A 0.40-mL portion of the solution was removed after 60 min and analyzed by NMR. The ratio of trans to cis isomers was approximately 1:1.3 as judged from the intensities of the resonances at 2.02 and 2.10 ppm and the ester methyls at 3.67 and 3.68 ppm. CD and ORD spectra of (1*R*,3*S*)-**4** and the mixture of (1*R*,3*S*)-**4** and (1*S*,3*S*)-**5** between 250 and 450 nm in isooctane were virtually identical with those obtained in deuteriochloroform.

Acknowledgment. This work was supported by Grant GM 21328 from the National Institutes of Health. We thank Dr. Fred Wolf of Amoco Corporation for helpful discussions.

Stereoselective Reactions. 14.[1] Efficient Enantioselective Construction of Quaternary Carbon Centers by the Sequential Dialkylation of (*S*)-γ-[(Trityloxy)methyl]-γ-butyrolactone. Synthesis of Optically Active β,β-Disubstituted γ-Butyrolactones

Kiyoshi Tomioka, Youn-Sang Cho,[2] Fuminori Sato, and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

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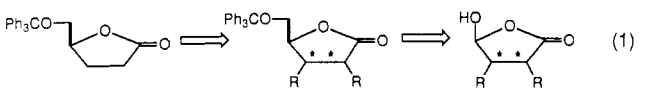
Sequential dialkylation of the lithium enolate, generated from (*S*)-γ-[(trityloxy)methyl]-γ-butyrolactone (**1**), with two different alkyl halides created chiral quaternary carbon centers with extremely high diastereoface selection. A unique conformation of **1**, shown by NMR analysis and MM2 force field calculations, is proposed to be the controlling factor of the stereoselectivity.

Molecules with an appropriate carbon arrangement and asymmetric carbon centers have been developed as a chiral pool in modern synthetic chemistry.[3] Asymmetric carbon centers of these molecules are directly incorporated into the chiral centers of the target molecules. Although this type of methodology assures the integrity of the absolute configuration and optical purity, this approach lacks flexibility and efficiency. Based on these considerations, we designed a new type of chiral synthon (**1**).[4]

A basic scheme for the use of **1** as a chiral synthon is represented in eq 1. The first step of the transformation to **2** is the creation of new asymmetric carbon centers on the ring carbons under the influence of the resident asymmetric center of **1**. The second step to **3** is removal



(1)

1 **2** **3**

of the resident asymmetric center which has played its role in the asymmetric induction, via oxidative cleavage of the glycol part of **2**. The product (**3**) contains a four-carbon unit with two asymmetric carbon centers and two differentiated carbonyl functionalities.

Successful syntheses of a variety of optically active compounds by this approach have been published from our laboratories and others.[4-6] However, factors which control the diastereoface differentiation in the creation of new asymmetric centers, the most important step, remain to be elucidated. In the present article we describe the details of an efficient construction of quaternary carbon centers[7] and the determination of the conformation of **1** which is probably responsible for the high diastereoface differentiation.[8] Furthermore, molecular mechanics calculations performed on **1** appear to be generally consistent with the experimental results.

Results and Discussion

Sequential Dialkylation of 1. The chiral synthon **1** was prepared from L-glutamic acid as described before.[4a] Methylation of **1** (lithium diisopropylamide (LDA)–THF, then MeI (R^1X)) afforded a crystalline product **4** in 73% yield.[4a] Alkylation of **4** (LDA/hexamethyl phosphoric triamide (HMPA)–THF, then R^2X) gave, after detritylation, **5a** (R^1 = Me) with nearly complete stereoselectivity (Table I, runs 1–4).

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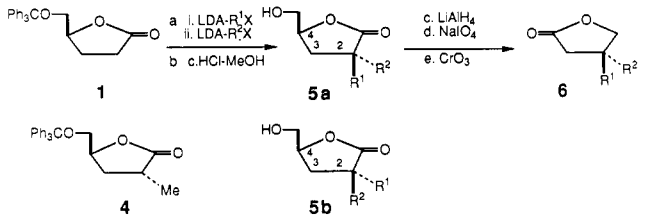
Table I. Diastereoface Differentiation in the Alkylation of 1

			5			6	
run	R^1X	R^2X	yield,[a] %	5a:5b[b]	$[\alpha]^{25}_D$, deg[c]	yield,[d] %	$[\alpha]^{25}_D$, deg[c]
1	CH_3I	CH_3CH_2I	59	99:1	+20.8	53	−15.8[e]
2	CH_3I	$CH_3(CH_2)_2I$	49	97:3	+22.6	44	−11.2
3	CH_3I	CH_2=$CHCH_2Br$	53	98:2	+12.2	43	−3.2
4	CH_3I	$PhCH_2Br$	47	98:2	−19.4	64	−8.5
5	CH_3CH_2I	CH_3I	65	99:1	+64.8	47	+16.0[e]
6	$CH_3(CH_2)_2I$	CH_3I	60	97:3	+23.7		
7	CH_2=$CHCH_2Br$	CH_3I	47	98:2	+88.7		
8	$PhCH_2Br$	CH_3I	56	96:4	+75.5	66	+8.6

[a] Overall yield from 4 (runs 1–4) and from 1 (runs 5–8). [b] Ratios were determined by HPLC [Waters Radial Pak B, ether/EtOAc/*n*-hexane (1:0.5–1.5:4) (runs 1–3 and 5–7) and THF/*n*-hexane (1:4) (runs 4 and 8), 2 mL/min, RI detector; the compounds 5 with R^1 = Me move faster than 5 with R^2 = Me] and NMR (^1H, ^{13}C) analyses. [c] Taken in $CHCl_3$. [d] Overall yield from 5. [e] Maximum optical rotation reported for (*S*)-6 is $[\alpha]^{25}_D$ +15.7° ($CHCl_3$). See ref 9.

The sequential dialkylation of 1 was also carried out with two different alkyl halides in one operation (runs 5–8). Lithiation of 1 with LDA and alkylation of the corresponding enolate were best conducted in the presence of HMPA in THF at −78 °C. In the absence of HMPA, especially at the second lithiation stage, the formation of the lithium enolate was extremely slow and precipitation of enolates was observed in some cases. In the first alkylation step 1.2 equiv of alkyl halide was adequate, and 1.4 equiv of the second alkyl halide was used. The crude dialkylation products were detritylated with concentrated HCl in methanol (1/99, v/v) and purified by silica gel column chromatography to afford 5. Diastereomeric excesses of 5 were determined by high performance liquid chromatography (HPLC) of the crude detritylated products.



The diastereomeric excesses of 5 were extremely high (Table I). It is noteworthy that the second alkyl halides were, without exception, introduced from the α-face of 1.

The removal of the resident asymmetric center was easily carried out via the sequence of reactions of 5 ($LiAlH_4$ reduction, $NaIO_4$ oxidative cleavage of the glycol part, and then Jones oxidation) to give β,β-disubstituted γ-butyrolactone 6 in a high optical purity. The absolute configuration of 6 (R^1 = Me, R^2 = Et; run 1 and also run 5) thus obtained was, as expected, opposite to that reported for the enantiomer of 6.[9]

A particularly significant feature of the present approach is that either enantiomer can be obtained with predictable absolute configuration in quite high optical purity simply by inverting the introduction order of electrophiles (see runs 1, 5 and 4, 8).

NMR Characteristics of 5. The relative stereochemistry of 5 was assigned by NMR analysis. The coupling constants ($J_{3,4}$) between the methylene protons (H-3) and the methine proton (H-4) are characteristic (Table II). In compounds **5a** bearing R^1 = CH_3 group, the coupling constants ($J_{3,4}$) of the signals (H-3) appearing at higher field are 9–10 Hz and are larger than those (7 Hz) appearing at lower field. In compounds **5a** bearing R^2 = CH_3 group, $J_{3,4}$ are also characteristic and show the opposite trend to those bearing R^1 = CH_3 group.

(9) Ledo, H.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1973**, 25.

Table II. Diagnostic ^1H and ^{13}C NMR Spectral Data for 5a

	R^1 = CH_3, R^2 =			
	CH_2CH_3	$(CH_2)_2CH_3$	CH_2CH=CH_2	CH_2Ph
H-3, δ	1.90, 2.17	1.90, 2.18	1.90, 2.18	1.85, 2.23
$J_{3,4}$, Hz	9, 7	9, 7	9, 7	10, 7
H-4, δ	4.50	4.48	4.50	3.5
CH_3, δ	22.9	23.5	23.4	25.0
	R^2 = CH_3, R^1 =			
	CH_2CH_3	$(CH_2)_2CH_3$	CH_2CH=CH_2	CH_2Ph
H-3, δ	1.88, 2.07	1.88, 2.12	1.83, 2.12	1.76, 2.11
$J_{3,4}$, Hz	7, 9	7, 10	7, 11	6, 10
H-4, δ	4.55	4.55	4.52	4.48
CH_3, δ	22.6	23.1	23.1	23.3

Table III. 400-MHz ^1H NMR Spectral Data for 1

	proton						
	H_a-2	H_b-2	H_a-3	H_b-3	H-4	H_a-5	H_b-5
obsd							
δ	2.51	2.69	2.04	2.24	4.64	3.15	3.42
$J_{n,n+1}$, Hz	7.0[a]	6.5[b]	5.8	8.1		4.4[c]	3.4[c]
	10.0[d]	10.0[e]					
calcd[f]							
$J_{n,n+}$, Hz			5.1	7.6		4.4[c]	3.4[c]

[a] $J_{2a,3a}$. [b] $J_{2b,3b}$. [c] $J_{4,5}$. [d] $J_{2a,3b}$. [e] $J_{2b,3a}$. [f] Calculated based on the dihedral angle and % population (25 °C) shown in Table IV according to the Pachler's equation (see ref 12).

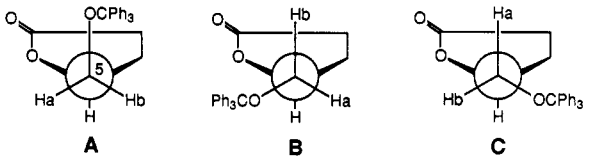


Figure 1.

^{13}C NMR spectra are also characteristic, in which the CH_3 signals of **5a** bearing R^1 = CH_3 group appeared at the slightly lower field than those of **5a** bearing R^2 = CH_3 group.

These characteristic features are useful in the assignment of the relative configuration of 5.

Conformational Analysis of 1. Then we turned our attention to analyzing the conformation of 1 in $CDCl_3$ by using 400-MHz NMR spectroscopy (Table III). The coupling constants, 3.4 and 4.4 Hz, between the methine proton (H-4) and methylene protons (H-5) of the (trityloxy)methyl group are explained by the predominance of preferred conformation A over the alternative conformations B and C (Figure 1). In A, the C–O bond of the bulky (trityloxy)methyl group is positioned anti to the C–H bond, an unexpected alignment considering the apparently unfavorable steric interactions present. It is also noteworthy that, the coupling constants, 5.8 and 8.1 Hz, between H-4

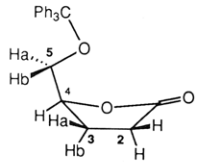
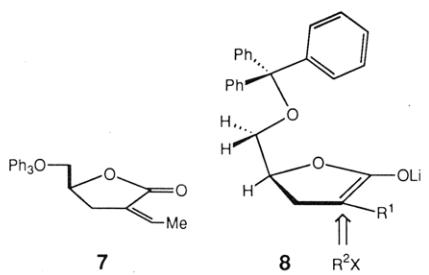


Figure 2.

Table IV. Energy Differences, Populations, and Dihedral Angles of the Conformations A–C Calculated by MM2 Force Field

	Aa	Ba	Ca	Ae	Be	Ce
E, kcal/mol	0	1.38	1.56	0.95	0.82	1.40
% (25 °C)	58	6	4	12	15	5
% (−78 °C)	78	3	1	7	9	2
H_a3–H4, deg	−96.8	−93.6	−94.6	−159.9	−157.4	−158.0
H_b3–H4, deg	24.4	28.1	27.0	−37.0	−35.2	−36.6
H4–H_a5, deg	−57.7	66.2	175.7	−58.5	68.4	−178.2
H4–H_b5, deg	61.5	−173.6	−64.5	60.6	−171.8	−58.2

and $H_{a,b}$-3, indicate that the (trityloxy)methyl group is located above the plane of γ-lactone ring (Figure 2). A similar conformation of **1** has been determined for **7**, the sp^2 analogue at the α-position of the carbonyl of **1**, by X-ray crystallographic and ^1H NMR analyses.[4h]



7 **8**

If a similar conformation is assumed for the enolate of **1**, one of the phenyl groups would be placed just above the plane of the C=C bond as shown in **8**. Attack of an electrophile from the β-face would encounter steric hindrance, dictating α-face entry of the alkylating agent. The rationalization is based upon the assumption of a reactant-like transition state in the alkylation.[10]

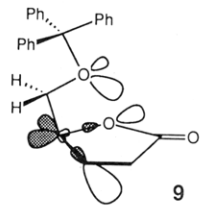
In support of this rationalization for the stereochemical alkylation, molecular mechanics calculations were performed on **1** using Allinger MM2 force field.[11] Six conformations with local energy minima were obtained. These correspond to conformations A–C with a nearly axial (trityloxy)methyl group (Aa–Ca) and with equatorial orientation (Ae–Ce). The energy differences, calculated populations, and dihedral angles of these conformers are presented in Table IV. The most stable conformation Aa (58% and 78% population at 25 and −78 °C, respectively, by calculation) is shown in Figure 2. The coupling constants ($J_{3,4}$ and $J_{4,5}$) were calculated according to the Pachler's equation[12] using these populations and dihedral angles and are in good agreement with those observed (Table III).

Discussion

The origin of the high diastereoface differentiation is mainly attributable to the specific conformation of the enolate **8** generated from **1**. The specific alignment of the (trityloxy)methyl group is evidently responsible for the directed attack of electrophiles as shown in **8**. The most stable conformation of the enolate **8** (R^1 = CH_3: 73% population at −78 °C) was also supported by MM2 calculations.[13]

The gauche conformation of O–C–C–O bond arrangement is a well-known phenomenon, the so-called gauche effect.[14] Although the O–C–C–O bonds exist in gauche conformations in both A and B, analysis of molecular models suggests that conformation B is more favorable than A on the basis of steric effects. However, this is not the case.

An alternative explanation for the stability of conformation A is intramolecular orbital mixing. The energy level of the antibonding orbital of the polarized O–C σ-bond of the lactone may be low enough to interact with the orbital of the oxygen lone pair of the (trityloxy)methyl group.[15] Assuming this type of interaction is operative, the orbital interactions would stabilize conformation A rather than B as shown in **9**, where additional stabilizing interactions between the lone pair of oxygen and antibonding orbital of C–C σ-bond are operative.



9

Conclusion

High diastereofacial differentiation was demonstrated in the sequential dialkylation of **1** to create chiral quaternary carbon centers. The origin of the high stereoselectivity is attributed to a unique conformation of **1**. Application of this new type of methodology in which the conformation is fixed by intramolecular orbital interactions is a subject of our current research.[16,17]

Experimental Section

Melting points are not corrected. Optical rotations were taken with a Jasco DIP-181 digital polarimeter. ^1H NMR spectra were taken in $CDCl_3$ at 400 MHz or at 100 MHz. ^{13}C NMR spectra were taken in $CDCl_3$ at 25 MHz.

(2*R*,4*S*)-2-Methyl-4-[(trityloxy)methyl]-4-butanolide (4). To a cooled (−78 °C) solution of LDA in THF (55 mL), prepared from diisopropylamine (7.8 mL, 55 mmol) and a hexane solution of BuLi (36.6 mL, 55 mmol), was added a solution of **1** (17.9 g, 50 mmol) in THF (90 mL). After the mixture was stirred at −78 °C for 20 min, methyl iodide (3.1 mL, 50 mmol) was added, and the whole was stirred at −78 °C for 2 h. The mixture was quenched

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(11) We are grateful to Professor Eiji Osawa, Department of Chemistry, Hokkaido University, Japan, for providing the MM2 program.

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(13) Populations (%) at −78 °C and energy differences (kcal/mol) of the conformers corresponding to Aa–Ce are as follows: 73, 0; 6, 0.93; 4, 1.07; 5, 1.02; 6, 0.96; 6, 0.94. For computation, OLi was treated as O^-, and parameters developed by Still are used. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *23*, 3981.

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(17) An extremely high diastereoface differentiation was realized even in the remote 1,5-asymmetric induction. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369. Fleming, I.; Kindon, N. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1177.

with saturated aqueous NH_4Cl (100 mL) and extracted with three portions of 100 mL of benzene. The extracts were successively washed with 10% aqueous HCl (20 mL), saturated $NaHSO_3$ (20 mL), saturated $NaHCO_3$ (50 mL), and saturated NaCl (100 mL) and then dried over $MgSO_4$. Concentration and recrystallization of the crude solid from a 1:1 mixture of ethyl acetate and hexane afforded **4** as colorless needles (13.6 g, 73%), mp 149 °C. $[\alpha]^{25}_D$ +36.1° (*c* 1.13, $CHCl_3$). NMR: δ 1.26 (3 H, d, *J* = 7 Hz, CH_3), 1.7–2.4 (2 H, m, CH_2CH), 2.6–3.1 (1 H, m, $CHCH_3$), 3.10 (1 H, dd, *J* = 5, 11 Hz, CH_2O), 3.43 (1 H, dd, *J* = 4, 11 Hz, CH_2O), 4.56 (1 H, m, CHO), 7.1–7.5 (15 H, m, C_6H_5). IR (KBr): 1770 cm^{-1}. MS, *m/z*: 372. Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.65; H, 6.45. Found: C, 80.48; H, 6.50.

(2*R*,4*S*)-2-Ethyl-4-(hydroxymethyl)-2-methyl-4-butanolide (5 (R^1 = Me, R^2 = Et)) (From 4) (Table I, Run 1). To a solution of LDA (6.5 mmol) in THF (5.5 mL) was added a solution of HMPA (1.13 mL, 6.5 mmol) and **4** (1.86 g, 5.0 mmol) in THF (10 mL). After the mixture was stirred at −78 °C for 30 min, ethyl iodide (0.52 mL, 6.5 mmol) was added. The whole was stirred at −78 °C for 4 h and quenched with saturated aqueous NH_4Cl (30 mL). The mixture was extracted with benzene (50 mL × 3). The extracts were washed in the same way as described for the preparation of **4**. Concentration afforded a yellow oil (2.07 g). A yellow oil obtained above (1.24 g) was treated with concentrated HCl–MeOH (1:99, 15 mL) at room temperature for 12 h and filtered. The filtrate was concentrated in vacuo and purified through silica gel column chromatography (ether) to give **5** (400 mg, 81%) as a pale yellow oil. $[\alpha]^{24}_D$ +20.8° (*c* 1.40, $CHCl_3$). IR (film): 3420, 1780 cm^{-1}. NMR: δ 0.95 (3 H, t, *J* = 7 Hz, CH_3), 1.24 (3 H, s, CH_3), 1.60 (2 H, q, *J* = 7 Hz, CH_2CH_3), 1.90 (1 H, dd, *J* = 9, 12 Hz, CH_2CH), 2.17 (1 H, dd, *J* = 7, 12 Hz, CH_2CH), 3.18 (1 H, s, OH), 3.57 (1 H, dd, *J* = 7, 12 Hz, CH_2CH), 3.84 (1 H, dd, *J* = 4, 12 Hz, CH_2OH), 4.50 (1 H, m, CH). ^{13}C NMR: δ 8.82 (q), 22.9 (q), 31.0 (t), 35.5 (s), 44.3 (s), 64.0 (t), 77.6 (d), 181.9 (s). MS, *m/z*: calcd for $C_8H_{14}O_3$ 159.1019, found 159.0959.

(3*R*)-3-Ethyl-3-methyl-4-butanolide (6 (R^1 = Me, R^2 = Et)) (Table I, Run 1). To a suspension of lithium aluminum hydride (219 mg, 5.76 mmol) in THF (10 mL) was added a solution of **5** (302 mg, 1.92 mmol) in THF (5 mL). After being stirred at room temperature for 12 h, the mixture was successively treated with water (0.22 mL), 15% aqueous NaOH (0.28 mL), and water (0.66 mL) and filtered. The filtrate was concentrated to afford a pale yellow oil (313 mg). The solution of the oil obtained above (290 mg) in ethyl acetate (18 mL) was added to a solution of $NaIO_4$ (756 mg, 3.56 mmol) in water (9 mL), and the whole was stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate. The extracts were successively washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$, and brine and then dried over $MgSO_4$. Concentration afforded a lactol as a yellow oil (190 mg).

A solution of the lactol (90 mg) obtained above in acetone (5 mL) was added to a 1.1 M solution of Jones reagent (0.9 mL) under ice–water bath cooling, and the mixture was stirred at room temperature for 1 h. After being quenched with 2-propanol, the mixture was diluted with brine and extracted with ether. The extract was successively washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration and purification through silica gel chromatography (hexane–ether) afforded **6** (56 mg) as a pale yellow oil in 64% overall yield. $[\alpha]^{24}_D$ −15.8° (*c* 2.26, $CHCl_3$) [lit.[9] for enantiomer, $[\alpha]^{24}_D$ +15.7° (*c* 3.3, $CHCl_3$)]. IR (film): 1775 cm^{-1}. NMR: δ 0.92 (3 H, t, *J* = 7 Hz, CH_3), 1.25 (3 H, s, CH_3), 1.52 (2 H, d, *J* = 7 Hz, CH_2CH_3), 2.26 and 2.40 (each 1 H, each d, *J* = 18 Hz, CH_2CO), 3.95 and 4.02 (each 1 H, each d, *J* = 8 Hz, CH_2O). MS, *m/z*: calcd for $C_7H_{12}O_2$ 128.0836, found 128.0823.

(2*R*,4*S*)-4-(Hydroxymethyl)-2-methyl-2-propyl-4-butanolide (5 (R^1 = Me, R^2 = $(CH_2)_2CH_3$)) (Table I, run 2) was prepared in the same way as described for **5** (R^1 = Me, R^2 = Et): a pale yellow oil in 67% yield. $[\alpha]^{24}_D$ +22.6° (*c* 1.75, $CHCl_3$). IR (film): 3420, 1765 cm^{-1}. NMR: δ 0.90 (3 H, t, *J* = 7 Hz, CH_3), 1.26 (3 H, s, CH_3), 1.3–1.6 (4 H, m, $CH_2CH_2CH_3$), 1.90 (1 H, dd, *J* = 9, 13 Hz, CH_2CH), 2.18 (1 H, dd, *J* = 7, 13 Hz, CH_2CH), 3.38 (1 H, s, OH), 3.58 (1 H, dd, *J* = 5, 14 Hz, CH_2OH), 3.86 (1 H, dd, *J* = 3, 14 Hz, CH_2OH), 4.48 (1 H, m, CH). ^{13}C NMR: δ 14.3 (q), 17.8 (t), 23.5 (q), 36.0 (t), 40.6 (t), 44.0 (s), 63.8 (t), 77.8 (d), 182.2 (s). MS, *m/z*: calcd for $C_9H_{16}O_3$ 172.1100, found 172.1121.

(3*R*)-3-Methyl-3-propyl-4-butanolide (6 (R^1 = Me, R^2 = $(CH_2)_2CH_3$) (Table I, run 2) was prepared in the same way as described for **6** (R^1 = Me, R^2 = Et): a colorless oil in 44% yield. $[\alpha]^{24}_D$ −11.2° (*c* 1.30, $CHCl_3$). IR (film): 1780 cm^{-1}. NMR: δ 0.94 (3 H, t, *J* = 6 Hz, CH_3), 2.18 (3 H, s, CH_3), 1.2–1.6 (4 H, m, CH_2CH_2), 2.25 and 2.42 (each 1 H, each d, *J* = 18 Hz, CH_2CO), 3.92 and 4.04 (each 1 H, each d, *J* = 8 Hz, CH_2O). MS, *m/z*: calcd for $C_8H_{15}O_2$ (M^+ + 1) 143.1072, found 143.1080.

(2*R*,4*S*)-2-Allyl-4-(hydroxymethyl)-2-methyl-4-butanolide (5 (R^1 = Me, R^2 = $CH_2CH{=}CH_2$)) (Table I, run 3) was prepared in the same way as described for **5** (R^1 = Me, R^2 = Et): a pale yellow oil in 75% yield. $[\alpha]^{22}_D$ +12.2° (*c* 1.29, $CHCl_3$). IR (film): 3420, 1765 cm^{-1}. NMR: δ 1.26 (3 H, s, CH_3), 1.90 (1 H, dd, *J* = 9, 14 Hz, CH_2CH), 2.24 (1 H, dd, *J* = 7, 14 Hz, CH_2OH), 2.29 (2 H, d, *J* = 8 Hz, $CH_2CH{=}CH_2$), 3.58 (1 H, dd, *J* = 5, 13 Hz, CH_2OH), 3.68 (1 H, s, OH), 3.84 (1 H, dd, *J* = 3, 13 Hz, CH_2OH), 4.48 (1 H, m, CH), 5.0–5.2 (2 H, m, $CH{=}CH_2$), 5.5–6.0 (1 H, m, $CH{=}CH_2$). ^{13}C NMR: δ 23.4 (q), 34.9 (t), 42.4 (t), 44.0 (s), 63.7 (t), 77.7 (d), 119.6 (t), 132.5 (d), 181.7 (s). MS, *m/z*: calcd for $C_9H_{14}O_3$ 170.0943, found 170.0983.

(3*R*)-3-Allyl-3-methyl-4-butanolide (6 (R^1 = Me, R^2 = $CH_2CH{=}CH_2$)) (Table I, run 3) was prepared in the same way as described for **6** (R^1 = Me, R^2 = Et): a colorless oil in 43% yield. $[\alpha]^{23}_D$ −3.2° (*c* 1.48, $CHCl_3$). IR (film): 1780 cm^{-1}. NMR: δ 1.17 (3 H, s, CH_3), 2.20 (2 H, d, *J* = 8 Hz, $CH_2CH{=}CH_2$), 2.26 and 2.44 (each d, *J* = 18 Hz, CH_2CO), 3.92 and 4.10 (each 1 H, each d, *J* = 10 Hz, CH_2O), 5.0–5.2 (2 H, m, $CH{=}CH_2$), 5.5–6.0 (1 H, m, $CH{=}CH_2$). MS, *m/z*: calcd for $C_8H_{12}O_2$ 140.0836, found 140.0818.

(2*R*,4*S*)-2-Benzyl-4-(hydroxymethyl)-2-methyl-4-butanolide (5 (R^1 = Me, R^2 = CH_2Ph)) (Table I, run 4) was prepared in the same way as described for **5** (R^1 = Me, R^2 = Et): a pale yellow oil in 65% yield. $[\alpha]^{22}_D$ −19.4° (*c* 1.36, $CHCl_3$). IR (film): 3420, 1780 cm^{-1}. NMR: δ 1.28 (3 H, s, CH_3), 1.85 (1 H, dd, *J* = 10, 14 Hz, CH_2CH), 2.23 (1 H, dd, *J* = 7, 14 Hz, CH_2CH), 2.64 (1 H, d, *J* = 13 Hz, CH_2Ph), 2.96 (1 H, d, *J* = 13 Hz, CH_2Ph), 3.2–3.8 (4 H, m, $CHCH_2OH$), 7.16 (5 H, s, C_6H_5). ^{13}C NMR: δ 25.0 (q), 34.4 (t), 44.5 (t), 45.9 (s), 63.6 (t), 78.4 (d), 127.2 (d), 128.6 (d), 129.8 (d), 136.5 (s), 181.7 (s). MS, *m/z*: calcd for $C_{13}H_{16}O_3$ 220.1098, found 220.1092.

(3*R*)-3-Benzyl-3-methyl-4-butanolide (6 (R^1 = Me, R^2 = CH_2Ph)) (Table I, run 4) was prepared in the same way as described for **6** (R^1 = Me, R^2 = Et): colorless needles, mp 49.5 °C (from $CHCl_3$), 64% yield. $[\alpha]^{24}_D$ −8.5° (*c* 1.48, $CHCl_3$). IR (KBr): 1775 cm^{-1}. NMR: δ 1.10 (3 H, s, CH_3), 2.12 and 2.47 (each 1 H, each d, *J* = 18 Hz, CH_2CO), 2.70 (2 H, s, CH_2Ph), 3.83 and 4.11 (each 1 H, each d, *J* = 9 Hz, CH_2O), 7.0–7.03 (5 H, m, C_6H_5). MS, *m/z*: 190 (M^+). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.05; H, 7.55.

(2*S*,4*S*)-2-Ethyl-4-(hydroxymethyl)-2-methyl-4-butanolide (5 (R^1 = Et, R^2 = Me)) (From 1) (Table I, Run 5). To a solution of LDA (9.4 mmol) and HMPA (9.4 mmol) in THF (10 mL) was added to solution of **1** (2.89 g, 8.1 mmol) in THF (10 mL). After the mixture was stirred at −78 °C for 30 min, ethyl iodide (0.72 mL, 9.0 mmol) was added. The whole was stirred at −78 °C for 5 h. To the solution above was added another solution of LDA (9.4 mmol) and HMPA (9.4 mmol) in THF (10 mL). After the mixture was stirred for 30 min, a solution of methyl iodide (0.70 mL, 11.3 mmol) in THF (2 mL) was added. The whole was stirred at −78 °C for 5 h. Workup as described for **5** (R^1 = Me, R^2 = Et) gave a yellow oil (3.67 g), which was detritylated in concentrated HCl in MeOH (1:99, 20 mL). Purification through silica gel column chromatography (ether) afforded **5** (833 mg) as a colorless oil in 65% overall yield. $[\alpha]^{22}_D$ +64.8° (*c* 1.55, $CHCl_3$). IR (film): 3420, 1780 cm^{-1}. NMR: δ 0.92 (3 H, t, *J* = 7 Hz, CH_3), 1.27 (3 H, s, CH_3), 1.62 (2 H, d, *J* = 7 Hz, CH_2CH_3), 1.88 (1 H, dd, *J* = 7, 12 Hz, CH_2CH), 2.07 (1 H, dd, *J* = 9, 12 Hz, CH_2CH), 3.4–4.1 (3 H, m, CH_2OH), 4.55 (1 H, m, CH). ^{13}C NMR: δ 8.60 (q), 22.6 (q), 30.2 (t), 34.6 (t), 44.5 (s), 63.7 (t), 77.7 (d), 182.1 (s). MS, *m/z*: calcd for $C_8H_{15}O_3$ (M^+ + 1) 159.1020, found 159.0983.

(3*S*)-3-Ethyl-3-methyl-4-butanolide (6 (R^1 = Et, R^2 = Me)) (Table I, run 5) was prepared in the same way as described for **6** (R^1 = Me, R^2 = Et): a colorless oil, 68% yield. $[\alpha]^{23}_D$ +16.0° (*c* 2.28, $CHCl_3$). IR, NMR, and MS are identical with those of **6** (R^1 = Me, R^2 = Et).

(2*S*,4*S*)-4-(Hydroxymethyl)-2-methyl-2-propyl-4-butanolide (5 (R^1 = $CH_2CH_2CH_3$, R^2 = Me)) (Table I, run 6) was prepared in the same way as described for **5** (R^1 = Et, R^2 = Me):

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

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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.

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