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Synthesis of some 2-*C*-alkyl-2,3-dideoxy-α,β-L-*glycero*-tetrurono-1,4-lactones. Evaluation as antitumor agents *

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ABSTRACT

A series of 3-*C*-alkyl-2,3-dideoxy-5-*O*-trityl-D-*erythro*-pentono-1,4-lactones were detritylated. The resultant free-hydroxy compounds were converted to their respective 2-*C*-alkyl-2,3-dideoxy-α,β-L-*glycero*-tetrurono-1,4-lactones (L-sugar numbering) in a one-vessel reaction sequence of (a) conversion of the lactones to their aldonic acid sodium salts, (b) cleavage of the resulting aldonates with sodium metaperiodate, and (c) acidification, followed by acetylation, to give the title compounds. The unsubstituted tetrurono-1,4-lactones were inhibitory toward L1210 leukemia cells at concentrations in the 10^{-4} M range.

INTRODUCTION

Acetomycin (**1**), an antibiotic first isolated from *Streptomyces ramulosus* ETH 17633 by Prelog and co-workers[1], has recently been shown to exhibit antitumor activity[2], particularly against HCT-8 human adenocarcinoma ($IC_{50} = 1.5$ μg/mL). Little is known about the mode of action of the compound; however, studies have shown that the drug undergoes facile enzymic *O*-deacetylation, leading to a total loss of biological activity[3]. In a program designed to probe the structure–activity relationships among **1** and its congeners, a series of simplified acetomycin analogues (**4a** and **4b**, and **4d–4f**) devoid of substituents at the quaternary center (C-3, L-sugar numbering) were synthesized for evaluation as antitumor agents.

RESULTS AND DISCUSSION

Chemistry.—Single-crystal X-ray studies on acetomycin carried out in this laboratory[4] and elsewhere on both the bromo derivative[5] and on the compound itself[6], indicate the absolute stereochemistry shown as **1**.

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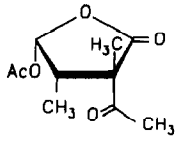

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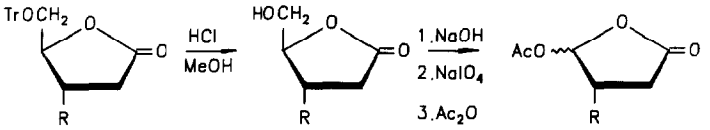
A synthetic approach to a series of simplified acetomycin analogues **4a** and **4b**, and **4d–4f** that are lacking C-3 substituents (L-sugar numbering) is provided via stereospecific Michael addition of suitable organometallic reagents to 5-protected-2,3-dideoxy-D-*glycero*-pent-2-enono-1,4-lactones [*O*-protected (*S*)-5-(hydroxymethyl)-2(5*H*)-furanones], which give compounds of the type **2a–2g** (Scheme 1)[7]. Thus with suitable precursors in hand, the chemistry as depicted in Scheme 1 was carried out *.

Detritylation of compounds **2a–2g** (ref 7) was effected by treating methanolic solutions of these compounds with a small proportion of concd hydrochloric acid at room temperature to give, upon neutralization and extractive workup, **3a–3g** in yields of 55–91%. The products, which were all syrups that were purified by column chromatography, were fully characterized by ^{1}H NMR spectroscopy and by elemental analysis (see Tables I and II). Interpretation of the ^{1}H NMR spectrum of **3f** was complicated by the fact that introduction of a chiral *sec*-butyl side chain resulted in a diastereomeric mixture of products with overlapping resonances.

The mass spectra for compounds **3a–3g** (see Table III) revealed molecular ions, with principal fragmentations being $M^+ - 18$ (loss of water) and $M^+ - 31$ (loss of the $-CH_2OH$ group). The latter cleavage, which gave rise to the base peak in all examples except **3g**, was useful in ascertaining the size of the C-3 side chain in these compounds.

Conversion of the free hydroxy products **3a** and **3b** and **3d–3f** to 2-alkyl-2,3-dideoxy-α,β-L-*glycero*-tetrurono-1,4-lactones (**4a** and **4b**, and **4d–4f**) was carried out by the sequence of reactions shown in Scheme 2. The lactones **3a** and **3b**, and **3d–3f** were converted with aqueous sodium hydroxide to their respective aldonic acid sodium salts **A**, which, without isolation, were reacted with sodium metaperiodate at pH 8 to give the aldehydic products (tetruonic acid salts) **B**, isolated as their hemiacetals **C** by extractive workup at pH 2. The crude 2-*C*-alkyl-2,3-dideoxy-α,β-L-*glycero*-tetrurono-1,4-lactones were, without further delay, acetylated with acetic anhydride in the presence of a dry, strongly acidic, macroreticular cation-exchange resin to give the 1-*O*-acetyl-2-*C*-alkyl-2,3-dideoxy-α,β-L-*glycero*-tetrurono-1,4-lactones **4a** and **4b**, and **4d–4f**. Purification of these compounds by column chromatography furnished **4a** and **4b**, and **4d–4f** in yields of 48–58%. The

* It is worth noting that of the *O*-protected compounds reported in the previous paper[7], only the trityl-protected examples proved to be satisfactory intermediates for the chemistry depicted in Scheme 1.



2a–2g **3a–3g** **4a, 4b, 4d–4f**

R =
a. Me e. Bu
b. Et f. *sec*-Bu
c. Pr g. Ph
d. 2-Pr

Scheme 1.

products, as determined by ^{1}H NMR spectroscopy (see Table IV), were mixtures of anomers, with the β-L anomer predominating for every example, due presumably to the favored 1,2-*trans* disposition of the substituents between C-1 and C-2 (L-sugar numbering). The α- and β-anomeric resonances were differentiated by

TABLE I

^{1}H NMR spectral data [a] for compounds **3a–3g**

Compound No.	Chemical shifts (δ) and apparent first-order couplings (Hz)								
	H-2a	H-2b	H-3	H-4	H-5a	H-5b	C_nH_{2n}	CH_3	Other
3a	2.23dd [b] (J_{AX} 8.6, J_{AB} 16.9)	2.77dd [b] (J_{BX} 8.6)	2.53m	4.16m	3.67dd [b] (J_{AX} 4.5, J_{AB} 12.7)	3.93dd [b] (J_{BX} 2.5)		1.18d (J 6.7)	
3b	2.24m [c]	2.77dd [b] (J_{BX} 8.0, J_{AB} 16.4)	2.36m	4.25m	3.67dd [b] (J_{AX} 4.6, J_{AB} 12.7)	3.93dd [b] (J_{BX} 2.6)	1.53m [n = 1]	0.97t (J 7.4)	
3c	2.24dd [b] (J_{AX} 8.4, J_{AB} 16.8)	2.75dd [b] (J_{BX} 8.3)	2.42m	4.22m	3.64dd [b] (J_{AX} 4.6, J_{AB} 12.7)	3.91dd [b] (J_{BX} 2.1)	1.42m [n = 2]	0.94t (J 6.9)	2.10t (J 6.2) 5-OH
3d	2.33m [c]	2.71dd [b] (J_{BX} 8.2, J_{AB} 16.5)	2.33m	4.38m	3.64dd (J_{AX} 4.9, J_{AB} 12.5)	3.93m		0.93d [d] (J 2.8) 0.96d (J 2.8)	1.73sp $CHMe_2$
3e	2.24dd [b,c] (J_{AX} 8.1, J_{AB} 16.9)	2.76dd [b] (J_{BX} 8.3)	2.40m	4.23m	3.66dd [b] (J_{AX} 4.5, J_{AB} 12.6)	3.92dd [b] (J_{BX} 2.4)	1.40m [n = 3]	0.91t (J 6.3)	3.05bs 5-OH
3f [e]	2.31m [c]	2.69m	2.31m	4.24m	3.66m	3.90m		0.92m	1.34m $-CH_2-CH$
3g	2.78dd [b] (J_{AX} 9.7, J_{AB} 17.8)	3.04dd [b] (J_{BX} 9.1)	3.03m	4.56m	3.03 [c]	3.95dd [b] (J_{BX} 2.3, J_{AB} 12.8)			4.80bs 5-OH [f]

[a] Spectra were obtained at 200 MHz in $CDCl_3$ with Me_4Si as internal standard. Values are downfield (ppm) from Me_4Si. Spin–spin splittings are apparent, first-order values reported in Hz (in parentheses): d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; sp, septet; and t, triplet. [b] AB of an ABX system. Absolute assignments for H-2a (or H-5a) and H-2b (or H-5b) are uncertain. J_{AX} or J_{BX} may be interchanged. [c] Partially obscured by H-3. [d] CH_3 groups are nonequivalent. [e] Mixture of diastereomers. [f] ArH 7.25–7.42 m (5 H).

TABLE II

Physicochemical data for compounds **3a–3g**, **4a**, **4b**, and **4d–4f**

Compound no.	Method [a]	Yield (%)	TLC		Physical State	Optical Rotation $[\alpha]_D^c$ (c, $CHCl_3$)	Formula	Elemental Analysis				Ref
			(R_f)	Solvent [b]				Calculated		Found		
								C	H	C	H	
3a	A	62	0.17	A	syrup							[d]
3b	A	55	0.28	A	syrup	+60.7, 4.80	$C_7H_{12}O_3$	58.32	8.39	58.18	8.40	
3c	A	66	0.33	A	syrup	+70.8, 2.45	$C_8H_{14}O_3$	60.74	8.92	60.62	8.95	
3d	A	66	0.24	A	syrup	+40.2, 4.05	$C_8H_{14}O_3$	60.74	8.92	60.83	8.94	
3e	A	91	0.36	A	syrup	+47.4, 10.30	$C_9H_{16}O_3 \cdot 0.13H_2O$	61.93	9.36	61.97	9.29	
3f	A	81	0.29	A	syrup	[e]	$C_9H_{16}O_3$	62.77	9.36	62.55	9.38	
3g	A	90	0.30	A	crystal [f]	172.5, 4.25	$C_{11}H_{12}O_3$	68.74	6.29	68.64	6.30	
4a	B	49	0.21	B	syrup	[e]	$C_7H_{10}O_4$	53.16	6.37	53.10	6.41	[g]
4b	B	48	0.24	B	syrup	[e]	$C_8H_{12}O_4 \cdot 0.18H_2O$	54.78	7.10	54.73	6.92	
4d	B	54	0.27	B	syrup	[e]	$C_9H_{14}O_4$	58.05	7.58	57.96	7.57	
4e	B	58	0.33	B	syrup	[e]	$C_{10}H_{16}O_4$	59.98	8.06	59.85	8.10	
4f	B	53	0.28	B	syrup	[e]	$C_{10}H_{16}O_4$	59.98	8.06	59.84	8.06	

[a] *A*, Detritylation and B, periodate cleavage reactions are described in the Experimental section. [b] Solvents include the following: A, 4:6 hexanes–EtOAc; B, 8:2 hexanes–EtOAc. [c] t, 22±1°C. [d] See ref 11. [e] No optical rotations were determined on mixtures of isomers. [f] mp 84–85°C. [g] See ref 12.

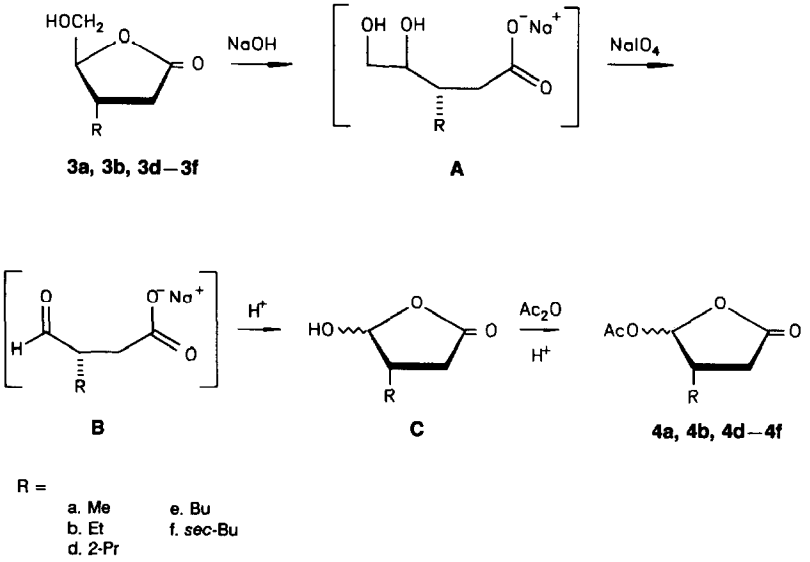
TABLE III

Mass spectral data for compounds **3a–3g**, **4a** and **4b**, and **4d–4f**

Compound no.	Mass-spectral peaks (relative intensities and probable assignments in parenthesis)
3a	131 (0.2, $[M+1]^+$), 130 (1.0, $[M]^+$), 113 (0.2, $[M+1-H_2O]^+$), 112 (2.2, $[M-H_2O]^+$), 101 (0.7, $[M+2-CH_3O]^+$), 100 (7.9, $[M+1-CH_3O]^+$), 99 (100, $[M-CH_3O]^+$), 71 (34.6), 43 (31.4, $[C_2H_3O]^+$), 41 (28.8)
3b	144 (0.8 $[M]^+$), 127 (1.0, $[M+1-H_2O]^+$), 126 (2.2, $[M-H_2O]^+$), 115 (1.2, $[M+2-CH_3O]^+$), 114 (6.5, $[M+1-CH_3O]^+$), 113 (100, $[M-CH_3O]^+$), 67 (32.3), 57 (35.5), 43 (23.7, $[C_2H_3O]^+$), 41 (48.8)
3c	158 (0.3, $[M]^+$), 141 (0.3, $[M+1-H_2O]^+$), 140 (1.6, $[M-H_2O]^+$), 129 (0.7, $[M+2-CH_3O]^+$), 128 (8.0, $[M+1-CH_3O]^+$), 127 (100.0, $[M-CH_3O]^+$), 115 (0.4, $[M-C_3H_7]^+$), 81 (48.4), 55 (27.8), 43 (36.1, $[C_2H_3O]^+$), 41 (25.5)
3d	158 (0.5, $[M]^+$), 141 (1.5, $[M+1-H_2O]$), 140 (0.9, $[M-H_2O]^+$), 129 (0.8, $[M+2-CH_3O]^+$), 128 (8.0, $[M+1-CH_3O]^+$), 127 (100, $[M-CH_3O]^+$), 81 (61.5), 55 (27.2), 43 (26.4, $[C_2H_3O]^+$), 41 (27.2)
3e	172 (0.5, $[M]^+$), 155 (1.3, $[M+1-H_2O]^+$), 154 (1.1, $[M-H_2O]^+$), 143 (1.0, $[M+2-CH_3O]^+$), 142 (7.9, $[M+1-CH_3O]^+$), 141 (89.7, $[M-CH_3O]^+$), 95 (100), 81 (65.5), 69 (78.8), 57 (32.7, $[C_4H_9]^+$)
3f	172 (0.5, $[M]^+$), 154 (1.3, $[M-H_2O]^+$), 143 (0.9, $[M+2-CH_3O]^+$), 142 (8.5, $[M+1-CH_3O]^+$), 141 (100, $[M-CH_3O]^+$), 95 (32.7), 85 (52.2), 69 (41.1), 57 (23.4, $[C_4H_9]^+$)
3g	192 (1.4, $[M]^+$), 175 (1.7, $[M+1-H_2O]^+$), 174 (7.2, $[M-H_2O]^+$), 162 (2.9, $[M+1-CH_3O]^+$), 161 (20.7, $[M-CH_3O]^+$), 146 (23.3), 105 (32.8), 104 (100), 91 (19.5, $[C_7H_7]^+$
4a	115 (2.8, $[M-C_2H_3O]^+$), 114 (2.4, $[M-CO_2]^+$), 99 (100, $[M-C_2H_3O_2]^+$), 72 (22.4), 71 (32.1), 43 (52.2, $[C_2H_3O]^+$)
4b	129 (2.4, $[M-C_2H_3O]^+$), 128 (2.1, $[M-CO_2]^+$), 113 (100, $[M-C_2H_3O_2]^+$, 99 (2.4, $[M-C_3H_5O_2]^+$), 86 (36.5), 56 (70.0), 43 (91.7, $[C_2H_3O]^+$
4d	143 (1.8, $[M-C_2H_3O]^+$), 142 (0.5, $[M-CO_2]^+$), 127 (81.4, $[M-C_2H_3O_2]^+$), 81 (30.3), 70 (93.7), 55 (67.0), 43 (100, $[C_2H_3O]^+$)
4e	157 (1.4, $[M-C_2H_3O]^+$), 141 (36.5, $[M-C_2H_3O_2]^+$), 86 (39.4), 84 (100, $[C_4H_4O_2]^+$), 43 (45.3, $[C_2H_3O]^+$)
4f	157 (1.4, $[M-C_2H_3O]^+$), 141 (67.0, $[M-C_2H_3O_2]^+$), 85 (36.9), 84 (75.5), 69 (100), 57 (15.9), 43 (21.5, $[C_2H_3O]^+$)

NOE experiments, and the hydrogens in the *cis* configurations (i.e., for the α-L anomers) were shown to have the larger spin–spin couplings ($J_{1,2}$ 4.4 to 5.1 Hz compared to the J_{trans} couplings of 1.1 to 1.9 Hz; see Table IV). Other resonances were determined to support the assigned structures, although some of the resonances of the minor α-L anomers were obscured by those of the major components. Mass spectral data (Table III) further supported these structures with prominent M – Ac peaks observed as the highest mass peaks for each example. The syrupy products all gave acceptable elemental analyses (Table II).

Inasmuch as intermediate **B** could possibly enolize during the reaction (Scheme 2) and lose its optical integrity at C-2, a sample of **4d** was enriched in the



Scheme 2.

predominating β-L anomer by column chromatography to an α : β ratio of 1.0 : 22.2, examined by optical rotation, and determined to be optically active {$[\alpha]_D^{22}$ + 92.4° (*c* 0.6, $CHCl_3$)}. Thus **B** did not extensively racemize during the process of glycol cleavage and ring closure.

Antitumor evaluation.—Compounds **4a** and **4b** and **4d–4f** were examined for antitumor activity in cultures of proliferating L1210 murine leukemia cells according to the procedure of Leopold and co-workers[8]. Whereas acetomycin (**1**) showed an ID_{50} = 3.38 μg/mL (see Table V), the simplified analogues showed ID_{50} values ten-fold and greater, indicating far less potency than that of the parent **1**. Thus the substituents at C-3 (i.e., at the quaternary center) are apparently important factors in determining the antitumor activity shown by **1**. A total synthesis of **1**, which incorporates the difficult-to-synthesize quaternary center at C-3 by two lengthy processes, has been reported[9,10].

EXPERIMENTAL

General.—For general procedures, refer to the preceding paper[7].

*Detritylation of 3-C-alkyl-2,3-dideoxy-5-O-triphenylmethyl-*D-erythro-*pentono-1,4-lactones* (**2a–2g**) *to give 3-C-alkyl-2,3-dideoxy-*D-erythro-*pentono-1,4-lactones* (**3a–3g**).—To a solution of 5-*O*-trityl lactone **2a–2g** (3 mmol) (ref 7) in MeOH (15 mL) and CH_2Cl_2 (10 mL) was added concd HCl (0.5 mL). The mixture was stirred for 1 h at room temperature, at the end of which time TLC (7 : 3 hexanes–EtOAc) showed the absence of starting material. The solvent was evaporated at ca. 30°C, and the resulting syrupy product was chromatographed on a column of silica gel (40 g, 60–200 mesh ASTM) eluting with 4 : 6 hexanes–EtOAc. For yield and

TABLE IV

^{1}H NMR spectral data [a] for compounds **4a**, **4b**, and **4d–4f**

Compound [b] no.		Chemical shifts (δ) and apparent first-order couplings (Hz)						
		H-1	H-2	H-3b	H-3a	OAc	CH_3	Other
4a [d]	α	6.57d ($J_{1,2}$ 5.1)	2.75m	2.33dd [c] (J_{BX} 11.7, J_{AB} 17.3)	2.60dd [c] (J_{AX} 8.3)	2.12s	1.15d (J 6.64)	
	β	6.24d ($J_{1,2}$ 1.1)	2.55m	2.17dd [c] (J_{BX} 2.8, J_{AB} 17.6)	2.88dd [c] (J_{AX} 8.3)	2.14s	1.20d (J 7.34)	
4b	α	6.61d ($J_{1,2}$ 4.9)			[e]	2.13s		
				2.10–3.19m			0.96m	1.40–1.68m
	β	6.32d ($J_{1,2}$ 1.3)			2.85dd [c] (J_{AX} 8.2, J_{AB} 17.6)	2.12s		CH_2
4d	α	6.61d ($J_{1,2}$ 4.5)	2.10–3.00m		[e]	2.13s		
	β	6.40d ($J_{1,2}$ 1.9)	2.29m	2.34dd [c] (J_{BX} 4.4, J_{AB} 18.9)	2.78dd [c] (J_{AX} 10.1)	2.12s	0.98d 0.95d	1.91sp CH
4e	α	6.58d ($J_{1,2}$ 4.9)			[e]	2.13s		
			2.04–2.63m				0.91m	1.18–1.65m
	β	6.31d ($J_{1,2}$ 1.4)			2.84dd [c] (J_{AX} 8.4, J_{AB} 17.7)	2.12s		$(CH_2)_3$
4f [f]	α	6.62d ($J_{1,2}$ 4.4)			[e]	2.13s		
			2.10–2.84m				0.92m	1.11–1.66m
	β	6.42d ($J_{1,2}$ 1.9)			2.85m	2.12s		CH_2-CH

[a] Spectra were obtained at 200 MHz in $CDCl_3$ with Me_4Si as internal standard, except where noted otherwise. δ-Values are downfield (ppm) from Me_4Si. Spin–spin splittings are apparent, first-order values reported in Hz (in parentheses): d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; sp, septet. [b] Note that compounds **4a** and **b**, and **4d–f** are L-*glycero*-tetrurono-1,4-lactones; hence, β- is "up" and α- is "down" as depicted in Scheme 1. $\alpha:\beta$ Ratios: **4a**, 1:2.2; **4b**, 1:2.4; **4d**, 1:3.3; **4e**, 1:2.6; and **4f**, 1:4.5. Resonances other than H-1 for the minor components were often obscured by those of the major components. [c] AB of an ABX system. Absolute assignments for H-3a and H-3b are uncertain. J_{AX} or J_{BX} may be interchanged. [d] Determined at 360 MHz. [e] H-2 and H-3b overlap. The pattern is complicated by resonances from both α and β anomers. [f] Mixture of diastereomers due to chiral group at C-3.

physicochemical data see Table II; for mass spectral data, see Table III, and for ^{1}H NMR data, see Table I. Typical infrared data (**3a–3f**, neat) show 3440, 2960, 1780, 1460, 1010, and 936 cm^{-1}; (**3g**, KBr) 3482, 2950, 2925, 1770, 1455, 1008, and 940 cm^{-1}.

*1-O-Acetyl-2-C-alkyl-2,3-dideoxy-α-β-*L-glycero-*tetrurono-1,4-lactones* (**4a** *and* **4b**, *and* **4d–4f**).—Pentono-1,4-lactone **3a** or **3b** or **3d–3f** (1.27 mmol) was suspended in

TABLE V

Assays of compounds **1**, **4a** and **4b**, and **4d–4f** for antiproliferative activity against L1210 murine leukemia cells in vitro [a]

Compound no.	IC_{50} Titer Against L1210 in vitro	
	(g/mL)	($M \times 10^4$)
1	3.38	0.158
4a	92.5	5.85
4b	36.5	2.12
4d	≥ 80.0	≥ 4.30
4e	98.0	4.89
4f	≥ 100	4.99

[a] According to the procedure in ref 8. [b] IC_{50}, Inhibitory concentration for 50% inhibition of proliferating L1210 cells. The values are the mean values of two experiments.

a solution of NaOH (0.20 g, 5.2 mmol) in water (5 mL) and stirred for 30 min at room temperature, at the end of which time a solution had formed. Dry ice was added until the solution reached pH 8, and the solution was cooled to and maintained at 0°C while a solution of $NaIO_4$ (0.38 g, 1.9 mmol) in water (15 mL) was added dropwise with stirring over 15 min. The mixture was allowed to stir for another 30 min at 0°C, after which time the pH was adjusted to pH 2 with concd HCl. The aqueous solution was extracted consecutively with $CHCl_3$ (2 × 50 mL), EtOAc (2 × 50 mL), and diethyl ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvents were evaporated at < 30°C. The residue * was dissolved in anhyd CH_2Cl_2 (10 mL), and to this solution was added Ac_2O (0.32 mL, 3.5 mmol) and Amberlyst-15 [H^+] resin (~ 250 mg). After 8 h the resin was filtered, and the filtrate was washed with satd aq $NaHCO_3$ (3 × 20 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The crude product was chromatographed over silica gel, using 7:3, hexanes–EtOAc as eluent to give the pure products **4a** or **4b**, or **4d–4f**. Typical IR spectral data (neat): 2965, 2940, 2880, 1800, 1760, 1370, 1220, 1153, and 980 cm^{-1}. Yields and other physicochemical data are provided in Table II, mass spectral data in Table III, and ^1H NMR data in Table IV.

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* The ^1H NMR spectrum ($CDCl_3$ for the 2-(2-propyl) analogue [C (where R = 2-propyl) in Scheme 2] was as follows: δ 5.81 (d, 1 H, $J_{1,2}$ 4.6 Hz, α-H-1), 5.63 (d 1 H, $J_{1,2}$ 3.26 Hz, β-H-1), 2.79 (dd, A of an ABX, 1 H, $J_{A,X}$ 9.0, $J_{A,B}$ 17.9 Hz, β-H-3a), 1.90–2.50 (m, 6 H, β- and α-H-2, β- and α-, H-3b, α-H-3a, α-CH), 1.70–1.88 (sp, β-CH), 0.96 [m, 6 H, β- and α-$(CH_3)_2$].

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