressure. Blastmycinolactol (**10**) was isolated by flash chromatography (7:3 hexane–AcOEt) as a white solid (10 mg, 69%).

Double Bond Reduction of 8. Method A. A solution of methylene lactone **8** (20 mg, 0.156 mmol) in methanol (3 mL) was hydrogenated in the presence of 10% Pd/C (4 mg) for 30 min at room temperature. The crude reaction mixture was filtered through a Celite pad and the solvent evaporated to give 19 mg (94%) of a mixture of **15** (87.5%) and **16** (12.5%), which were separated by flash chromatography (1:1 *n*-hexane–AcOEt).

Method B. To a solution of lactone **8** (20 mg, 0.156 mmol) and thiophenol (19 mg, 0.17 mmol) in dry methanol (0.3 mL) was added Et_3N (1 μL). After 10 min at room temperature an excess of Raney Ni was added and the mixture stirred for 2 h under hydrogen atmosphere. The catalyst was filtered off and the solvent evaporated to give 17 mg (85%) of a mixture of **15** (75%) and **16** (25%), which were isolated as in A.

(2*R*,3*R*,4*S*)-2-Methyl-3,4-dihydroxypentanoic acid 1,4-lactone (15): IR (neat) ν_{max} 3450, 1960, 1455, 1380 cm^{-1}; $[\alpha]^{20}_D$ −10.3° (*c* 0.22, MeOH); ^1H NMR (80 MHz, $CDCl_3/D_2O$) δ 1.3 (3 H, d, *J* = 6.4 Hz, MeCHC=O), 1.46 (3 H, d, *J* = 6.4 Hz, *Me*CHC=O), 2.6 (1 H, dq, *J* = 6.4 Hz, *J* = 8.5 Hz, CHC=O), 3.7 (1 H, dd, *J* = 7.2 Hz, *J* = 8.5 Hz, CHOD), 4.2 (1 H, dq, *J* = 7.2 Hz, *J* = 6.4 Hz, CHC–O); ^{13}C NMR (25.14 MHz, $CDCl_3$) δ 80.4, 80.2, 43.8, 17.9, 12.4. Anal. Found: C, 55.20; H, 7.85. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74.

(2*S*,3*R*,4*S*)-2-Methyl-3,4-dihydroxypentanoic acid 1,4-lactone (16): IR (neat) ν_{max} 3450, 1760, 1460, 1380 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3/D_2O$) δ 1.25 (3 H, d, *J* = 6 Hz, *Me*CHC=O), 1.35 (3 H, d, *J* = 6 Hz, *Me*CHCO), 2.75 (1 H, dq, *J* = 6 Hz, *J* = 5.9 Hz, CHC=O), 4.15 (1 H, dd, *J* = 5.9 Hz, *J* = 1.3 Hz, CHOD), 4.5 (1 H, dq. *J* = 5.9 Hz, *J* = 1.3 Hz, CHCO). Anal. Found: C, 55.25; H, 7.84. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74.

Double Bond Reduction of 9. Method A. The catalytic hydrogenation was carried out as described for lactone **8** to give in 90% overall yield a 1:1 mixture of lactones **17** and **18** as indicated by the ^1H NMR spectrum (intensities of the corresponding methyl group signals).

Method B. The same procedure described for lactone **8** was used, resulting in 80% yield in a 75:25 mixture of **17** and **18**, which was purified by flash chromatography (65:35 CH_2Cl_2–acetone).

(3*S*,4*R*)-2-Methyl-3,4,5-trihydroxypentanoic acid 1,4-lactone (17 and 18): ^1H NMR (80 MHz, D_2O) δ 1.18 (3 H, d, *J* = 6.5 Hz, ribo isomer), 1.3 (3 H, d, *J* = 8 Hz, arabino isomer), 2.65–3.15 (1 H, m), 3.65–4.6 (series of complex m); ^{13}C NMR (25.14 MHz, Me_2SO-d_6) δ 8.3 (ribo), 12.5, 39.1 (ribo), 43.2, 60.0, 60.9 (ribo), 70.1 (ribo), 73.1, 84.6, 86.9 (ribo), 177.1, 179.2 (ribo). Anal Found: C, 49.38; H, 6.84. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90.

Arabino and ribo configurations were assigned respectively to **17** and **18** by transformation into the corresponding dibenzoates.[14]

(3*S*,4*R*)-2-Methyl-3,5-dibenzoyl-4-hydroxypentanoic Acid 1,4-Lactones. To a solution of 32 mg (0.22 mmol) of diol lactones **17** (75%) and **18** (25%) in pyridine (0.3 mL) was added benzoyl chloride (65 μL, 0.54 mmol), and the mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue taken up in chloroform and washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O. The solvent was evaporated and the crude product purified by flash chromatography (CH_2Cl_2) to give pure dibenzoates (75:25) in 85% yield: (Found: C 67.83, H 5.09%; $C_{20}H_{18}O_6$ requires: C 67.79, H 5.12%). IR ν_{max} 1790 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.35 (3 H, d, *J* = 8 Hz, Me, ribo isomer), 1.48 (3 H, d, *J* = 8 Hz, Me, arabino isomer), 2.8–3.25 (1 H, m, CHC=O), 4.95–5.95 (3 H, m, CH_2OBz, CH–O), 5.38 (1 H, dd, *J* = 6.1 Hz, *J* = 4.9 Hz, *CH*OBz, arabino isomer), 5.68 (1 H, dd, *J* = 7 Hz, *J* = 1 Hz, *CH*OBz, ribo isomer).

(3*S*,4*R*)-*tert*-Butyl 2-Methylene-3-[(dimethyl-*tert*-butylsilyl)oxy]-4,5-(isopropylidenedioxy)pentanoate (19). To a solution of **6** (325 mg, 1.26 mmol) and 2,6-lutidine (0.29 mL, 2.52 mmol) in dry CH_2Cl_2 (1.25 mL) was added dimethyl-*tert*-butylsilyl triflate (0.44 mL, 1.9 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature and kept at this temperature for 10 min, and then the solvent was evaporated and the product isolated as a yellow oil by flash chromatography (95:5 *n*-hexane–AcOEt) (412 mg, 88%): IR ($CHCl_3$) ν_{max} 1695, 1250 cm^{-1}; $[\alpha]^{20}_D$ +11.6° (*c* 0.67, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 0.00 (3 H, s, MeSi), 0.09 (3 H, s, MeSi), 0.85 (9 H, s, *t*-BuSi), 1.3 (3 H, s, isopropylidene), 1.4 (3 H, s, isopropylidene), 1.5 (9 H, s, O-*t*-Bu), 3.7–4.2 (3 H, m, 4,5-H), 4.68 (1 H, dd, *J* = 4.8 Hz, *J* = 1.45 Hz, CHOSi), 5.82 (1 H, dd, *J* = 1.7 Hz, *J* = 1.45 Hz, trans HC=CCO), 6.28 (1 H, d, *J* = 1.17 Hz, cis HC=CCO). Anal. Found: C, 61.05; H, 9.78. Calcd for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74.

(3*S*,4*R*)-*tert*-Butyl 2-Methyl-3-[(dimethyl-*tert*-butylsilyl)oxy]-4,5-(isopropylidenedioxy)pentanoate (20 and 21). To a solution of ester **19** (100 mg, 0.27 mmol) and thiophenol (60 mg, 0.54 mmol) in dry methanol (0.5 mL) was added triethylamine (0.002 mL). The reaction was stirred overnight at 60 °C, then an excess of Raney Ni was added, and the mixture was stirred for 5 h at room temperature under a hydrogen atmosphere. The catalyst was filtered off and the solvent evaporated to give an oil which was analyzed by GLC (15:1 **20**–**21**). The product was purified by flash chromatography (95:5 *n*-hexane–AcOEt) to give 70 mg (69%) of **20** and **21** as a colorless oil: IR (neat) ν_{max} 1725 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.1 (6 H, s, Me_2Si), 0.85 (9 H, s, *t*-BuSi), 1.08 (3 H, d, *J* = 7.2 Hz, *Me*CH, ribo isomer), 1.12 (3 H, d, *J* = 7.2 Hz, *Me*CH, arabino isomer), 1.3 (3 H, s, isopropylidene), 1.35 (3 H, s, isopropylidene, ribo isomer), 1.38 (3 H, s, isopropylidene, arabino isomer), 1.42 (9 H, s, O-*t*-Bu), 2.35–2.75 (1 H, m, MeC*H*), 3.6–4.2 (series of complex m). Anal. Found: C, 61.03; H, 10.15. Calcd for $C_{19}H_{38}O_5Si$: C, 60.92; H, 10.22.

Lactonization of 20 and 21. The reaction was conducted as described for the synthesis of **9**. The crude reaction product was purified by flash chromatography (65:35 CH_2Cl_2–acetone) to give a 15:1 mixture of lactones **17** and **18**.

(2*S*,3*S*,4*R*)-*tert*-Butyl 2-(Hydroxymethyl)-2,3-dihydroxy-4,5-(isopropylidenedioxy)pentanoate (25). To a solution of *N*-methylmorpholine *N*-oxide (135 mg, 1 mmol) and OsO_4 (0.6 mL of a 0.0393 N solution in *t*-BuOH, 0.025 mmol) in 8:1 acetone–H_2O (1 mL) was added a solution of hydroxy ester **6** (129 mg, 0.5 mmol) in 8:1 acetone–H_2O (1.4 mL). The reaction was stirred overnight at room temperature and then Na_2SO_3 (35 mg, 0.22 mmol) was added. After the mixture was stirred 1 h, the solvent was evaporated and the crude product purified by flash chromatography (7:3 AcOEt–*n*-hexane) to give **25** as a white solid (139 mg, 95%): (Found: C 53.36, H 8.31%; $C_{13}H_{24}O_7$ requires: C 53.41, H 8.27%). mp 95 °C; $[\alpha]^{20}_D$ +22.1° (*c* 0.98, MeOH); IR ($CHCl_3$) ν_{max} 3550, 3470, 1725, 1280, 1250, 1150, 1050 cm^{-1}; ^1H NMR (200 MHz, Me_2SO-d_6) δ 1.30 (3 H, s, Me), 1.35 (3 H, s, Me), 1.46 (9 H, s, *t*-Bu), 3.44–3.65 (2 H, m, CH_2OH), 3.71 (1 H, dd, *J* = 10.5 Hz, *J* = 8 Hz, *CH*OH), 3.89 (1 H, d, *J* = 9.5 Hz, 5-H), 3.90 (1 H, d, *J* = 7 Hz, 5′-H), 4.11 (1 H, ddd, *J* = 8 Hz, *J* = 7 Hz, *J* = 9.5 Hz, 4-H), 4.44 (1 H, s, CHO*H*), 4.66 (1 H, m, CH_2OH), 5.08 (1 H, d, *J* = 10.5 Hz, CHO*H*); ^{13}C NMR (25.14 MHz, $CDCl_3$) δ 172.28, 129.04, 83.39, 80.50, 75.21, 73.17, 66.52, 64.89, 27.89, 26.48, 25.43.

2-*C*-(Hydroxymethyl)-D-arabono-γ-lactone (23) (2-*epi*-D-Hamamelolactone). A solution of **25** (800 mg, 2.74 mmol) in 70% aqueous AcOH (18 mL) was stirred at 50 °C for 1 h. The solution was then cooled to room temperature, 12 N HCl (0.45 mL) was added, and the reaction was stirred overnight at this temperature before adding a second portion of 12 N HCl (0.4 mL). After 2 h. AcONa (2.4 g) was added, the solvent evaporated, and the crude product purified by flash chromatography (7:3 acetone–CH_2Cl_2) to give **23** as a syrup (320 mg, 66%): IR ν_{max} 1780 cm^{-1}; $[\alpha]^{20}_D$ +59° (*c* 1.02, H_2O); ^1H NMR (200 MHz, Me_2SO-d_6/D_2O) δ 3.34–3.56 (2 H, m, 5-CH_2), 3.76 (2 H, AB system, *J* = 5 Hz, 2′-CH_2), 4.1 (1 H, d, *J* = 5 Hz, 3-H), 4.15–4.22 (1 H, m, 4-H); ^{13}C NMR (25.14 MHz, D_2O) δ 83.09, 79.16, 74.52, 62.23, 60.74. Anal. Found: C, 40.38; H, 5.71. Calcd for $C_6H_{10}O_6$: C, 40.45; H, 5.66.

Hydrolysis with aqueous ammonia gave a solution of ammonium 2-*C*-(hydroxymethyl)-D-arabonate, $[\alpha]^{20}_D$ +13° (*c* 0.5, 1 N NH_4OH) [lit.[16] $[\alpha]^{20}_D$ for the L-isomer −11.5° (*c* 1.2, 1 N NH_4OH)].

Osmylation of 9. Lactone **9** was osmylated as described for the synthesis of **25**. The crude reaction product was purified by flash chromatography (7:3 acetone–CH_2Cl_2) to give 115 mg (90%) of pure **23** and **24** (3:1) as a colorless syrup: ^1H NMR (200 MHz, Me_2SO-d_6) δ 3.34–3.66 (2 H, m, 5-CH_2), 3.72–3.86 (2 H, m, 2′-CH_2), 4.03–4.25 (2 H, m, 3,4-H), 4.94–5.12 (4 H, 3 t, 4 × CH_2OH), 5.4 (1 H, d, *J* = 4 Hz, CHO*H* minor), 5.71 (1 H, d, *J* = 2 Hz, CHO*H* major), 5.75 (1 H, s, COH major), 5.77 (1 H, s, CO*H* minor); ^{13}C

NMR (25.14 MHz, D_2O) δ 84.44 (minor), 83.09 (major), 79.16 (major), 76.20 (minor), 74.52 (major), 68.25 (minor), 62.23 (major), 61.87 (minor), 60.74. Anal. Found: C, 40.51; H, 5.73. Calcd for $C_6H_{10}O_6$: C, 40.45; H, 5.66.

(3*S*,4*R*)-2-Methylene-3-hydroxy-4-[(trityloxy)methyl]-γ-butyrolactone (22). To a suspension of lactone **9** (152 mg, 1.05 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (192 μL), trityl chloride (382 mg, 1.37 mmol), and (dimethylamino)pyridine (5 mg). The mixture was stirred overnight at 40 °C, then the solvent was evaporated, and the product was isolated by flash chromatography (55:45 *n*-hexane–AcOEt) (162 mg, 40%): (Found: C 77.64, H 5.80%; $C_{25}H_{22}O_4$ requires: C 77.70, H 5.74%). IR ν_{max} 3600, 1765, 1600 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3/D_2O$) δ 3.43 (2 H, AB part of ABX system, J_{AB} = 6.4 Hz, J_{BX} = 3.6 Hz, J_{AX} = 3.6 Hz, CH_2OTry), 4.39 (1 H, X part of ABX system, $J_{AX} = J_{BX} = J_{XY}$ = 3.6 Hz, 4-H), 4.80 (1 H, m, 3-H), 5.99 (1 H, d, J = 2.0 Hz, trans HC=CCO), 6.51 (1 H, d, J = 2.0 Hz, cis HC=CCO), 7.23–7.50 (15 H, m, Ar).

Osmylation of 22. Lactone **22** was osmylated as described for the synthesis of **25**. Reaction products were isolated by flash chromatography (85:15 AcOEt–*n*-hexane) in 80% yield and subsequently detritylated with CF_3COOH to give a 8:1 mixture of lactones **23** and **24** (ratio determined by 200-MHz ^1H NMR).

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Synthesis of Hydrophenanthrene Natural Products: A Novel Approach. 1. Stereoselective Synthesis of Resin Acid Synthons†,‡

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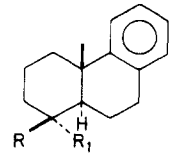
We report the conversion of 4a-methyl-2,4a,9,10-tetrahydrophenanthrene, (**8**), readily available from phenanthrene by reductive alkylation, via 4a-methyl-3,4,4a,9,10,10a-hexahydro-1(2*H*)-phenanthrone, (**5**), into both C-1 isomers of 1,4aβ-dimethyl-1,2,3,4,4a,9,10,10aα-octahydrophenanthrene-1-carboxylic acid (**1a** and **1b**) by an efficient and stereoselective route. This is a new route to diterpenoid acids of the podocarpate and abietate families.

Numerous syntheses of resin acids and of structurally related compounds, both naturally occurring and synthetic, have been reported.[1] These include group **1a** structures with the abietic acid stereochemistry as well as group **1b** structures with podocarpic acid stereochemistry.

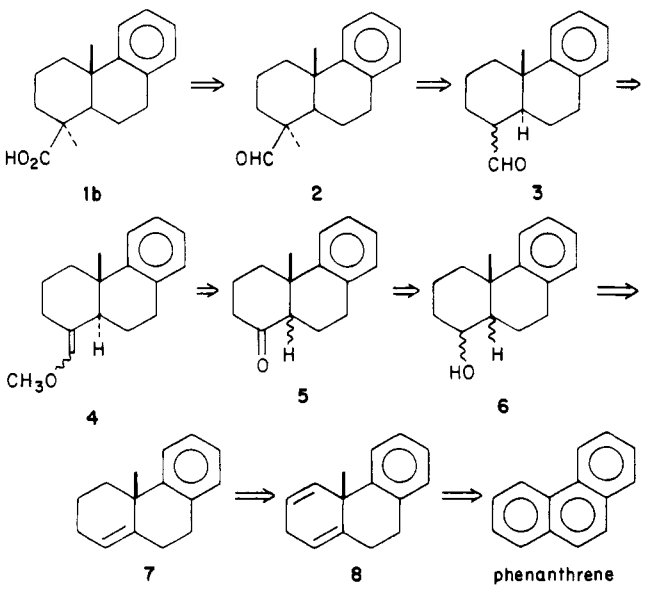


1a, R = CH_3; R_1 = CO_2H
1b, R = CO_2H; R_1 = CH_3

Unlike most efforts wherein efficient syntheses of specific natural products are the objective, we set as our goal the development of an efficient stereoselective total synthesis of both C-1 epimers, (±)-deoxypodocarpic acid and (±)-deisopropyldehydroabietic acid, from a common intermediate late in the synthetic sequence.

In the case of deoxypodocarpic acid, there is ample precedent that the correct stereochemistry can be established selectively by base-catalyzed alkylation of a 1-carboxaldehyde, presumably because the relatively bulky 4aβ-methyl group directs alkylation to the opposite (α) face of the molecule (Scheme I). There is adequate precedent for the preparation of octahydrophenanthrene-1-carboxaldehydes from the corresponding octahydro-1(2*H*)-phenanthrone via a Wittig homologation reaction. In addition to the homologation, Wittig reactions run under equilibrating conditions (i.e., sodium dimsyl in dimethyl sulfoxide) are known to establish stereoselectively the AB

Scheme I



trans stereochemistry.[1f] The 1(2*H*)-hydrophenanthrone, in turn, would be the expected product from an oxidation of the corresponding 1-hydrophenanthrol which has been prepared in three steps from phenanthrene by a reductive

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‡ Taken in part from the dissertation presented by T.N.T. to the Graduate School of the University of Kansas (1980) in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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