a colorless oil, 60% yield. $[\alpha]^{23}_D$ +23.7° (c 1.30, $CHCl_3$). IR (film): 3440, 1760 cm^{-1}. NMR: δ 0.91 (3 H, t, J = 7 Hz, CH_3), 1.25 (3 H, s, CH_3), 1.4-1.6 (4 H, m, $CH_2CH_2CH_3$), 1.88 (1 H, dd, J = 7, 13 Hz, CH_2CH), 2.12 (1 H, dd, J = 11, 13 Hz, CH_2CH), 3.58 (1 H, dd, J = 5, 13 Hz, CH_2OH), 3.88 (1 H, dd, J = 3, 13 Hz, CH_2OH), 4.55 (1 H, m, CH). ^{13}C NMR: δ 14.4 (q), 17.7 (t), 23.1 (q), 35.1 (t), 39.7 (t), 44.1 (s), 63.8 (t), 77.4 (d), 181.6 (s). MS, m/z: 172 (M^+).

(2S,4S)-2-Allyl-4-(hydroxymethyl)-2-methyl-4-butanolide (5 (R^1 = $CH_2CH{=}CH_2$, R^2 = Me)) (Table I, run 7) was prepared in the same way as described for **5** (R^1 = Et, R^2 = Me): a colorless oil in 47% yield. $[\alpha]^{24}_D$ +88.7° (c 1.34, $CHCl_3$). IR (film): 3440, 1760 cm^{-1}. NMR: δ 1.27 (3 H, s, CH_3), 1.83 (1 H, dd, J = 7, 14 Hz, CH_2CH), 2.12 (1 H, dd, J = 11, 14 Hz, CH_2CH), 2.3-2.6 (3 H, m, $CH_2CH{=}CH_2$, OH), 3.4-4.0 (2 H, m, CH_2OH), 4.52 (1 H, m, CHO), 4.9-5.2 (m, 2 H, $CH{=}CH_2$), 5.4-5.9 (1 H, m, $CH{=}CH_2$). ^{13}C NMR: δ 23.1 (q), 34.7 (t), 41.8 (t), 43.9 (s), 63.9 (t), 77.6 (d), 119.5 (t), 132.9 (d), 181.1 (s). MS, m/z: 170 (M^+).

(2S,4S)-2-Benzyl-4-(hydroxymethyl)-2-methyl-4-butanolide (5 (R^1 = CH_2Ph, R^2 = Me)) (Table I, run 8) was prepared in the same way as described for **5** (R^1 = Et, R^2 = Me): a colorless oil, 56% yield. $[\alpha]^{23}_D$ +75.5° (c 1.60, $CHCl_3$). IR (film): 3420, 1765 cm^{-1}. NMR: δ 1.26 (3 H, s, CH_3), 1.76 (1 H, dd, J = 6, 14 Hz, CH_2C), 2.11 (1 H, dd, J = 10, 14 Hz, CH_2CH), 2.75 (1 H, d, J = 14 Hz, CH_2Ph), 3.00 (1 H, d, J = 14 Hz, CH_2Ph), 3.1-3.8 (3 H, m, CH_2OH), 4.48 (1 H, m, CH), 7.18 (5 H, s, C_6H_5). ^{13}C NMR: δ 23.3 (q), 34.5 (t), 43.1 (t), 45.3 (s), 63.7 (t), 77.8 (d), 126.8 (d), 128.3 (d), 130.1 (d), 136.9 (s), 181.5 (s). MS, m/z: calcd for $C_{13}H_{16}O_3$ 220.1098, found 220.1023.

(3S)-3-Benzyl-3-methyl-4-butanolide (6 (R^1 = CH_2Ph, R^2 = Me)) (Table I, run 8) was prepared in the same way as described for **6** (R^1 = Me, R^2 = Et): colorless needles, mp 49.5-50.5 °C in 85% yield. $[\alpha]^{24}_D$ +8.6° (c 1.33, $CHCl_3$). IR, NMR, and MS spectra were identical with those of (-)-**6** (R^1 = Me, R^2 = CH_2Ph). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.55; H, 7.37. Found: C, 75.76; H, 7.42.

400-MHz ^1H NMR of 1 ($CDCl_3$): δ 2.04 (1 H, dddd, J = 5.8, 7.9, 10.0, 12.9 Hz, H_a-3), 2.24 (1 H, dddd, J = 6.5, 8.1, 10.0, 12.9 Hz, H_b-3), 2.51 (1 H, ddd, J = 7.0, 10.0, 17.5 Hz, H_a-2), 2.69 (1 H, ddd, J = 6.5, 10.0, 17.5 Hz, H_b-2), 3.15 (1 H, dd, J = 4.4, 10.4 Hz, H_a-5), 3.42 (1 H, dd, J = 3.4, 10.4 Hz, H_b-5), 4.64 (1 H, J = 3.4, 4.4, 5.8, 8.1 Hz, H-4).

Registry No. 1, 73968-62-4; 4, 101901-31-9; 5 (R′ = Me, R^2 = Et), 80348-83-0; 5 (R′ = Me, R^2 = $(CH_2)_2CH_3$), 80348-85-2; 5 (R′ = Me, R^2 = $(CH_2CH{=}CH_2)$), 80348-87-4; 5 (R′ = Me, R^2 = CH_2Ph), 80348-88-5; 5 (R′ = Et, R^2 = Me), 80348-82-9; 5 (R′ = $CH_2CH_2CH_3$, R^2 = Me), 80348-84-1; 5 (R′ = $(CH_2CH{=}CH_2)$, R^2 = Me), 80348-86-3; 5 (R′ = CH_2Ph, R^2 = Me), 80386-12-5; 6 (R′ = Me, R^2 = Et), 80348-89-6; 6 (intermediate lactol), 115306-93-9; 6 (R′ = Me, R^2 = $(CH_2)_2CH_3$), 80348-90-9; 6 (R′ = Me, R^2 = $(CH_2CH{=}CH_2)$), 80348-91-0; 6 (R′ = Me, R^2 = CH_2Ph), 80348-92-1; 6 (R′ = Et, R^2 = Me), 40710-01-8; 6 (R′ = CH_2Ph, R^2 = Me), 80348-93-2.

Felkin-Anh-Selective Hiyama Addition to O-Protected Lactaldehydes: A General Solution to the Blastmycinone Stereoproblem†

Johann Mulzer,* Thomas Schulze, Achim Strecker, and Wolfgang Denzer

Institut für Organische Chemie der Freien Universität Berlin, Takustrasse 3, D-1000 Berlin 33, FRG

Received March 15, 1988

The Hiyama addition of **6a-c** to the O-protected lactaldehydes **5a,b** proceeds with high Felkin-Anh selectivity. **7c**, readily available in 20-g quantities, is the key intermediate in diastereocontrolled syntheses of all blastmycinolactol diastereomers (**1-4a**) in enantiomerically pure form.

Among the molecular fragments containing three contiguous stereocenters (stereotriads)[1] the antimycin A_3 degradation product blastmycinone[2] (**1b**) has received unusual attention, resulting in an number of syntheses of both the racemic[3] and the optically active[4] material, with varying degrees of diastereo- and enantiocontrol. By their very nature, most approaches were directed to the all-trans stereochemistry present in **1**, and very few systematic attempts have been made in elaborating selective pathways to the diastereomers **2-4**. The highest flexibility so far has been achieved by Kinoshita's route[4b] utilizing D-glucose for the preparation of diastereomerically and enantiomerically pure **1-4a,b** in the indicated absolute and relative configurations; in view of the high price of L-glucose, however, this approach is not acceptable for the enantiomers.

We designed stereocontrolled syntheses of each of the eight possible blastmycinone stereoisomers, which rest on the "Hiyama reaction"[5] between O-protected lactaldehyde (**5a,b**), readily available in both enantiomeric forms,[6] and the organometallic species **6c**, prepared in situ from 1-bromo-2-(*E*)-heptene and $CrCl_2$, as the key transformation. In view of the well-established 3,4-anti stereoselectivity[7]

Table I. Stereoselectivity of Hiyama Additions of 6a-c to 5a,b and 13

addition	product distribution[a]	tot yield, %
6a + 13	**14a:15a** = 60:37[b,c]	75
6b + 13	**14b:15b** = 53:45[c]	71
6a + 5a	**7a:8a** = 89:11	80
6b + 5a	**7b:8b** = 91:9	71
6c + 5a	**7c:8c** = >99:1	75
6c + 5b	**7d:8d** = >99:1	90

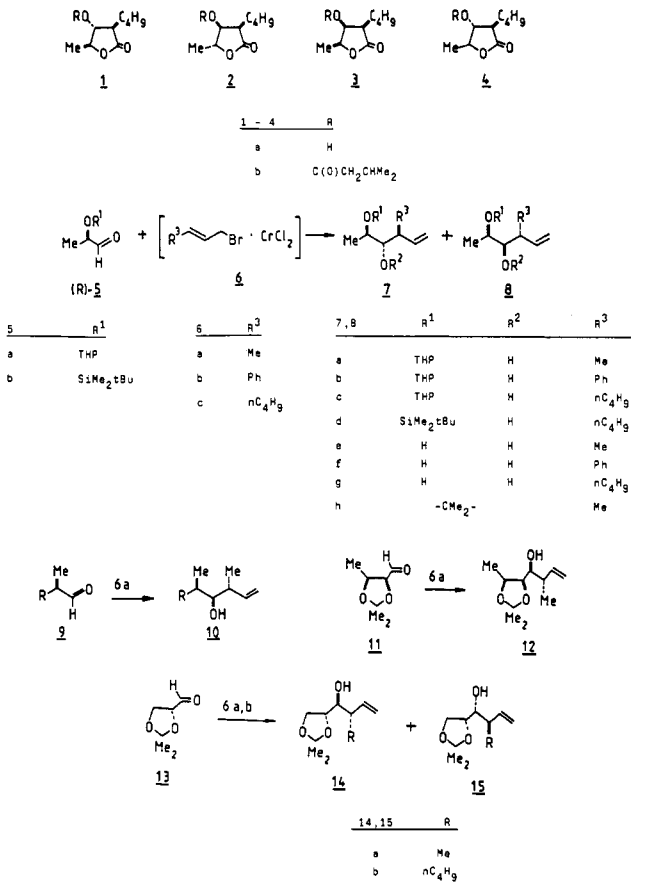
[a] Determined by HPLC. [b] Detailed data; see ref 11. A stereocontrolled synthesis of **14a/b** using chiral crotyl boronates was reported by: Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. [c] Small amounts (2-3%) of the 2,3-anti-3,4-syn adduct were also formed.

† Dedicated to Professor R. Wiechert on the occasion of his 60th birthday.

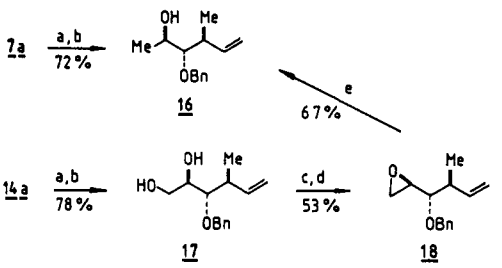
(1) Hoffmann, R. W., *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145.
(2) Yonehara, H.; Takeuchi, S. *J. Antibiot., Ser. A* **1958**, *11*, 254.
(3) (a) Kinoshita, M.; Aburaki, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279. (b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290. (c) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1983**, *23*, 2657. (d) Kozikowski, A. P.; Gosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (e) Wassermann, H. H.; Gabale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423.

0022-3263/88/1953-4098$01.50/0

Chart I



Scheme I (Bn = CH_2Ph)[a]



[a] (a) NaH, DMSO, THF, BnCl, 22 °C. (b) MeOH, TsOH, 22 °C. (c) TsCl, pyridine, 0–22 °C. (d) NaOMe/MeOH in chloroform, 22 °C. (e) $LiBEt_3H$, THF, 22 °C.

of the reaction, the formation of adducts **7** and **8** could be expected. According to the usual terminology, **7** is described as the Felkin–Anh product and **8** as the chelate Cram product.[8] The Hiyama reaction has repeatedly been applied in the synthesis of propionate macrolide subunits from **6b** and α-methylated aldehydes (e.g., **9**) and found to show significant selectivity in favor of the Felkin–Anh adduct **10**.[9] By contrast, little—and contradictory—information was available on the stereochemical outcome from α-alkoxy aldehydes. Fuganti reported the highly selective formation of the chelate Cram product **12** from **6a** and aldehyde **11**,[10] whereas slight Felkin–Anh selection was found for the addition of **6a** to 2,3-isopropylideneglyceraldehyde (**13**).[11] Furthermore, in the vast majority of the examples reported so far,[5,7,9–11] only **6a** or its allyl analogue (R^3 = H) has been used, and it was not clear which effect on the steric course would arise from a variation of R^3 in **6**. Therefore, a more systematic study was started, the results of which are summarized in Table I. To avoid complications from the THP group, the diastereomeric ratios of **7**/**8** were determined after quantitative removal of the protecting groups, i.e., on the stage of **7**/**8e–g**. As expected, **7c** and **7d** gave the same product **7g** on deprotection.

In all cases Felkin–Anh selectivity was observed; however, varying degrees of stereoselection were found. **13** showed very moderate preference for adducts **14a,b**, and additionally, the 2,3-anti-3,4-syn adducts were formed in low quantity. **5** exhibited a far superior Felkin–Anh selectivity, and when the size of the O-protecting group in **5** and of R^3 in **6** was increased, virtually exclusive formation of the 2,3-anti-3,4-anti adduct **7** was accomplished. To prove the stereochemical assignment, **7a** was correlated with the known[11] compound **14a** by the transformations shown in Scheme I. The diol derivative **16** was prepared from **7a** and **14a**, respectively, and the samples obtained from both sources were indistinguishable with respect to ^1H and ^{13}C NMR, TLC and HPLC data, and the optical rotation.

On the basis of these results we returned to the synthesis of 1–4 and envisaged **7c** as our key intermediate. **7c** is readily available in 20-g quantities per experiment and can be prepared in the form of either enantiomer, depending on the configuration of **5**. Due to the differentiability of the 2- and 3-OH group, any one of the four 2,3-diol diastereomers is accessible by retention or appropriate single or double inversion at C-2/3, the 5-ene moiety serving as an ideal CO_2H equivalent. In fact, double retention of C-2/3 and single inversion at C-2 uneventfully converted **7c** into **2a** and **3a**, respectively, via the routine operations shown in Scheme II. Single inversion at C-3, however, met with problems, as the 3-OH in **7c** was too hindered for a Mitsunobu reaction.[12] Hence, via **7g** and **19a/b**, **7c** was transformed into a 2:1 mixture of the anomers **24**, which were separated by column chromatography. Only the minor anomer[13] furnished the desired benzoate **25** under Mitsunobu conditions, whereas the other one gave a mixture of elimination products; to overcome this problem, the useless anomer was equilibrated with methanol/*p*-toluene sulfonic acid and could thus be recycled with only little loss of material. The further elaboration of **25** into

(4) (a) See ref 3a. (b) Aburaki, S.; Konishi, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1254. (c) Fujisawa, C. T.; Kohama, H.; Tajima, K.; Sato, T. *Tetrahedron Lett.* **1984**, *25*, 5155. (d) Uenishi, J.; Tomozane, H.; Yamato, M. *J. Chem. Soc., Chem. Commun.* **1985**, 717. (e) Cardellach, J.; Font, J.; Ortuno, R. M. *Tetrahedron Lett.* **1985**, *26*, 2815. (f) Sayo, N.; Nakai, E.; Nakai, T. *Chem. Lett.* **1985**, 1723. (g) Frater, G.; Müller, U.; Günther, W. *Helv. Chim. Acta* **1986**, *69*, 1858.

(5) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

(6) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.

(7) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685.

(8) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Reviews: Mulzer, J. *Nachr. Chem. Tech. Lab.* **1984**, *32*, 16. Reetz, M. T.; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(9) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343. Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *J. Org. Chem.* **1984**, *49*, 2512. Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221. Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

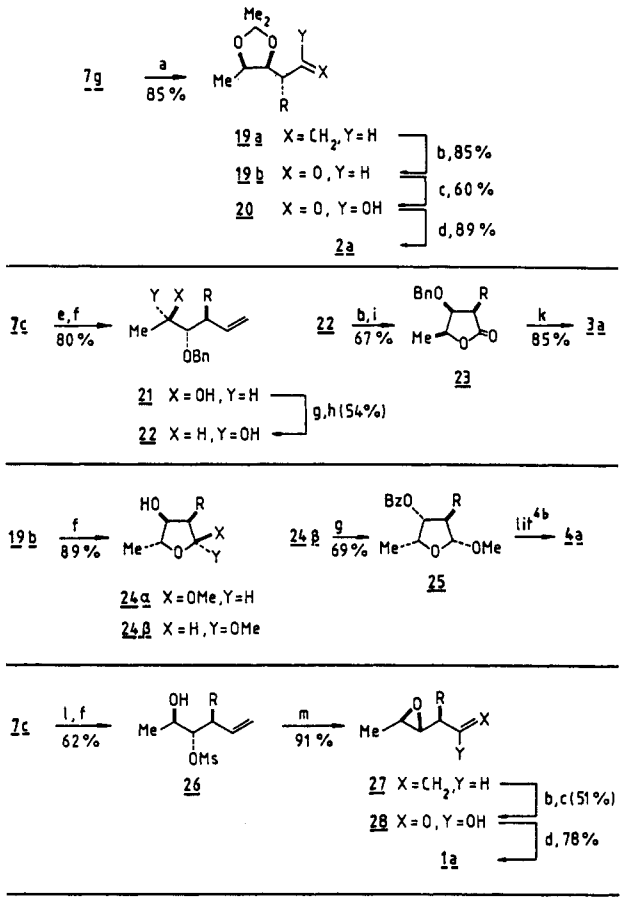
(10) Fronza, G.; Fuganti, C.; Grasselli, P.; Petrocchi-Fantoni, G.; Zirotti, C. *Chem. Lett.* **1984**, 335.

(11) Mulzer, J.; de Lasalle, P.; Freissler, A. *Liebigs Ann. Chem.* **1986**, 1152.

(12) Mitsunobu, O. *Synthesis* **1981**, 1.

(13) The α,β assignment was made by Kinoshita[4b] and we adopted it without any proof. Kinoshita also described the inversion of **24**β, however, by a different method. The behavior of **24**α was not mentioned in this paper.

Scheme II (R = nC_4H_9, Bn = CH_2Ph, Bz = C(O)Ph)[a]



[a] (a) 2,2-Dimethoxypropane, TsOH, MeOH, 22 °C, 3 h. (b) O_3, MeOH, −78 °C, then PPh_3. (c) $NaIO_4$, RuO_2 (cat.), CH_3CN, CCl_4, H_2O, 22 °C. (d) 2 N H_2SO_4, THF, 22 °C. (e) NaH, DMSO, THF, then BnCl, 22 °C. (f) MeOH, TsOH, 22 °C. (g) Diethyl azodicarboxylate, PPh_3, benzoic acid, THF, 22 °C. (h) 10% KOH in MeOH, 22 °C. (i) Pyridinium chlorochromate, CH_2Cl_2, 22 °C. (k) H_2/Pd(C) (10%), MeOH, concentrated HCl (cat.), 1 bar, 50 °C. (l) Methanesulfonyl chloride, NEt_3, chloroform, 22 °C. (m) NaOMe/MeOH in chloroform, 22 °C.

4a was already described by Kinoshita[4b] and we did not repeat this procedure. Finally, the 2,3-OH double inversion of **7c** (Scheme II) was straightforwardly achieved via the epoxy acid **28**, which cleanly isomerized to blastmycinolactol (**1a**) on treatment with acid.

The epoxide thus strongly differs from the corresponding olefin, for which such an endo 5-cyclization is strongly disfavored according to Baldwin's rules.[14] The analytical data of our compounds agree very well with those reported in the literature; in particular, the optical rotations of **1–4a** and **25** are almost identical with Kinoshita's values.[4b] The conversion of the blastmycinolactols (**1–4a**) into the blastmycinones (**1–4b**) has been described; we repeated the given procedure[3,4] only for the acylation of **1a** to **1b**.

In conclusion, we have demonstrated that the Hiyama addition of **6a–c** to lactaldehydes **5a,b** proceeds with high Felkin–Anh selectivity, in particular for bulky substituents on either component. Adduct **7c** has proven a versatile intermediate for achieving perfect stereocontrol in the synthesis of all blastmycinolactol/blastmycinone diastereomers, which are thus accessible from **7c** in a reasonable number of steps and with acceptable overall yields (**1a**, seven steps, 23%; **2a**, five steps, 34%; **3a**, seven steps, 24%; **4a**, seven steps, 39% up to **25**, including recycling of **24**, and nine steps, 24% up to **4a**, using Kinoshita's procedure for converting **25** into **4a**[4b]).

Experimental Section

Nuclear magnetic resonance spectra (NMR) were recorded with a Bruker WH 270 or AC 250 spectrometer in $CDCl_3$ unless noted otherwise. Optical rotations were obtained in $CHCl_3$, unless stated otherwise, with a Perkin-Elmer 121 polarimeter. HPLC separations were performed on Nucleosil 50 with particle size 5 μm (analytical) and 7 μm (preparative), with UV and RI detection. All reactions were performed in purified solvents under an argon atmosphere and were monitored with TLC plates (Merck 5554). Preparative column chromatography was performed on silica gel Merck 60, 0.063–0.2 mm.

O-Tetrahydropyranyl- and *O*-(*tert*-butyldimethylsilyl)lactaldehydes (**5a,b**) were prepared from the corresponding O-protected lactates ((*S*) series, ethyl ester; (*R*) series, *n*-butyl ester[15]) according to ref 6. (*R*)-2,3-*O*-Isopropylideneglyceraldehyde (**13**) was prepared from D-mannitol as described.[11] Crotyl bromide was purchased from Fluka as an (*E*)/(*Z*) mixture containing ca. 15% 2-bromo-1-butene. Isomerically pure (*E*)-1-bromo-2-heptene was prepared by a standard sequence from butyraldehyde (Wittig–Horner reaction, reduction to the allylic alcohol with Dibal-H, bromination with PBr_3 in ether).

Hiyama Reaction. General Procedure. Lithium aluminum hydride (2.66 g, 70 mmol) was added in small portions to anhydrous $CrCl_3$ (20.52 g, 135 mmol) suspended in THF (200 mL) under vigorous stirring at 0 °C. After the evolution of hydrogen had ceased, the aldehyde (50 mmol) in THF (20 mL) and the allylic bromide (70 mmol) in THF (20 mL) were added dropwise in succession and the mixture was stirred at 0–20 °C for 2 h. Saturated aqueous sodium hydroxide was added, so that the pH of the solution was maintained well above 10. Anhydrous $MgSO_4$ was added to absorb the water and the chromous salts. The mixture was stirred and filtered over a pad of Celite. The organic phase was washed with water, dried ($MgSO_4$), concentrated under reduced pressure, and purified by vacuum distillation or column chromatography. The THP-protected adducts (**7/8a–c**) were hydrolyzed with methanol (50 mL/mmol) and *p*-toluenesulfonic acid at 22 °C. The solvent was evaporated under reduced pressure, and the residues were dissolved in ether, washed with sodium bicarbonate, dried ($MgSO_4$), evaporated to dryness, and distilled to give **7/8e–g** in 80–95% yield.

(2*R*,3*S*,4*R*)-4-Butyl-2-(*tert*-butyldimethylsilyl)-5-hexene-2,3-diol (7d): colorless oil; $[\alpha]^{20}_D$ +2.1° (*c* 3); ^1H NMR δ 0.04 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.86 (s, 9 H, tBu), 0.9 (mc, 3 H, CH_3), 1.10 (d, *J* = 6 Hz, 3 H, 1-H), 1.03–1.45 (m, 6 H, $(CH_2)_3$), 2.13 (mc, 2 H, 4-H + OH), 3.36 (dd, *J* = 7 Hz, *J* = 4.5 Hz, 1 H, 3-H), 3.84 (dq, *J* = 6 Hz, *J* = 4.5 Hz, 1 H, 2-H), 5.05 (dd, *J* = 16 Hz, *J* = 2 Hz, 1 H, 6-H), 5.12 (dd, *J* = 10.5 Hz, *J* = 2 Hz, 1 H, 6-H), 5.69 (ddd, *J* = 16 Hz, *J* = 10.5 Hz, *J* = 9 Hz, 1 H, 5-H); ^{13}C NMR δ −4.81, −4.23, 14.00, 17.57, 18.02, 22.68, 25.82, 29.16, 30.20, 45.31, 69.72, 77.20, 116.42, 139.19; IR (film) 3495, 3090, 2960, 2940, 2870, 1640, 1470, 1260, 1105, 1075, 1010, 970, 915, 840, 780 cm^{-1}; MS *m/e* 287 (M + H)$^+$, 269, 229, 189, 155, 137, 119, 75.

(2*R*,3*S*,4*S*)- and (2*R*,3*R*,4*R*)-4-Methyl-5-hexene-2,3-diol (7e and 8e). **7e**: colorless needles; mp 40 °C; $[\alpha]^{20}_D$ −17.9° (*c* 1.2); ^1H NMR δ 1.01 (d, *J* = 6.8 Hz, 3 H, 4-CH_3), 1.21 (d, *J* = 6.8 Hz, 3 H, 1-H), 2.32 (sextet, *J* = 7.5 Hz, 1 H, 4-H), 2.52 (s, br, 1 H, OH), 2.75 (s, br, 1 H, OH), 3.41 (dd, *J* = 8 Hz, *J* = 4Hz, 1 H, 3-H), 3.88 (quint, *J* = 6.75 Hz, 1 H, 2-H), 5.15 (dd, *J* = 16.2 Hz, *J* = 1.5 Hz, 1 H, 6-H), 5.17 (dd, *J* = 10.8 Hz, *J* = 1.5 Hz, 1 H, 6-H), 5.84 (ddd, *J* = 16.2 Hz, *J* = 10.8 Hz, *J* = 8.1 Hz, 1 H, 5-H); ^{13}C NMR δ 16.36, 16.76, 40.47, 68.43, 77.69, 115.78, 140.70. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.53; H, 10.66.

8e: oil; $[\alpha]^{20}_D$ +7.75° (*c* 0.37); ^1H NMR δ 1.12 (d, *J* = 6.75 Hz, 3 H, 4-CH_3), 1.22 (d, *J* = 6.75 Hz, 3 H, 1-H), 2.36 (sextet, *J* = 7.5 Hz, 1 H, 4-H), 2.6 (s, br, 2 H, OH), 3.16 (dd, *J* = 8 Hz, *J* = 4 Hz, 1 H, 3-H), 4.73 (quint, *J* = 6.75 Hz, 1 H, 2-H), 5.06 (dd, *J* = 16.2 Hz, *J* = 1.5 Hz, 1 H, 6-H), 5.12 (dd, *J* = 10.8 Hz, *J* = 1.5 Hz, 1 H, 6-H), 5.82 (ddd, *J* = 16.2 Hz, *J* = 10.8 Hz, *J* = 8 Hz, 1 H, 5-H);

(14) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(15) We thank BASF AG, Ludwigshafen, for a generous sample of (*R*)-*n*-butyl lactate with ee > 99%.

^{13}C NMR δ 17.20, 19.78, 40.82, 68.30, 78.66, 116.33, 139.61; MS m/e 131 $(M + H)^+$, 113, 95, 69.

Additionally, the acetonides **7h** and **8h** were prepared with 2,2-dimethoxypropane and TsOH in methanol at 22 °C/3 h and separated by HPLC (2-propanol/hexane (5:95)).

7h: ^1H NMR δ 0.88 (d, J = 7 Hz, 3 H, 4-CH_3), 1.18 (d, J = 7 Hz, 3 H, 1-H), 1.33 and 1.46 (s, 2 × 3 H, acetonide-CH_3), 2.35 (mc, 1 H, 4-H), 3.85 (dd, J = 9.4 Hz, J = 5.4 Hz, 1 H, 3-H), 4.22 (quint, J = 5.4 Hz, 1 H, 2-H), 5.03 (mc, 1 H, 6-H), 5.05 (mc, 1 H, 6-H), 5.80 (ddd, J = 16.2 Hz, J = 10.8 Hz, J = 5.4 Hz, 1 H, 5-H). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.65. Found: C, 70.48; H, 10.22.

8h: ^1H NMR δ 1.09 (d, J = 7 Hz, 3 H, 4-CH_3), 1.26 (d, J = 7 Hz, 3 H, 1-H), 1.36 and 1.41 (s, 2 × 3 H, acetonide-CH_3), 2.35 (mc, 1 H, 4-H), 3.48 (dd, J = 9.5 Hz, J = 5.4 Hz, 1 H, 3-H), 3.90 (quint, J = 5.4 Hz, 1 H, H-2), 5.03 (mc, 1 H, 6-H), 5.05 (mc, 1 H, 6-H), 5.93 (ddd, J = 16.2 Hz, J = 11.5 Hz, J = 5.2 Hz, 1 H, 5-H).

(2*R*,3*S*,4*R*)-4-Phenyl-5-hexene-2,3-diol (7f): colorless oil; $[\alpha]^{20}_D$ +54.9° (c 2.8); ^1H NMR δ 1.17 (d, J = 6.5 Hz, 3 H, 1-H), 2.07 (br s, 2 H, OH), 3.34 (dd, J = 7.5 Hz, J = 8 Hz, 1 H, 4-H), 3.56 (dq, J = 6.5 Hz, J = 4 Hz, 1 H, 2-H), 3.94 (dd, J = 8 Hz, J = 4 Hz, 1 H, 3-H), 5.18 (dd, J = 11 Hz, J = 2 Hz, 1 H, 6-H), 5.22 (dd, J = 17 Hz, J = 2 Hz, 1 H, 6-H), 6.15 (ddd, J = 17 Hz, J = 11 Hz, J = 8 Hz, 1 H, 5-H), 7.28 (mc, phenyl-H); ^{13}C NMR δ 16.63, 53.46, 68.28, 117.47, 126.93, 128.87, 132.82, 140.65; IR (film) 3400, 3070, 3050, 3010, 2970, 1630, 1590, 1485, 1445, 1120, 1055, 985, 930, 845, 830, 755, 695 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.38. Found: C, 74.97; H, 8.24.

(2*R*,3*R*,4*S*)-4-Phenyl-5-hexene-2,3-diol (8f): ^1H NMR δ 1.20 (d, J = 6.5 Hz, 3 H, 1-H), 2.3 (br s, 2 H, OH), 3.4–3.6 (m, 3 H, 2-H, 3-H, 4-H), 5.20 (dd, J = 11 Hz, J = 2 Hz, 1 H, 6-H), 5.25 (dd, J = 17 Hz, J = 2 Hz, 1 H, 6-H), 6.20 (ddd, J = 17 Hz, J = 11 Hz, J = 8.5 Hz, 1 H, 5-H), 7.25 (mc, phenyl-H); MS m/e 193 $(M + H)^+$, 175, 157, 147, 131, 117, 57.

(2*R*,3*S*,4*S*)-4-Butyl-5-hexene-2,3-diol (7g): colorless crystals; mp 35 °C; $[\alpha]^{20}_D$ +8.6° (c 1.6); ^1H NMR δ 0.88 (t, J = 6.7 Hz, 3 H, CH_3, n-butyl), 1.23 (d, J = 6.4 Hz, 3 H, 1-H), 1.15–1.47 (m, 6 H, $(CH_2)_3CH_3$), 1.98 (d, J = 5 Hz, 1 H, OH), 2.04 (d, J = 7.5 Hz, 1 H, OH), 2.16 (mc, 1 H, 4-H), 3.44 (dd, J = 7 Hz, J = 4.8 Hz, 1 H, 3-H), 3.84 (dq, J = 7 Hz, J = 5.6 Hz, 1 H, 2-H), 5.14 (dd, J = 17 Hz, J = 3 Hz, 1 H, 6-H), 5.2 (dd, J = 10 Hz, J = 3 Hz, 1 H, 6-H), 5.7 (ddd, J = 17 Hz, J = 10 Hz, J = 9 Hz, 1 H, 5-H); ^{13}C NMR δ 13.88, 17.48, 22.54, 29.18, 30.26, 46.57, 68.73, 76.60, 117.50, 139.20; IR (film) 3380 s, 3080 m, 2960 vs, 2940 vs, 2880 s, 2860 s, 1640 m, 1460 s, 1425 s, 1380 m, 1255 m, 1115 s, 1055 vs, 1000 m, 985 w, 945 w, 915 s, 870 w, 835 w, 785 w, 750 w; MS m/e 173 $(M + H^+$, 155, 137, 111, 98, 85, 75, 57, 43. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.65; H, 11.62.

(4*R*,1′*S*,2′*S*)- and (4*R*,1′*R*,2′*R*)-2,2-dimethyl-4-(1′-hydroxy-2′-methyl-3′-butenyl)-1,3-dioxolane (14a and 15a) have been described earlier.[11] **(4*R*,1′*S*,2′*S*)-** and **(4*R*,1′*R*,2′*R*)-2,2-dimethyl-4-(1′-hydroxy-2′-butyl-3′-butenyl)-1,3-dioxolane (14b and 15b)** were prepared according to the general procedure as a 53:45 mixture. Additionally, 2% of the (4*R*,1′*S*,2′*R*) isomer was detected by HPLC analysis.

14b: ^1H NMR δ 0.90 (t, J = 6.3 Hz, 3 H, CH_3), 1.20–1.56 (m, 6 H, $(CH_2)_3$), 1.34 and 1.42 (s, 2 × CH_3), 1.88 (br s, OH), 2.22 (mc, 1 H, 4-H), 3.68 (dd, J = 3.5 Hz, J = 4 Hz, 1 H, 3-H), 3.86–4.14 (m, 3 H, 1-H, 2-H), 5.10 (dd, J = 16.8 Hz, J = 2 Hz, 1 H, 6-H), 5.16 (dd, J = 11 Hz, J = 2 Hz, 1 H, 6-H), 5.72 (ddd, J = 16.8 Hz, J = 11 Hz, J = 9 Hz, 1 H, 5-H).

15b: ^1H NMR δ 0.88 (t, J = 6.3 Hz, 3 H, CH_3), 1.2–1.6 (m, 6 H, $(CH_2)_3$), 1.16 and 1.54 (s, 2 × CH_3), 1.86 (mc, 1 H, 4-H), 2.1 (br s, OH), 3.46 (q, J = 3.8 Hz, 1 H, 3-H), 3.66 (t, J = 6.3 Hz, 1 H, 2-H), 4.04 (mc, 2 H, 1-H), 4.98 (dd, J = 16.8 Hz, J = 2 Hz, 1 H, 6-H), 5.10 (dd, J = 11 Hz, J = 2 Hz, 1 H, 6-H), 5.76 (ddd, J = 16.8 Hz, J = 11 Hz, J = 9 Hz, 1 H, 5-H).

HPLC Analysis. The ratios of **7**:**8e,f,g** and **14**:**15b** were determined by HPLC (Nucleosil 50, 5 μm, 4 × 250 mm, hexane/ethyl acetate (97:3), 110 bar, flow 2 mL/min). Furthermore, the optical purity of **7d** was secured by the familiar Mosher method[16] (ee > 98%).

(16) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Configurational Correlation of 7a and 14a (Scheme I). (2*R*,3*S*,4*S*)-4-Methyl-3-(phenylmethoxy)-5-hexen-2-ol (16). **7a** (5.0 g, 23 mmol) in THF (30 mL) was treated with sodium hydride (1.30 g, 58 mmol), DMSO (8.5 mL, 117 mmol), and benzyl chloride (4.4 g, 35 mmol) at 22 °C for 12 h. Workup with water and extraction with ether furnished the 3-benzyl ether (6.0 g, 85%) as a colorless oil (bp 129 °C/0.05 mbar), which was stirred overnight at 22 °C in methanol (100 mL) containing p-toluenesulfonic acid (1 g). The usual workup gave **16** (3.84 g, 88%) as a colorless oil: bp 78–80 C/0.05 mbar; $[\alpha]^{20}_D$ +6.8° (c 1.2); ^1H NMR δ 1.05 (d, J = 7.5 Hz, 3 H, 1-H), 1.1 (d, J = 7.5 Hz, 3 H, 4-CH_3), 1.95 (s, 1 H, OH), 2.54 (m, 1 H, 4-H), 3.23 (dd = t, J = 5.4 Hz, 1 H, 3-H), 3.88 (dq = quint, J = 6.7 Hz, 1 H, H-2), AB system (δ_A 4.60, δ_B 4.68, J = 11 Hz, 2 H, benzyl-H), 5.04 (dd, J = 16.2 Hz, J = 1.5 Hz, 1 H, 6-H), 5.09 (dd, J = 10.8 Hz, J = 1.5 Hz, 1 H, 6-H), 5.98 (ddd, J = 16.2 Hz, J = 10.8 Hz, J = 8.1 Hz, 1 H, 5-H), 7.35 (mc, 5 H, phenyl-H); ^{13}C NMR δ 16.99, 17.92, 39.76, 68.25, 74.23, 86.94, 114.24, 127.52, 128.04, 136.65, 141.05; IR (film) 3340 m, 3075 vs, 3025 vs, 2970 w, 2925 s, 2870 s, 1640 vs, 1610 m, 1585 s, 1500 m, 1450 s, 1425 s, 1395 s, 1350 m, 1210 s, 1035, 1000 s, 915 s, 874 vs, 850 s, 740 s, 700 vs. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.27; H, 9.15. Found: C, 76.65; H, 8.87.

(2*R*,3*S*,4*S*)-4-Methyl-3-(phenylmethoxy)-5-hexene-1,2-diol (17). Likewise, **14a** (17.0 g, 100 mmol) was converted into **17** (18.7 g, 76%); colorless; viscous oil, bp 158 °C/0.05 mbar; ^1H NMR δ 1.2 (d, J = 8.1 Hz, 3 H, 4-CH_3), 2.6 (dq, J = 8.1 Hz, J = 5.4 Hz, 4-H), 3.38 (dd, J = 5.4 Hz, 2.7 Hz, 1 H, 3-H), 3.48 (s, 1 H, OH), 3.5 (s, 1 H, OH), 3.7 (mc, 3 H, 1-H, 2-H), 4.56 (d, J = 10.8 Hz, 1 H, benzyl-H), 4.63 (d, J = 9.45 Hz, 1 H, benzyl-H), 5.04 (dd, J = 10.8 Hz, J = 2.7 Hz, 1 H, 6-H), 5.08 (dd, J = 16.2 Hz, J = 2.7 Hz, 1 H, 6-H), 5.92 (ddd, J = 16.2 Hz, J = 10.8 Hz, J = 8.1 Hz, 1 H, 5-H), 7.28 (mc, 5 H, phenyl-H). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 70.98; H, 8.50.

(2*R*,1′*S*,2′*S*)-(1′-(Phenylmethoxy)-2′-methyl-3′-butenyl)-oxirane (18). **17** (7.0 g, 30 mmol) in pyridine (200 mL) was treated dropwise with tosyl chloride (5.7 g, 30 mmol) in pyridine (50 mL) at 0 °C. The mixture was stirred at 0–20 °C for 3 h and hydrolyzed. Extraction with ether furnished the 1-tosylate (8.7 g, 75%) as a viscous oil, which was treated in chloroform (130 mL) with a solution of sodium (520 mg) in methanol (25 mL) at 0 °C. After 5 h at 22 °C the mixture was filtered, washed with water, and dried ($MgSO_4$) to give **18** (3.4 g, 70%) as a colorless oil: bp 75 °C (0.05 mbar); ^1H NMR δ 1.16 (d, J = 8.1 Hz, 3 H, 4-CH_3), 2.56 (dquint, J = 8 Hz, J = 4.1 Hz, 1 H, 4-H), 2.72 (dd, J = 6.75 Hz, J = 2.7 Hz, 1 H, 1-H), 2.78 (dd, J = 6.75 Hz, J = 4 Hz, 1 H, 1-H), 2.98 (m, 1 H, 2-H), 3.19 (dd, J = 6.75 Hz, J = 4.1 Hz, 1 H, 3-H), 4.5 (d, J = 12.5 Hz, 1 H, benzyl-H), 4.65 (d, J = 12 Hz, 1 H, benzyl-H), 5.05 (dd, J = 10.8 Hz, J = 1 Hz, 6-H), 5.14 (dd, J = 16.2 Hz, J = 1 Hz, 1 H, 6-H), 5.92 (ddd, J = 16.2 Hz, J = 10.8 Hz, J = 8.4 Hz, 1 H, H-5), 7.35 (mc, 5 H, phenyl-H); ^{13}C NMR δ 16.20, 41.35, 45.56, 51.99, 72.90, 81.48, 115.18, 127.56, 128.28, 138.65, 139.70. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.95; H, 8.29.

(2*R*,3*S*,4*S*)-4-Methyl-3-(phenylmethoxy)-5-hexen-2-ol (16). **18** (1.70 g, 7.8 mmol) in THF (50 mL) was added dropwise to lithium triethylborohydride (Super Hydride) (11 mL of a 1 M solution in THF) at 0 °C. After 1 h at 22 °C the mixture was quenched with 3 N NaOH (4 mL) and H_2O_2 (35% in water, 3 mL) and stirred at 22 °C for another 12 h. The organic phase was washed with water, dried ($MgSO_4$), evaporated, and distilled to give **16** (1.14 g, 67%) identical in ^1H NMR, ^{13}C NMR, HPLC, and MS data with the compound obtained from **7a**. $[\alpha]^{20}_D$ 7.0° (c 1.9).

Synthesis of 2a (Scheme II). (4*S*,5*R*,1′*S*)-2,2,5-Trimethyl-4-(1′-butyl-3′-butenyl)-1,3-dioxolane (19a). **7g** (5.0 g, 29 mmol) in CH_2Cl_2 (100 mL) was stirred with 2,2-dimethoxypropane (4.3 mL, 35 mmol) and p-toluenesulfonic acid (500 mg) at 22 °C for 10 h. The usual workup furnished **19a** (5.3 g, 85%) as a colorless oil: bp 41 °C/0.05 mbar; $[\alpha]^{20}_D$ +40.3° (c 1.19); ^1H NMR δ 0.9 (t, J = 7 Hz, CH_3, n-butyl), 1.18 (d, J = 6.6 Hz, 3 H, CH_3, 1-H), 1.12–1.42 (m, 6 H, n-butyl, $(CH_2)_3CH_3$), 1.33 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 2.18 (mc, 1 H, 4-H), 3.94 (dd, J = 9 Hz, J = 5.6 Hz, 1 H, 3-H), 4.26 (quint, J = 6.8 Hz, 1 H, 2-H), 5.09 (dd, J = 17.2 Hz, J = 2.4 Hz, 1 H, 6-H), 5.14 (dd, J = 10.6 Hz, J = 2.4 Hz, 1 H, 6-H), 5.70 (ddd, J = 17.2 Hz, J = 10.6 Hz, J = 8.6 Hz, 1 H, 5-H); ^{13}C NMR δ 13.95, 16.06, 22.62, 25.80, 28.32, 28.89, 30.98, 43.91, 73.76, 80.41, 107.41, 115.91, 139.42; IR (film) 3080

m, 2990 vs, 2960 vs, 2940 vs, 2860 vs, 1645 m, 1455 s, 1425 w, 1375 vs, 1300 w, 1250 vs, 1220 vs, 1175 s, 1080 vs, 1010 s, 920 s, 860 s, 800 m, 735 w, 675 w, 520 m cm^{-1}. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.41; H, 11.41.

(2*R*,1′*S*,5′*R*)-2-(3′,3′,5′-Trimethyl-2′,4′-dioxolanyl)hexanal (19b). **19a** (5.0 g, 23.5 mmol) in methanol (250 mL) was ozonized at −78 °C until the solution was faintly blue. Triphenylphosphane (7.4 g, 28 mmol) was added, and the mixture was stirred at 22 °C for 2 h, concentrated under reduced pressure, diluted with ether/pentane, and left for crystallization. The filtrate was concentrated and chromatographed (hexane–ethyl acetate (5:1), R_f 0.42) to yield **19b** (4.30 g, 85%) as a clear oil: $[\alpha]^{20}_D$ −37.9° (*c* 3.8); ^{1}H NMR δ 0.88 (t, *J* = 6 Hz, 3 H, CH_3), 1.20 (d, *J* = 6 Hz, 3 H, 5-H), 1.32 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.20–1.45 (m, 5 H, $(CH_2)_3CH_3$), 1.68 (mc, 1 H, $CH_2C_3H_7$), 2.44 (mc, 1 H, 2-H), 4.22 (dd, *J* = 9.2 Hz, *J* = 5.4 Hz, 1 H, 3-H), 4.36 (quint, *J* = 6 Hz, 1 H, 4-H), 9.68 (d, *J* = 4.6 Hz, 1 H, CHO). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.21; H, 10.37.

(2*R*,1′*S*,5′*R*)-2-(3′,3′,5′-Trimethyl-2′,4′-dioxolanyl)hexanoic Acid (20). **19b** (4.00 g, 18.6 mmol) in CCl_4 (40 mL), acetonitrile (40 mL), and water (60 mL) was stirred with sodium metaperiodate (16.3 g, 76 mmol) and ruthenium(IV) oxide hydrate (1 g) at 22 °C for 4 h.[17] The mixture was diluted with CH_2Cl_2, and the organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by chromatography (hexane–ethyl acetate (3:1), R_f 0.21) to give **20** (2.56 g, 60%) as colorless crystals: mp 59–60 °C (pentane); $[\alpha]^{20}_D$ +25.5° (*c* 1.1); ^{1}H NMR δ 0.9 (t, *J* = 6 Hz, 3 H, CH_3), 1.20 (d, *J* = 5 Hz, 3 H, 5-H), 1.33 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.25–1.45 (m, 5 H, $CH_2(CH_2)_3CH_3$), 1.64 (mc, 1 H, $CH_2C_3H_7$), 2.58 (dt, *J* = 10 Hz, *J* = 2.5 Hz, 1 H, 2-H), 4.19 (dd, *J* = 10 Hz, *J* = 5 Hz, 1 H, 3-H), 4.32 (quint, *J* = 5 Hz, 1 H, 4-H), 10.22 (s, 1 H, COOH); ^{13}C NMR δ 13.72, 15.69, 22.38, 25.77, 28.25, 28.78, 29.36, 46.56, 73.19, 78.37, 108.02, 179.35; MS (*m*/*e*) 231 $(M + H)^+$, 215, 173, 155, 115, 109, 86, 57, 43; IR (KBr) 3200 vs, 2960 vs, 2940 vs, 2880 s, 1785 w, 1740 s, 1710 vs, 1455 m, 1415 m, 1380 s, 1245 s, 1220 s, 1170 s, 1080, 930 s, 850 s, 800 s, 740 m, 665 m, 565 w, 515 m cm^{-1}.

(3*R*,4*S*,5*R*)-3-Butyl-4-hydroxy-5-methyltetrahydrofuran-2-one (2a). **20** (2.70 g, 11.7 mmol) was stirred in acetonitrile (60 mL) and 2 N sulfuric acid (9 mL) at 22 °C for 14 h. The mixture was concentrated under reduced pressure, diluted with CH_2Cl_2, washed with sodium bicarbonate and water, dried ($MgSO_4$), evaporated, and purified by chromatography (hexane–ethyl acetate (1:1), R_f 0.18) to furnish **2a** (1.73 g, 89%) as a colorless, viscous oil: $[\alpha]^{20}_D$ −28.5° (*c* 2.4), −68° (*c* 0.36, CH_3OH) (lit.[4b] −69° (*c* 0.28, CH_3OH); ^{1}H NMR δ 0.92 (t, *J* = 7 Hz, 3 H, CH_3, *n*-butyl), 1.33 (d, *J* = 7 Hz, 3 H, 6-H), 1.28–1.52 (m, 5 H, $CH_2(CH_2)_2CH_3$), 1.72 (mc, 1 H, $CH_2(CH_2)_2CH_3$), 2.59 (dt, *J* = 5.5 Hz, *J* = 9 Hz, 1 H, 3-H), 3.02 (d, *J* = 5 Hz, 1 H, OH), 4.19 (ddd, *J* = 5.5 Hz, *J* = 5 Hz, *J* = 1.5 Hz, 1 H, 4-H), 4.52 (dq, *J* = 7 Hz, *J* = 1.5 Hz, 1 H, H-5); ^{13}C NMR δ 13.76, 17.93, 22.54, 22.97, 29.70, 43.74, 73.63, 82.78 (C-2 not detectable). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.67; H, 9.33.

Synthesis of 3a (Scheme II). (2*R*,3*S*,4*S*)-4-Butyl-3-(phenylmethoxy)-5-hexen-2-ol (21). **7c** (10.0 g, 39 mmol) was converted into **21** (8.21 g, 80%) as described for the synthesis of **16** from **7a**: colorless oil; $[\alpha]^{20}_D$ +21.7° (*c* 3.1); ^{1}H NMR δ 0.90 (t, *J* = 7 Hz, 3 H, CH_3), 1.10–1.43 (m, 6 H, $(CH_2)_3$-*n*-butyl), 1.14 (d, *J* = 6.5 Hz, 3 H, 1-H), 1.93 (d, *J* = 6 Hz, 1 H, OH), 2.36 (mc, 1 H, 4-H), 3.28 (dd, *J* = 5.5 Hz, *J* = 3.5 Hz, 1 H, 3-H), 3.88 (quint, *J* = 6 Hz, 1 H, 2-H), 4.60 (d, J_{AB} = 11 Hz, 1 H, $OCH_2C_6H_5$), 4.66 (d, J_{AB} = 11 Hz, 1 H, $OCH_2C_6H_5$), 5.00–5.14 (m, 2 H, 6-H), 5.84 (ddd, *J* = 17 Hz, *J* = 10.5 Hz, *J* = 9.5 Hz, 1 H, 5-H), 7.35 (s, 5 H, C_6H_5); ^{13}C NMR δ 13.97, 19.11, 22.60, 29.49, 31.37, 46.05, 68.21, 74.11, 85.99, 116.12, 127.53, 127.60, 128.28, 138.61, 139.63; IR (film) 3440 vs, 3070 m, 3030 m, 2960 vs, 2930 vs, 2860 vs, 1635 w, 1495 m, 1450 s, 1380 s, 1250 m, 1210 m, 1080 vs, 1000 m, 910 s, 825 w, 735 s, 695 s cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.61; H, 9.93.

(2*S*,3*S*,4*S*)-4-Butyl-3-(phenylmethoxy)-5-hexen-2-ol (22). **21** (24.8 g, 94 mmol) was treated with triphenylphosphane (30.2 g, 115 mmol), benzoic acid (12.8 g, 105 mmol), and diethyl azodicarboxylate (20.0 g, 115 mmol) in THF (400 mL) at 0 °C and stirred at 22 °C for 40 h. The mixture was concentrated under reduced pressure, diluted with ether, and left for crystallization. The filtrate was purified by chromatography (hexane–ethyl acetate (10:1)) to furnish the inverted benzoate (23.2 g, 67%) as a clear oil ($[\alpha]^{20}_D$ +60.2° (*c* 2.7)), which was saponified with 10% KOH in methanol (350 mL) at 22 °C for 10 h. The usual workup delivered **22** (13.3 g, 54%) as a clear mobile oil: $[\alpha]^{20}_D$ +41.9° (*c* 2.4); ^{1}H NMR δ 0.88 (t, *J* = 7 Hz, 3 H, CH_3), 1.16 (d, *J* = 6.5 Hz, 3 H, 1-H), 1.18–1.62 (m, 6 H, CH_2, *n*-butyl), 2.21 (mc, 1 H, 4-H), 2.26 (s, 1 H, OH), 3.18 (dd, *J* = 7 Hz, *J* = 3 Hz, 1 H, 3-H), 3.76 (quint, *J* = 6.8 Hz, 1 H, 2-H), 4.64 (d, J_{AB} = 11.5 Hz, 1 H, $OCH_2C_6H_5$), 5.00 (dd, *J* = 17 Hz, *J* = 2 Hz, 1 H, 6-H), 5.08 (dd, *J* = 10 Hz, *J* = 2 Hz, 1 H, 6-H), 5.78 (ddd, *J* = 17 Hz, *J* = 10 Hz, *J* = 9.5 Hz, 1 H, 5-H), 7.34 (s, 5 H, C_6H_5); ^{13}C NMR δ 13.99, 19.38, 22.40, 29.66, 31.62, 46.74, 68.68, 75.33, 87.67, 116.33, 127.68, 127.71, 128.43, 138.54, 138.70. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.75; H, 9.91.

(3*S*,4*S*,5*S*)-3-Butyl-5-methyl-4-(phenylmethoxy)tetrahydrofuran-2-one (23). **22** (5.0 g, 19.1 mmol) in methanol (200 mL) was ozonized as described for the conversion of **19a** into **19b**. The crude lactol (4.7 g, 93%) was oxidized with pyridinium chlorochromate (5.8 g, 26 mmol) in CH_2Cl_2 (70 mL) at 22 °C for 3 h. The mixture was diluted with ether (500 mL) and decanted, and the residue was washed with ether until it became filterable. The combined extracts were chromatographed (hexane–ethyl acetate (3:1), R_f 0.21) to give **23** (3.38 g, 72%) as a colorless oil: ^{1}H NMR δ 0.89 (t, *J* = 7 Hz, 3 H, CH_3), 1.12–1.38 (m, 4 H, *n*-butyl), 1.48 (d, *J* = 6.5 Hz, 3 H, CH_3, 6-H), 1.59–1.92 (m, 2 H, $CH_2(CH_2)_2CH_3$), 2.54 (q, *J* = 5 Hz, 1 H, 3-H), 4.10 (dd, *J* = 5 Hz, *J* = 3 Hz, 1 H, 4-H), 4.48 (dq, *J* = 6.5 Hz, *J* = 3 Hz, 1 H, 5-H), 4.51 (d, J_{AB} = 11 Hz, 1 H, $OCH_2C_6H_5$), 4.69 (d, J_{AB} = 11 Hz, 1 H, $OCH_2C_6H_5$), 7.33 (s, 5 H, C_6H_5); ^{13}C NMR δ 13.77, 14.41, 22.56, 23.28, 29.99, 47.23, 74.36, 78.44, 78.86, 127.77, 127.97, 128.39, 137.30, 177.15.

(3*R*,4*S*,5*S*)-3-Butyl-4-hydroxy-5-methyltetrahydrofuran-2-one (3a). **23** (3.0 g, 11.4 mmol) was hydrogenated in methanol (150 mL)/concentrated HCl (1 mL) over 10% Pd/C at 50 °C/1 bar. After aqueous sodium bicarbonate was added, the mixture was concentrated under reduced pressure, diluted with ether, washed with water, dried ($MgSO_4$), and evaporated to furnish **3a** (1.65 g, 85%) as colorless needles: mp 100 °C (hexane–ethyl acetate) (lit.[4b] mp 99.5–100.5 °C); $[\alpha]^{20}_D$ −95° (*c* 0.32, CH_3OH) (lit.[4b] −96° (*c* 0.86, CH_3OH)); ^{1}H NMR δ 093 (t, *J* = 7 Hz, 3 H, CH_3, *n*-butyl), 1.29–1.56 (m, 4 H, *n*-butyl), 1.43 (d, *J* = 6.5 Hz, 3 H, 6-H), 1.66 (mc, 1 H, $CH_2C_3H_7$), 1.83 (mc, 1 H, $CH_2C_3H_7$), 1.93 (d, *J* = 5.5 Hz, 1 H, OH), 2.58 (dt, *J* = 5 Hz, *J* = 5 Hz, 1 H, 3-H), 4.33 (dt, *J* = 5 Hz, *J* = 3 Hz, 1 H, 4-H), 4.56 (dq, *J* = 6.5 Hz, *J* = 3 Hz, 1 H, 5-H); ^{13}C NMR δ 13.68, 13.85, 22.56, 23.03, 29.77, 47.60, 71.26, 78.63, 177.61. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.72; H, 9.35.

Synthesis of 4a (Scheme II). (2*R*/*S*,3*S*,4*R*,5*R*)-3-Butyl-4-hydroxy-2-methoxy-5-methyltetrahydrofuran (24). 19b (5.0 g, 23.4 mmol) was treated with *p*-toluenesulfonic acid (500 mg) in methanol (300 mL) at 22 °C for 20 h. The usual workup and chromatography (hexane–ethyl acetate (5:1)) furnished the anomers **24α** (3.15 g, 60%) and **24β** (1.30 g, 30%) with R_f values of 0.41 and 0.18, respectively.

24α: $[\alpha]^{20}_D$ −93.2° (*c* 1.2); ^{1}H NMR δ 0.92 (t, *J* = 7 Hz, 3 H, CH_3, *n*-butyl), 1.21 (d, *J* = 6.5 Hz, 3 H, 6-H), 1.24–1.71 (m, 6 H, *n*-butyl), 2.02 (tdd, *J* = 7 Hz, *J* ≈ 5 Hz, *J* = 4 Hz, 1 H, 3-H), 2.71 (s, 1 H, OH), 3.37 (s, 3 H, OCH_3), 3.70 (dd, *J* = 5 Hz, *J* = 0.1 Hz, 1 H, 4-H), 4.24 (dq, *J* = 6.7 Hz, *J* = 0.1 Hz, 1 H, 5-H), 4.86 (d, *J* = 4 Hz, 1 H, 2-H); ^{13}C NMR δ 13.90, 19.95, 22.37, 22.87, 30.26, 47.03, 54.70, 77.45, 84.17, 106.09; IR (film) 3540 vs, 2960 vs, 2930 vs, 2860 vs, 1450 m, 1420 w, 1375 m, 1185 m, 1150 m, 1100 s, 1060 s, 1040 s, 950 w, 920 m, 895 m, 840 w cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.67; H, 10.58.

24β: ^{1}H NMR δ 0.93 (t, *J* = 7 Hz, 3 H, CH_3), 1.27 (d, *J* = 6.5 Hz, 3 H, 5-CH_3, 6-H), 1.20–1.72 (m, 6 H, *n*-butyl), 2.12 (mc, 1 H, 3-H), 2.49 (s, 1 H, OH), 3.40 (s, 3 H, OCH_3), 4.00–4.13 (m, 2 H, 4-H, 5-H), 4.73 (d, *J* = 4 Hz, 1 H, 2-H); ^{13}C NMR δ 13.87, 20.20, 20.83, 24.66, 30.30, 48.92, 55.49, 77.53, 82.02, 109.90.

24β was treated with methanol and acid as described above to give the same 2:1 anomeric mixture as from **19b**. The α/β

(17) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B.; *J. Org. Chem.* **1981**, *46*, 3936.

assignments were adopted from Kinoshita[4b] without structural proof.

(2S,3R,4R,5R)-3-Butyl-4-benzoyl-2-methoxy-5-methyltetrahydrofuran (25). **24β** (2.0 g, 11.0 mmol) was submitted to the reaction conditions described for the conversion of **21** to **22** and gave after chromatography (hexane–ethyl acetate (5:1)) **25** (2.13 g, 69%) as a clear oil: $[\alpha]^{20}_D$ −15.3° (*c* 1.3) (lit.[4b] −15.0° (*c* 0.45); ^{1}H NMR δ 0.92 (t, *J* = 7 Hz, 3 H, CH_3), 1.26–1.60 (m, 6 H, CH_2, *n*-butyl), 1.32 (d, *J* = 6.5 Hz, 3 H, 5-H), 2.36 (mc, 1 H, 3-H), 3.44 (s, 3 H, OCH_3), 4.47 (quint, *J* = 6 Hz, 1 H, 5-H), 4.73 (d, *J* = 2.5 Hz, 1 H, 2-H), 5.18 (dd, *J* = 5.5 Hz, *J* = 3 Hz, 1 H, 4-H), 7.47 (mc, 2 H, meta-H), 7.58 (mc, 1 H, para-H), 8.08 (mc, 2 H, ortho-H); ^{13}C NMR δ 13.81, 16.02, 22.54, 29.62, 30.09, 51.48, 55.17, 76.38, 78.98, 109.20, 128.34, 129.67, 130.12, 132.97, 166.03; IR (film) 3070 w, 2960 vs, 2930 vs, 2860 vs, 1720 vs, 1600 w, 1450 m, 1380 m, 1275 vs, 1110 s, 1070 s, 710 s cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.71; H, 8.21.

Synthesis of 1a/1b (Scheme II). (2R,3S,4S)-4-Butyl-2-hydroxy-5-hexen-3-yl Methanesulfonate (26). **7c** (7.6 g, 29.6 mmol) in $CHCl_3$ (150 mL) was treated with methanesulfonyl chloride (2.5 mL, 33 mmol) and triethylamine (8.2 mL, 60 mmol) at 0 °C and stirred at 22 °C for 10 h. The mixture was washed with water, dried ($MgSO_4$), evaporated, and chromatographed (hexane–ethyl acetate (5:1)) to give the 3-mesylate (6.0 g, 67%) as a colorless oil, which was converted into **26** (4.15 g, 93%) as described for the preparation of **16** from **7a**: colorless oil; $[\alpha]^{20}_D$ +27.1° (*c* 2.1); ^{1}H NMR δ 0.9 (t, *J* = 6.5 Hz, 3 H, CH_3), 1.28 (d, *J* = 7 Hz, 3 H, 1-H), 1.10–1.54 (m, 6 H, $(CH_2)_3CH_3$, *n*-butyl), 2.34 (d, *J* = 7 Hz, 1 H, OH), 2.36 (mc, 1 H, 4-H), 3.10 (s, 3 H, OSO_2CH_3), 4.03 (dquint, *J* = 7 Hz, *J* = 4 Hz, 1 H, 2-H), 4.70 (dd, *J* = 7 Hz, *J* = 4 Hz, 1 H, 3-H), 5.12 (dd, *J* = 17 Hz, *J* = 2 Hz, 1 H, 6-H), 5.20 (dd, *J* = 10.5 Hz, *J* = 2 Hz, 1 H, 6-H), 5.68 (dt, *J* = 17 Hz, *J* = 10.5 Hz, 1 H, 5-H); ^{13}C NMR δ 13.67, 17.78, 22.38, 28.69, 30.79, 38.74, 45.76, 67.47, 88.57, 117.91, 137.61; IR (film) 3540 vs, 3080 m, 3040 m, 2940 vs, 2875 vs, 1645 m, 1465 s, 1420 s, 1340 vs, 1265 s, 1175 vs, 1100 s, 960 vs, 920 vs, 865 s, 820 m, 770 m, 735 w, 700 w, 620 w, 605 w, 535 s cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_4S$: C, 52.77; H, 8.86. Found: C, 52.68; H, 8.83.

(1R,2R,1′S)-2-(1′-Butyl-2′-propenyl)-3-methyloxirane (27). **26** (3.6 g, 14.4 mmol) in chloroform (80 mL) was treated dropwise with sodium (338 mg, 14.7 mmol) in methanol (20 mL) at 0 °C. The mixture was stirred at 22 °C for 3 h. Workup as described for the preparation of **18** from **17** furnished **27** (2.0 g, 91%) as a volatile oil: bp 55–60 °C/15 mbar; $[\alpha]^{20}_D$ +24.4° (*c* 3.6); ^{1}H NMR δ 0.9 (t, *J* = 6.5 Hz, 3 H, $(CH_2)_3CH_3$), 1.29 (d, *J* = 5.5 Hz, 3 H, 1-H), 1.21–1.70 (m, 6 H, $(CH_2)_3CH_3$), 1.86 (mc, 1 H, 4-H), 2.54 (dd, *J* = 7.5 Hz, *J* = 2 Hz, 1 H, 3-H), 2.80 (dq, *J* = 5.5 Hz, *J* = 2 Hz, 1 H, 2-H), 5.05 (mc, 2 H, 6-H), 5.70 (ddd, J = 17 Hz, *J* = 11 Hz, *J* = 8 Hz, 1 H, 5-H); ^{13}C NMR δ 13.91, 17.55, 22.72, 28.99, 31.75, 46.08, 53.46, 62.59, 115.83, 138.04; IR (film) 3080 s, 2960 vs, 2930 vs, 2860 vs, 1640 s, 1465 s, 1420 m, 1380 s, 1340 w, 1260 w, 1150 w, 1125 w, 1065 m, 995 s, 945 m, 915 s, 860 s, 810 w, 765 s, 730 w, 670 w cm^{-1}. MS *m/e* (relative intensity) 155 (4%, (M + H)$^+$), 137 (15%), 111 (13%), 97 (17%), 81 (19%), 57 (100%), 43 (85%).

(2S,3R,4R)-2-Butyl-3,4-epoxypentanoic Acid (28). **27** (1.7 g, 11.0 mmol) was ozonized in methanol as described for **19a** to give the aldehyde (1.46 g, 85%): ^{1}H NMR δ 0.94 (t, *J* = 7 Hz, 3 H, $(CH_2)_3CH_3$), 1.34 (d, *J* = 5.5 Hz, 3 H, 5-H), 1.24–1.54 (m, 4 H, $(CH_2)_2CH_3$, 1.54–1.94 (m, 2 H, $CH_2(CH_2)_2$), 2.27 (dq, *J* = 7.5 Hz, *J* = 2 Hz, 1 H, 2-H), 2.78 (dd, *J* = 7.5 Hz, *J* = 3 Hz, 1 H, 3-H), 2.89 (dq, *J* = 5.5 Hz, *J* = 3 Hz, 1 H, 4-H), 9.71 (d, *J* = 2 Hz, 1 H, CHO); ^{13}C NMR δ 13.73, 17.36, 22.70, 26.71, 29.04, 53.17, 54.25, 58.11, 201.90; IR (film) 2960 vs, 2930 vs, 2860 s, 2720 w, 1720 vs, 1460 m, 1375 m, 1345 w, 1255 w, 1150 w, 1120 w, 1030 w, 955 w, 860 m, 800 w, 755 w, 725 w cm^{-1}.

The aldehyde (1.30 g, 8.45 mmol) was oxidized with RuO_4 as described for **19b** to furnish epoxy acid **28** (861 mg, 60%) after chromatography (hexane–ethyl acetate (3:1), R_f 0.2): $[\alpha]^{20}_D$ +5.7° (*c* 2.1); ^{1}H NMR δ 0.94 (t, *J* = 7 Hz, 3 H, $(CH_2)_3CH_3$), 1.34 (d, *J* = 5.5 Hz, 3 H, CH_3, 5-H), 1.29–1.52 (m, 4 H, $(CH_2)_2CH_3$), 1.8 (mc, 2 H, $CH_2(CH_2)_2CH_3$), 2.22 (q, *J* = 7.5 Hz, 1 H, 2-H), 2.83 (dd, *J* = 7.5 Hz, *J* = 2.5 Hz, 1 H, 3-H), 2.96 (dq, *J* = 5.5 Hz, *J* = 2.5 Hz, 1 H, 4-H), 9.65 (s, 1 H, COOH); ^{13}C NMR δ 13.77, 17.22, 22.54, 29.08, 29.57, 48.16, 54.06, 59.43, 178.98; IR (film) 2960 vs, 2940 vs, 2870 vs, 1830 m, 1735 vs, 1710 vs, 1470 s, 1460 s, 1415 m, 1380 s, 1220 s, 1185 s, 1125 m, 1060 w, 955 s, 910 w, 860 s, 780 w, 735 w, 655 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.81; H, 9.28.

(3R,4R,5S)-3-Butyl-4-hydroxy-5-methyltetrahydrofuran-2-one (1a). **28** (800 mg, 4.6 mmol) was treated with 2 N sulfuric acid as described for the conversion of **20** into **2a** to give **1a** (620 mg, 78%) as colorless platelets: mp 51 °C (lit.[4b] mp 50–51 °C); $[\alpha]^{20}_D$ −17.8° (*c* 0.53, CH_3OH) (lit.[4b] −18° (*c* 1.09, CH_3OH)); ^{1}H NMR δ 0.94 (t, *J* = 7 Hz, 3 H, CH_3, *n*-butyl), 1.47 (d, *J* = 6.0 Hz, 3 H, 5-CH_3), 1.27–1.72 (m, 5 H, $(CH_2)_3CH_3$), 1.88 (mc, 1 H, $CH_2(CH_2)_2$), 2.18 (d, *J* = 6.25 Hz, 1 H, OH), 2.57 (mc, 1 H, 3-H), 3.81 (dd, *J* = 8 Hz, *J* = 6.26 Hz, 1 H, 4-H), 4.21 (quint, *J* = 7 Hz, 1 H, 5-H); ^{13}C NMR δ 13.79, 18.25, 22.62, 28.21, 28.89, 48.65, 79.00, 79.91, 175.97; IR (KBr) 3470 vs, 2950 vs, 2930 vs, 2860 s, 1735 vs, 1465 m, 1455 m, 1420 w, 1395 s, 1380 s, 1355 m, 1335 s, 1310 s, 1295 s, 1270 w, 1240 s, 1185 s, 1150 w, 1135 m, 1100 s, 1060 vs, 1020 s, 955 w, 940 s, 900 w, 845 m, 775 w, 730 w, 700 s, 645 s, 600 s, 525 s cm^{-1}; MS (relative intensity) *m/e* 172 (7%, M$^{+\cdot}$), 155 (4%), 129 (14%), 116 (87%), 99 (60%), 82 (42%), 71 (34%), 57 (100%), 43 (37%). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.74; H, 9.45. The acylation of **1a** to **1b** proceeds as described in ref 4b to give blastmycinone of $[\alpha]^{20}_D$ 10.2° (*c* 1.1) (lit.[4b] 10° (*c* 1.2)).

Acknowledgment. Financial support by the Fonds der Chemischen Industrie is gratefully acknowledged.

Notes

The Synthesis of Multiple *O*-Phosphoseryl-Containing Peptides via Phenyl Phosphate Protection

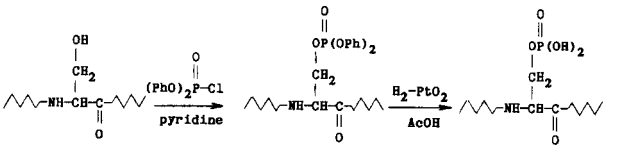
John W. Perich and R. B. Johns*

Department of Organic Chemistry, University of Melbourne, Parkville 3052, Victoria, Australia

Received June 17, 1987

A commonly used procedure for the synthesis of *O*-phosphoseryl-containing peptides involves initial diphenyl phosphorochloridate/pyridine phosphorylation of serine-containing peptides followed by the hydrogenolytic reduction of the phenyl groups from the *O*-(diphenylphosphoro)seryl peptide[1-7] (Scheme I). However, as past

Scheme I



(1) Fölsch, G.; Mellander, O. *Acta Chem. Scand.* **1957**, *11*, 1232.

0022-3263/88/1953-4103$01.50/0