Table I. OD(cation):OD(radical) Ratios and Cation Decay Rate Constants (20 ± 1 °C)

cation[a]	precursor[b]	solvent	λ_{max} R^+, $R^\bullet$	$OD(R^+)/OD(R^\bullet)$[c]	k_s,[d] s^{-1}	k_{az},[e] M^{-1} s^{-1}
$4,4'\text{-}(MeO)_2D^+$	-OAc, -OAr	1:4 AN:W	500, 350	0.6[f], 0.6[g]	1.0×10^5[h]	$(4.2 \pm 0.2) \times 10^9$
		MeOH		0.4[g]	8.4×10^6	$(9.0 \pm 0.3) \times 10^9$
		TFE			1.4×10^1	
4-Me, 4'-$MeOD^+$	-OAc, -OAr	1:4 AN:W	475, 345	0.6[f], 0.5[g]	8.2×10^5[h]	$(6.7 \pm 0.4) \times 10^9$
		TFE		0.7[f]	2.8×10^2	
4-$MeOD^+$	-OAc, -OAr	1:4 AN:W	455, 345	0.6[f], 0.4[g]	2.0×10^6[h]	$(6.9 \pm 0.4) \times 10^9$
		TFE		0.5[g]	1.2×10^3	
$3,4'(MeO)_2D^+$	-OAc	1:4 AN:W	440, 345	≥10	2.5×10^6[h]	$(7.1 \pm 0.3) \times 10^9$
	-OH	W	440, 345	2.0	2.1×10^6[h]	$(7.2 \pm 0.5) \times 10^9$
4-CF_3, 4'-$MeOD^+$	-OAr	1:4 AN:W	440, 345	2.0	4.4×10^6	$(6.7 \pm 0.4) \times 10^9$
$4,4'\text{-}Me_2D^+$	-OAr	1:4 AN:W	460, 335	~1.0	3.2×10^7	$(6.5 \pm 1.0) \times 10^9$
		TFE		0.8	2.4×10^4	
4-MeD^+	-OAr	TFE	450, 335	0.6	2.7×10^5[h]	
D^+	-OAr	TFE	440, 330	0.3	3.2×10^6	
9-xanthylium(X^+)	-OH	W	365	>10	1.3×10^4	$(5.7 \pm 0.1) \times 10^9$
AnC^+HCH_3	-OAc	TFE	340, 300	~0.3	3.5×10^5[i]	$(5.6 \pm 0.5) \times 10^9$
	$AnCH{=}CH_2$	TFE	340	>10	3.7×10^5[h]	
$Ph_2C^+CH_3$	$Ph_2C{=}CH_2$	TFE	425	>10	1.6×10^5	

[a] $D^+ \equiv Ar_2CH^+$. [b] OAc ≡ acetate. OAr = *p*-cyanophenyl ether. [c] Measured 30-35 ns after pulse initiation. In order to calculate from this ratio the concentrations of cation and radical, the extinction coefficients for R^+ and $R^\bullet$ have to be known. [d] First-order rate constant for cation decay. [e] Second-order rate constant for reaction with azide, from slope of plot of *k*(decay) versus [azide] for 4-6 azide concentrations from 0-1 mm. [f] For OAc. [g] For OAr. [h] Optical and conductivity detection. [i] Conductivity detection only. Overlap with radical perturbs optical decay traces.

observed upon photolysis of *p*-methoxystyrene. This is an example of alkene photoprotonation,[3c] with the solvent presumably the proton donor. As a second example, the tertiary $Ph_2C^+CH_3$ was observed on photolyzing $Ph_2C{=}CH_2$ in TFE.

The parent diphenylmethyl cation, its mono 4-Me derivative, and AnC^+HCH_3 were observed on photolysis of the *p*-cyanophenolates or acetate in TFE but not in 1:4 AN:W, though products indicate cation intermediate. Thus, in the aqueous solvent these cations must decay within the 20 ns laser pulse. TFE may be an important solvent for the study of photochemical reactions involving cations, since it is sufficiently polar to support cation production but is significantly less nucleophilic than water. As shown by the one example in Table I, methanol as a solvent is more nucleophilic than water. The Ph_2CH^+ ion and even $PhCH_2^+$ have been seen with the use of pulse radiolysis in halocarbon solvents.[11] Such solvents, however, will make it difficult to photolytically produce cations, while in more polar solvents where they can be formed, cations can be short-lived, as shown with the examples noted above. As a further example, we have observed only $PhCH_2^\bullet$ upon photolysis under a variety of conditions of $PhCH_2OAc$ and $PhCH_2Cl$.

The high reactivity of azide makes it an excellent indicator of cation in time-resolved experiments. This nucleophile has seen extensive study in ground-state solvolysis reactions, with the azide:water ratios k_{az}/k_s as determined by product analyses being a widely cited example of a reactivity–selectivity relationship, in that less stable cations are less selective.[12] A recent interpretation is that for reactive cations the azide combination is diffusion-limited, so that changes in k_{az}/k_s merely reflect changes in k_s.[13,14] The measurements reported here provide a direct proof of this. The k_{az} values for the diarylmethyl cations in 1:4 AN:W are $(7 \pm 0.5) \times 10^9$ M^{-1} s^{-1}, with only the bis-*p*-methoxy derivative slightly below this limit. Azide has recently served as a "clock" for the determination of cation reactivities, the k_{az}/k_s product ratios being converted to absolute k_s values with the assumption that $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}.[14] Our results also establish that this approach is valid, with the recognition that k_{az} limit is not uniformly 5×10^9 M^{-1} s^{-1}.[15]

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(15) This was not intended as a precise value.[14]

Total Synthesis of Both (+)-Compactin and (+)-Mevinolin. A General Strategy Based on the Use of a Special $TiCl_3/C_8K$ Mixture for Dicarbonyl Coupling

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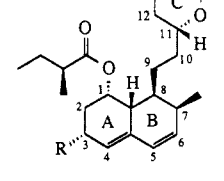
The two fungal metabolites (+)-compactin (**1a**)[2] and the biologically more powerful (+)-mevinolin (**1b**)[3] have been subject to intense scientific examination because of their relevance to the treatment of elevated levels of blood cholesterol.[3a,4]



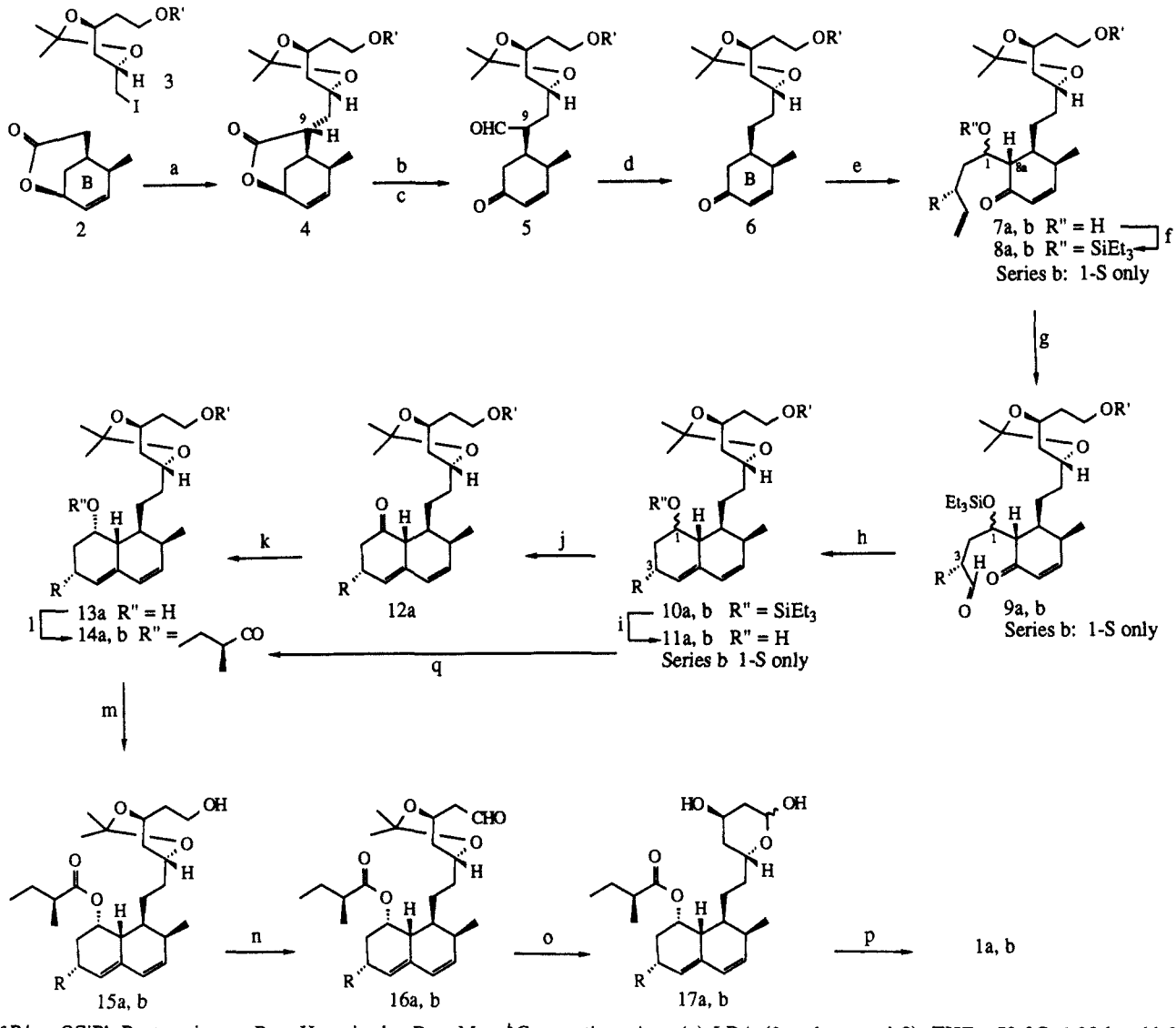
1a R = H
1b R = Me

We report a synthesis[5-7] of both compounds by reactions that proceed with high levels of stereoselection. Our aim was to develop a method that could provide, without the need for extensive redesign, a variety of substances that differ in the nature of the

(1) Dedication: To the memory of my father.

0002-7863/88/1510-6914$01.50/0

Scheme I[a,b]



[a] R' = $OSiPh_2Bu$-*t*; series a: R = H; series b: R = Me. [b] Compactin series: (a) LDA (2 mol per mol **2**), THF, −78 °C, 1.25 h; add **3** in THF–HMPA (2:1), −78 °C; room temperature, 12 h; 77% after correction for recovered pure **2** (54%). (b) DIBAL, CH_2Cl_2, −78 °C, 1.5 h; 90%. (c) MnO_2, AcONa, $CHCl_3$, room temperature; 69 h; 78%. (d) $(Ph_3P)_3RhCl$, PhMe–MeCN (8:1), reflux, 2.5 h; 50%; (e) LDA, Et_2O, −78 °C; add **6**; −78 °C, 1 h; add 4-pentenal, −78 °C, 10 min; 75%. (f) Et_3SiCl, *i*-Pr_2NH, DMAP (catalyst), Et_2O, room temperature, 36 h; 96%. (g) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C, 20 min, room temperature, 8 h; 78% after correction for recovered pure **8a** (12.5%). (h) C_8K, $TiCl_3$, DME; addition of **9a** over 9 h; room temperature, 5 h, reflux, 3 h; 85%. (i) 48% w/v aqueous HF diluted 50-fold with MeCN, room temperature, 1.75 h; 2-methoxypropene, pyridinium *p*-toluenesulfonate (catalyst), CH_2Cl_2, 0 °C, 40 min; 85% overall. (j) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; add **11a**, 15 min, −78 °C; Et_3N, −78 °C, 5 min; warm to room temperature over 20 min; 93% after correction for recovered pure **11a** (18%). (k) L-Selectride, THF, −78 °C, 1 h; −43 °C, 12 h; 80%. (l) (*S*)-2-Methylbutyric anhydride, DMAP (catalyst), Et_3N, CH_2Cl_2, room temperature, 68 h; 99%. (m) $Bu_4N^+F^-$, THF, room temperature, 1.75 h; 92%. (n) $(COCl)_2$, DMSO, CH_2Cl_2 −78 °C; add **15a**, 20 min, −78 °C; Et_3N, −78 °C, 10 min; warm to room temperature over 30 min; 91%. (o) 1.3 N HCl, THF, room temperature, 2 h; 88%. (p) Ag_2CO_3/Celite, PhMe, 95 °C, 2 h; 61%. Mevinolin series: (a), (b), (c), and (d) same as above. (e) LDA, Et_2O, −78 °C; add **6**; −78 °C, 45 min; add (3*R*)-3-methyl-4-pentenal, −78 °C, 10 min; 78%. (f) Et_3SiCl, *i*-Pr_2NH, DMAP, Et_2O, room temperature, arbitrarily stopped after 24 h; 85% after correction for recovered pure **7a** (19.5%). (g) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C, then remove cold bath, 3 h; 85% after correction for recovered pure **8b** (30%), see ref 16. (h) C_8K, $TiCl_3$, DME; addition of **9b** over 9 h; room temperature, 5 h, reflux, 4 h; 86%. (i) $Bu_4N^+F^-$, THF, room temperature, 22 h; *t*-$BuPh_2SiCl$, CH_2Cl_2, Et_3N, DMAP (catalyst), room temperature, 24 h; 94% overall. (m) $Bu_4N^+F^-$, THF, room temperature, 3 h; 95%. (n) $(COCl)_2$, DMSO, CH_2Cl_2 −78 °C; add **15b**, 20 min, −78 °C; Et_3N, −78 °C, 10 min; warm to room temperature over 20 min; 97%. (o) 1.3 N HCl, THF, room temperature, 4 h; 97%. (p) Ag_2CO_3/Celite, PhMe, 90 °C, 1 h; 77%. (q) (*S*)-2-Methylbutyric anhydride, DMAP, Et_3N, CH_2Cl_2, room temperature, arbitrarily stopped after 88 h; 97% after correction for recovered pure **11b** (9.6%).

substitution of ring A. The method we used (Scheme I) involves attaching ring A to the preformed BC ring system **6**, itself assembled from two homochiral units **2**[8] and **3**.[10]

Deprotonation of bicyclic lactone **2** with an excess of LDA followed by treatment with iodide **3** gave the coupled product **4**

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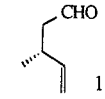
in 77% yield (after correction for recovered **2**) as a single isomer with the stereochemistry at C-9 tentatively assigned as shown.[14] Treatment of the coupled material with DIBAL produced a mixture of lactols which, on allylic oxidation, afforded the keto aldehyde **5** as a single substance, whose stereochemistry at C-9 was not determined. Decarbonylation of **5** served to form compound **6**. This is a key intermediate because it represents, in suitably protected form, the complete BC ring system of both (+)-compactin and (+)-mevinolin.

For synthesis of compactin, ketone **6** was deprotonated kinetically and condensed with 4-pentenal[15] to produce **7a** (as a mixture of C-1 epimers). The stereochemistry at C-8a was as shown, the aldehyde having approached the less hindered face of the enolate generated from **6**. The fact that two epimers are obtained does not matter as the stereochemistry at C-1 is easily adjusted later. Silylation (**7a** → **8a**) followed by ozonolysis[16] yielded keto aldehydes **9a**. These were subjected to a modified version of the McMurry reaction,[17] namely, use of the following *relative* molar amounts of reagents: keto aldehyde (1):C_8K (34):$TiCl_3$ (17) in DME.[18] Any departure from these proportions always gave drastically reduced yields.[19] The cyclized products **10a** were desilylated and subjected to ketalization conditions in order to compensate for partial loss of the ketal group (**10a** → **11a**, 85%). The epimeric alcohols **11a** were oxidized, and the resulting ketone **12a** was treated with L-Selectride to form a single alcohol **13a**. This was acylated (**13a** → **14a**) with (*S*)-2-methylbutyric anhydride[20] (99% yield), at which point all that was required to complete the synthesis was elaboration of the lactone. To prepare for that, the ester **14a** was desilylated, and the resulting alcohol **15a** was oxidized to aldehyde **16a**. Treatment with dilute hydrochloric acid produced the lactols **17a**. Finally, oxidation with Fêtizon's reagent[21] generated synthetic (+)-compactin (61%). The substance was indistinguishable [^{1}H NMR (400 MHz), ^{13}C NMR (50.32 MHz)], from natural material and had mp 148–151 °C [lit.[2] 152 °C] and $[\alpha]^{30}_D$ +218.6° (*c* 0.38749, CH_2Cl_2). The natural compound had $[\alpha]^{29}_D$ +221.2° (*c* 0.32873, CH_2Cl_2).

In order to synthesize (+)-mevinolin an entirely comparable sequence was followed, except that the aldol condensation was carried out with aldehyde **18b**.[22] Unlike the situation in the



18b

compactin series, only a single aldol (**7b**) was isolated (78% yield), and its stereochemistry at C-1 had the desired α configuration. Silylation (**7b** → **8b**), ozonolysis (**8b** → **9b**),[16,24] and intramolecular McMurry coupling under our special conditions gave **10b** (86%). A slightly different sequence from that used in the compactin series was then applied: Both silyl-protecting groups of **10b** were removed by exposure to tetrabutylammonium fluoride, a reagent which left the ketal unit intact. Then the *tert*-butyldiphenylsilyl group was replaced by selective reaction at the primary hydroxyl. The alcohol produced (**11b**) was acylated with (*S*)-2-methylbutyric anhydride, bringing the sequence to **14b**, from which point only elaboration of the lactone remained. This was accomplished as before: Desilylation (**14b** → **15b**), oxidation (**15b** → **16b**), and acid treatment gave lactols **17b**. Lastly, Fêtizon oxidation produced (+)-mevinolin (77%). The synthetic compound was indistinguishable [^{1}H NMR (300 MHz), ^{13}C NMR (75.47 MHz)] from natural material and had mp 155.5–158.5 °C [lit.[3] 157–159 °C] and $[\alpha]^{27.5}_D$ +334.7° (*c* 0.254275, CH_3CN). The natural material had $[\alpha]^{27.5}_D$ +331.6° (*c* 0.10675, CH_3CN).

The above syntheses demonstrate a general route that can accommodate alterations to ring A and illustrate an annulation method based on an experimental modification of the classical McMurry process. This modification works well even in circumstances where (in our hands) the traditional methods[17] proceed poorly or not at all. Our experiments also show that an asymmetric center adjacent to a carbonyl group is not epimerized during this titanium-induced coupling.

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Supplementary Material Available: Spectral and analytical data for key compounds with evidence of enantiomeric purity and charts (appropriately annotated with experimental conditions and yields) showing the general strategy and the synthesis of **2**, **3**, and **18b** (10 pages). Ordering information is given on any current masthead page.

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(6) Synthesis of (+)-compactin: (a) Hsu, C.-T.; Wang, N.-Y.; Latimer, L. H.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 593. (b) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501. Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1983**, *24*, 3687. Girotra, N. N.; Reamer, R. A.; Wendler, N. L. *Tetrahedron Lett.* **1984**, *25*, 5371. (c) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251. (d) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc.* **1986**, *108*, 5908. (e) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. (f) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. (g) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1987**, *52*, 3541.

(7) Review: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

(8) Made (see Supplementary Material) by epimerization at C(1) of optically pure methyl (1*S*,6*S*)-6-methyl-3-cyclohexenecarboxylate [available by asymmetric Diels–Alder reaction (cf. ref 9)], homologation (–COOMe → –CH_2COOH), iodolactonization, and elimination of HI.

(9) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(10) Made (see Supplementary Material) from (*S*)-malic acid analogously to our reported procedure (ref 11) but with improvements (cf. ref 12 and 13).

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(14) Nonsystematic numbering is used in this publication.

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(16) The reaction should be stopped just short (ca. 10%) of completion. This endpoint is difficult to judge, especially on a small scale, and in some runs we stopped the ozonolysis too early. The apparatus of M. B. Rubin is useful: Rubin, M. B. *J. Chem. Educ.* **1964**, *41*, 388.

(17) Review: McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405. Mechanism: Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H. Y. *J. Org. Chem.* **1982**, *47*, 248.

(18) Typical procedure: C_8K (2.69 mmol) and $TiCl_3$ (1.25 mmol) were added successively to dry DME (15 mL), and the stirred mixture was heated under argon for 2 h. The suspension was cooled to room temperature, and a solution of the enone-aldehyde **9b** (0.0736 mmol) in DME (5 mL) was injected with stirring over 9 h. The mixture was stirred for a further 5 h at room temperature and then refluxed for 4 h.

(19) Typically in the range 0–32% for **9a** using $LiAlH_4/TiCl_3$; $LiAlH_4/TiCl_3/Et_3N$; Zn(Cu)/$TiCl_3$. With $C_8K/TiCl_3$ (molar ratios of C_8K, $TiCl_3$, and **9a**): 4.2:1:0.1 (0%); 3:1:0.1 (30%).

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(23) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(24) **9b** contained a small amount (6.3%) of the C-3 epimer. The titanium-coupling product **10b** contained 7% of the C-3 epimer. This impurity was removed during chromatographic isolation of **14b**. In making another analogue we have found that this type of problem can be avoided by using Florisil for chromatography after ozonolysis, rather than silica gel.