Kinetic Aldol Reactions of α-Keto Amides. Synthesis of the β-Methyl Glycosides of (-)-Cladinose and (+)-Mycarose

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The first examples of nondehydrative, kinetic aldol condensations of 3-methyl and 3-phenoxy-2-oxo (tertiary) carboxamides are reported. Addition of hydride or methyl Grignard nucleophiles to the aldol products produced diol or monoprotected triol amides with high stereoselectivity in some cases. One of these compounds was elaborated to the methyl glycosides of (-)-cladinose and (+)-mycarose.

Introduction

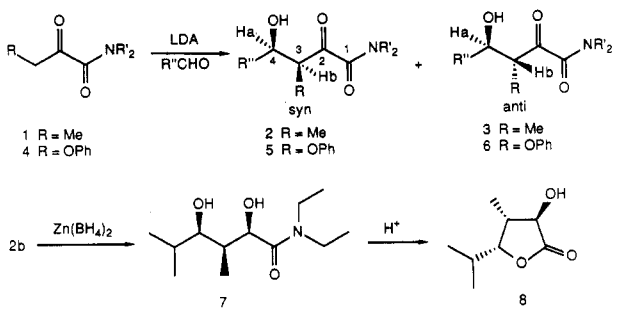
Several years ago we became interested in the enolate chemistry of α-oxocarboxyl compounds as potential methodology for the synthesis of highly oxygenated materials of the carbohydrate and polypropionate families.[1] A survey of the literature at that time revealed no examples of kinetic, nondehydrative aldol reactions involving these enolates as the donor moiety under aprotic conditions.[2-5] A series of trial reactions using 2-oxobutyric acid, its ethyl ester, and diethylamide quickly revealed the first two to be unsuitable in condensations run under standard, kinetic conditions (LDA/THF, -78 °C): the lithium carboxylate of the oxoacid is insoluble in THF-HMPA, and the highly enolic nature of the α-keto ester[6] prevented isolation of undehydrated aldol products.[4] The corresponding *N,N*-diethylamide, however, proved to be well behaved.

Results and Discussion

The results of reactions of the lithium enolate of *N,N*-dialkyl-2-oxobutyramides 1 with several aldehydes are shown in Table I, entries 1-4. Reactions were carried out in THF at -78 °C for 2 min and then quenched with acid at that temperature to minimize the opportunity for stereochemical equilibration via reversal or proton transfer. Longer reaction times or higher temperature did not improve yields, nor did the addition of more aldehyde, beyond the 1.2-1.5 equiv usually employed. Yields allowing for recovered **1** or **4** were generally 20-30% higher than those given in the table.

Coupling constants $J_{a,b}$ in the major (or exclusive) products obtained from **1** were uniformly in the 2-3.5-Hz range, suggesting syn structure **2** for these compounds.[7] Anti products **3**, when formed, could not be completely separated from the major syn isomers; their presence was indicated by the appropriate signals in the ^{1}H NMR spectrum, particularly that for H_a ($J_{a,b}$ = 5 Hz). The relative configuration of **2b** was confirmed by an experiment designed to assess the possibility of chelation-controlled reduction of the ketone carbonyl. Zinc borohydride reduction of **2b** in ether at 0 °C followed by acid catalyzed cyclization of intermediate diol **7** gave a single lactonic product (**8**), all four diastereomers of which have been unequivocally synthesized and well characterized.[8] Thus, the basic amide functionality of **2** is compatible with high stereoselectivity of the type observed with β-keto esters.[9]

We next turned our attention to the synthesis of vicinally oxygenated compounds via aldol reactions of *N,N*-dialkylphenoxypyruvamides **4**, easily prepared by the reaction of dilithium phenoxyacetate with the appropriate oxamate followed by in situ decarboxylation of the resultant β-keto acid. Results obtained with diethylamide



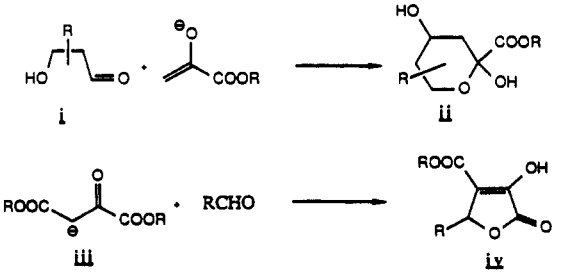
4a were not encouraging, as the derived lithium enolate showed only a moderate (3:2 → 4:1) bias toward the formation of anti products **6** ($J_{a,b}$ = 5.3 Hz). Switching to the bulky *N,N*-diisopropylamide **4b** considerably improved

(1) Koft, E. R.; Williams, M. D. *Tetrahedron Lett.* **1986**, *27*, 2227.

(2) However, for a stereoselective anti aldol reaction of an α-imino 2°-amide, see: Banks, B. J.; Barrett, A. G. M.; Russel, M. A.; Williams, D. J. *Chem. Commun.* **1983**, 873.

(3) (a) For nondehydrative aldol reactions of cyclohexane-1,2-dione dianions, see: Utaka, M.; Hojo, M.; Takeda, A. *Chem. Lett.* **1985**, 1471. (b) Very recently there has been reported the first kinetic aldol condensation of ethyl pyruvate leading directly to an α-hydroxybutenolide: Metternich, R.; Ludi, W. *Tetrahedron Lett.* **1988**, 3923. This reaction may be regarded as the pyruvate analogue of iii → iv in footnote 4.

(4) There are, however, numerous examples of the nondehydrative condensations, under protic conditions, of pyruvate and oxalacetate with aldoses to form 3-deoxy-2-octulosonic acid (KDO) or *N*-acetylneuraminic acid derivatives.[5] In most of these cases dehydration is prevented by trapping of the ketone carbonyl of the aldol adduct as a hemiketal (i → ii) or by rapid formation of a hydroxybutenolide (iii → iv) in which elimination is disfavored on stereoelectronic grounds.



(5) For representative examples of the chemical synthesis of KDO via aldol strategy, see: (a) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 324. (b) Schmidt, R. R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430.

(6) For structural effects on the enol content ($CDCl_3$) of simple α-keto esters, see: Coutrot, P.; Legris, C. *Synthesis* **1975**, 118.

(7) Heathcock, C. H. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3.

(8) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564. Rychnovsky, S. D. Ph.D. Thesis, Columbia University, 1985. We thank Professor Rychnovsky (University of Minnesota) for providing spectral data for **14**.

(9) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

† Deceased February 17, 1989; address correspondence concerning this paper to Professor Arthur G. Schultz at RPI.

‡ SWRI.

0022-3263/89/1954-2936$01.50/0

Table I. Condensations of Enolates of 1 and 4

entry	keto amide	R	R′	R″	yield, %	product(s)	syn:anti
1	**1a**	Me	Et	Ph	58	**2a**	syn only
2	**1a**	Me	Et	*i*-Pr	51	**2b**	syn only
3	**1a**	Me	Et	2-furyl	50	**2c**	syn only
4	**1b**	Me	*i*-Pr	Ph	60	**2d, 3d**	5:1
5	**4a**	PhO	Et	Me	50	**5a, 6a**	2:3
6	**4a**	PhO	Et	*trans*-1-propenyl	55	**5b, 6b**	1:3
7	**4b**	PhO	*i*-Pr	Me	63	**5c, 6c**	1:11
8	**4b**	PhO	*i*-Pr	vinyl	60	**6d**	anti only

Table II. Reactions of 6 with Nucleophiles (Nu)

ketone	R	Nu, solvent	products
6c	Me	MeMgCl, THF, −78 °C	**9b**
6d	vinyl	$NaBH_4$, EtOH, 25 °C	**9a, 10a** (1:2)
6d	vinyl	$Zn(BH_4)_2$, Et_2O, 0 °C	**9a**

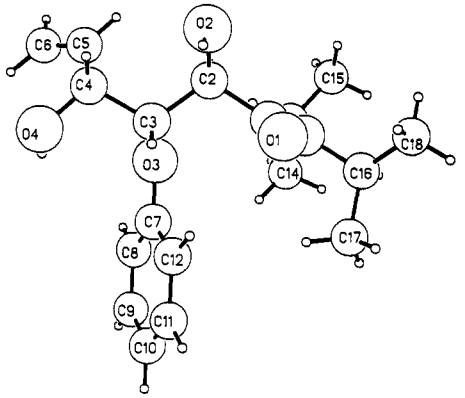
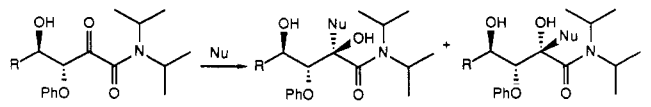


Figure 1. Structure and solid-state conformation of **9a**. Only one of the four molecules per asymmetric unit of the unit cell is shown.

stereoselectivity in the two cases examined (entries 7 and 8). It is not known whether this effect is due to substituent control of enolate geometry or transition-state topology, but the response of aldol stereoselectivity to the steric bulk of the α′ substituents in the present study follows the same trends established with other α-oxy enolate species.[7]

The stereochemical course of nucleophilic addition to the ketone carbonyl of **6** was found to vary according to reaction conditions (Table II). Reduction of **6d** with $NaBH_4$ in ethanol at 0 °C gave two products in a 2:1 ratio; the structure of the minor, crystalline diastereomer (**9a**) was determined by a single-crystal X-ray analysis (Figure 1).[10] The structure of the major $NaBH_4$ reduction product was, therefore, arabino diol **10a**. The crystallographic



6c,d

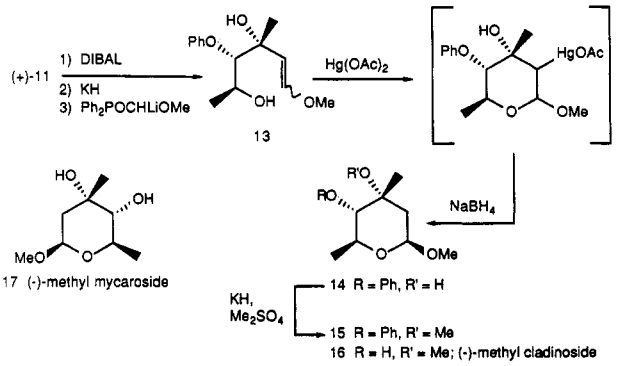
9a R = vinyl; Nu = H
9b R = Nu = Me

10a R = vinyl; Nu = H
10b R = Nu = Me

information also served to confirm the assignment of the phenoxypyruvamide aldol structure, which up until this point had been tentative, based on ^1H NMR coupling constants for C(3)H and C(4)H. The relationship of relative configuration to coupling constant is, therefore, the same in both the 3-methyl and 3-phenoxy series, probably as a result of six-membered ring intramolecular hydrogen bonding in each, even though a five-membered ring arrangement is possible in the latter. In contrast to the results with $NaBH_4$, reduction of **6d** with $Zn(BH_4)_2$ in ether

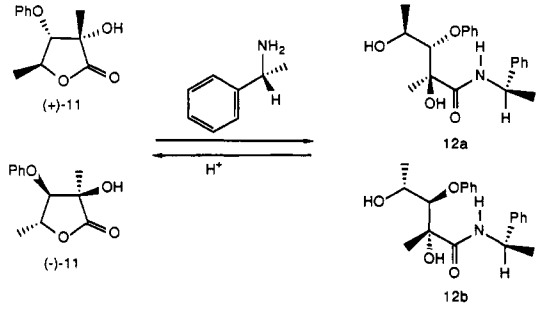
(10) Crystal data and atomic coordinates are contained in the supplementary material.

Scheme I



at 0 °C produced ribo isomer **9a** as the major product (>10:1). Similarly, addition of **6c** to 2.5 equiv of CH_3MgCl in THF at −78 °C gave ribo diol **9b** as the only detectable product of nucleophilic addition. Acid treatment of the crude reaction mixture furnished lactone **11**.[11,12]

Before homologation to pyranosides **16** and **17**, **11** was resolved efficiently via the method of Helmchen.[13] Heating **11** with (*R*)-(+)-α-methylbenzylamine gave diastereomeric amides **12a** and **12b**, which could be separated by either crystallization or chromatography. Stirring the individual amides with ether/aqueous 6 N H_2SO_4 at 25 °C in a two-phase system[14] gave (+)-**11** and (−)-**11**. Unfor-



tunately, the chemical shifts of the C-2 methyl groups in **12a** (1.70 ppm) and **12b** (1.68 ppm) were too close to make confident absolute configurational assignments of (+)- and (−)-**11** by application of the usual shielding/deshielding arguments.[15] The structures given for **11** and **12** ultimately rest on the conversion of (+)-**11** to the methyl glycoside of natural (−)-cladinose. Thus, (+)-**11** was first transformed into a 3:2 (*E*:*Z*) mixture of enol ethers **13** via

(11) Also produced was **10b**, via retroaldolization. Attempted addition of organolithium reagents to **12** led predominately to dehydration rather than nucleophilic attack or retroaldolization.

(12) While the present study was in progress, Scolastico and coworkers reported the preparation of unprotected, optically active **17** via a catalytic osmylation route: Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 491.

(13) Helmchen, G.; Nill, G.; Flockerzi, D.; Schule, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 62.

(14) These conditions are considerably milder than those given in ref 13 and may be of general value for resolution of sensitive lactones.

(15) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D, Ed.; Academic Press: New York, 1984; Vol. 1, pp 134–135.

a standard two-step sequence (Scheme I). Mercurioetherification–demercuration of **13** led to pyranoside **14** as a mixture of anomers or a single compound, depending on the time allowed to elapse before the reduction of the intermediate mercuriopyranosides. When $NaBH_4$ was added to the reaction mixture 20 min after $Hg(OAc)_2$ addition, **14** was isolated in 88% yield as a 10:1 mixture of equatorial and axial OCH_3 epimers, but after 90-min exposure to $Hg(OAc)_2$, only the former was produced in 85% yield. Proton-catalyzed equilibration (TsOH, CH_3OH) led to a 2.5:1 mixture favoring the equatorial glycoside; why the (presumably equatorial) HgOAc group in the equilibrating mercuriopyranosides leading to **14** should lend the equatorial glycoside increased stability is not apparent.

Interestingly, the ^1H NMR spectrum of **14** revealed that the tertiary alcoholic proton is coupled to the trans axial H at C(2) by ca. 2 Hz. Presumably the rigid W-shaped arrangement required for this relatively large coupling is enforced by intramolecular hydrogen bonding to the adjacent phenoxy oxygen. Methyl ether **15** was obtained in 96% yield by reaction of the potassium alkoxide of **14** with dimethyl sulfate. Removal of the phenyl protecting group via Li/NH_3 reduction followed by acidification (CH_3OH, PPTS, 25 °C) occurred in 88% yield without anomeric equilibration to afford (−)-methyl cladinoside (**16**), identical in all respects with the major isomer resulting from methanolysis[16] of (−)-erythromycin. The β-methyl glycoside of (unnatural) (+)-mycarose[17] was similarly prepared from (−)-**11** via an identical sequence, omitting the methyl ether formation step.

Experimental Section

General. IR spectra were recorded in the solvent indicated with a Perkin-Elmer 298 instrument. Proton NMR spectra were obtained with a Varian XL-200 spectrometer in $CDCl_3$ with Me_4Si and/or $CHCl_3$ as internal standard. Mass spectral data (70-eV electrical ionization; chemical ionization with methane or isobutane) was collected with a Hewlett-Packard 5987A instrument. Microanalyses were performed by Robertson Laboratory, Madison, NJ. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. All solvents are reagent grade and used without purification, except for THF, which was distilled from Na/benzophenone prior to use. Flash chromatography was performed with the solvents indicated, using Merck silica gel 60, 230–400 mesh, as adsorbent.

***N,N*-Diisopropylphenoxypyruvamide (4b).** Lithium diisopropylamide (0.22 mol) was prepared at 0 °C under N_2 in 200 mL of THF from 88 mL of *n*-BuLi and 34 mL (0.25 mol) diisopropylamine. This solution was stirred at −78 °C while a solution of phenoxyacetic acid (0.1 mol, 15.2 g) in 120 mL of THF was added over 5 min. After being stirred for 20 min, a solution of ethyl *N,N*-diisopropyloxamate (0.07 mol, 14.1 g) in 20 mL of THF was added rapidly. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and then acidified to pH 1 first with 2 N HCl and then with concentrated HCl (gas evolution). The acidified solution was stirred 30 min and then partitioned between H_2O and ether. The organic phase was washed successively with H_2O, 2 N NaOH, and brine. Drying (Na_2SO_4), filtration, and evaporation gave crude product, which was purified by flash chromatography (ethyl acetate/hexane, 1:10) to afford 12.2 g (66%) of **4b** as a thick oil. IR (CCl_4): 3040, 2970, 1715, 1630, 1595, 1445, 1220, 1210 cm^{-1}. 200-MHz NMR: δ 7.30–7.20 (m, 2 H), 7.06–6.92 (m, 3 H), 4.96 (s, 2 H), 3.81, 3.60 (septets, J = 7 Hz, 1 H each), 1.50, 1.23 (doublets, J = 7 Hz, 6 H each). MS, chemical ionization, m/e (rel intensity): 264 (M + 1, 100), 186 (20), 174 (16), 130 (15).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.12; H, 8.27; N, 5.41.

General Procedure for Aldol Condensations: (*R*,R)-4-Hydroxy-3-phenoxy-2-oxo-*N,N*-diisopropylvaleramide (6c).** LDA was prepared in the usual manner from 8 mL (20 mmol) of 2.5 M *n*-BuLi and 3.3 mL (24 mmol) of diisopropylamine in 20 mL of THF. The solution was cooled to −78 °C and 4.8 g (18.3 mmol) of **4b** in 15 mL of THF was added dropwise. After being stirred for 20 min, acetaldehyde (1.5 mL, freshly distilled from $MgSO_4$) was added rapidly. The reaction mixture was quenched with 2 N HCl after 1 min and then partitioned between H_2O and ether. The organic phase was washed with saturated $NaHCO_3$. Flash chromatography (ethyl acetate/hexane 1:5, SiO_2 deactivated with NH_3 vapor) of the residue obtained after drying (Na_2SO_4) and evaporation gave 3.66 g (63%) of product, mp 85–86 °C. IR: 3590, 3550–3200, 3050, 2985, 1710, 1620 (s), 1590, 1435, 1370, 1225 (s) cm^{-1}. 200-MHz NMR: δ 7.30–7.16 (m, 2 H), 6.97–6.86 (m, 3 H), 4.92 (d, J = 5.5 Hz, 1 H), 4.24–4.07 (m, 1 H), 3.77 (d, J = 5 Hz, O*H*), 3.76–3.57 (m, 1 H), 3.48–3.30 (m, 1 H), 1.38, 1.29, 1.06, 0.84, 0.68 (doublets, J = 7 Hz, 3 H each). MS m/e (rel intensity): 307 (M^+, 0.15), 289 (2), 263 (10), 133 (20), 128 (100).

Anal. Calcd for $C_{17}H_{25}O_4N$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.47; H, 8.29; N, 4.53.

The following aldol products were prepared from **1** or **4** and the appropriate aldehyde by using the foregoing procedure.

(*R*,R)-4-Hydroxy-3-phenoxy-2-oxo-*N,N*-diisopropyl-5-hexenamide (6d)**, mp 79–81 °C. IR ($CHCl_3$): 3590, 3540–3200, 3115, 2990, 1710, 1625, 1440, 1220 cm^{-1}. NMR δ 7.32–7.2 (m, 2 H), 7.05–6.92 (m, 3 H), 6.00 (ddd, J = 5, 10, 16 Hz, 1 H), 5.48 (ddd, J = 2, 2, 16 Hz, 1 H), 5.26 (ddd, J = 2, 2, 10 Hz, 1 H), 5.15 (d, J = 5 Hz, 1 H), 4.66 (m, $W_{h/2}$ = 11 Hz, 1 H), 4.10 (d, J = 7 Hz, 1 H), 3.70, 3.41 (septets, J = 7, 2 H), 1.38, 1.36, 1.09, 0.82 (d, J = 7 Hz, 3 H each). MS m/e (rel intensity) 319 (M^+, 0.1), 301 (2), 263 (11), 128 (100).

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.70; H, 7.80; N, 4.38.

(*R*,R)-4-Hydroxy-3-methyl-2-oxo-*N,N*-diethyl-4-phenylbutyramide (2a)**, mp 101–103 °C. IR ($CHCl_3$): 3600, 3580–3200, 2980, 1700, 1620, 1440, 1385 cm^{-1}. NMR: δ 7.30–7.18 (m, 5 H), 5.20 (m, sharpens to d, J = 3.0 Hz upon D exchange, 1 H), 3.89 (d, J = 3.2 Hz, O*H*), 3.51–3.00 (m, 4 H), 1.16–1.11 (m, 6 H), 0.99 (d, J = 7, 3 H). MS, chemical ionization m/e (rel intensity) 264 (M^+ + 1, 0.3), 246 (6), 158 (33), 107 (100).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04. Found: C, 68.12; H, 8.04.

(*R*,S)-4-Hydroxy-3,5-dimethyl-2-oxo-*N,N*-diethylhexanamide (2b).** IR (CCl_4): 3500, 3450–3300, 2950, 1700, 1620, 1375, 1090 cm^{-1}. NMR δ 4.80 (s, O*H*), 3.68 (dd, J = 1.8, 7 Hz, 1 H), 3.57–3.15 (m, 4 H), 1.88–1.60 (m, 1 H), 1.31–0.98 (m, 12 H), 0.88 (d, J = 7 Hz, 3 H). MS, chemical ionization m/e (rel intensity): 230 (M^+ + 1, 0.8), 212 (7), 158 (100), 100 (12).

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 63.01; H, 10.31; N, 6.12.

(*R*,R)-4-Hydroxy-3-methyl-2-oxo-*N,N*-diethyl-4-(2-furyl)butyramide (2c).** IR ($CHCl_3$): 3620–3200, 3050, 2980, 1700, 1620, 1030 cm^{-1}. NMR: δ 7.40 (s, 1 H), 6.38 (s, 2 H), 5.19 (t, J = 4 Hz, 1 H), 3.85 (d, J = 4 Hz, 1 H), 3.40–3.04 (m, 5 H), 1.25–0.96 (m, 8 H). MS, chemical ionization m/e (rel intensity): 254 (M^+ + 1, 5), 236 (100), 186 (8), 158 (22), 100 (17).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.84; H, 7.80; N, 5.49.

(*R*,R)- and (*R*,S**)-4-Hydroxy-3-methyl-2-oxo-*N,N*-diisopropyl-4-phenylbutyramide (2d, 3d).** These compounds were produced as a 5:1 syn/anti mixture. IR (CCl_4): 3620–3150, 3050, 3010, 2975, 1700, 1625, 1440, 1365 cm^{-1}. NMR δ 7.40–7.12 (m, 5 H), 5.25 (dd, J = 2.5, 2 Hz, 0.83 H, syn diastereomer), 4.70 (dd, J = 8.7, 2.5 Hz, 0.17 H, anti diastereomer), 4.08 (br s, 1 H, O*H*), 3.95–3.62 (m, 1 H), 3.48 (septet, J = 7 Hz, 1 H), 3.22–3.05 (m, 1 H), 1.45 (d, J = 7 Hz, 6 H), 1.19, 1.14, 1.00 (doublets, J = 7, 3 H each). MS, chemical ionization m/e (rel intensity): 293 (M^+ + 1, 100), 274 (29), 216 (6), 186 (6).

3(*R)-Hydroxy-4(*S**)-methyl-5(*R**)-isopropyltetrahydrofuran-2-one (8).** To a solution of ketone **2b** (530 mg, 2.3 mmol) in 5 mL ether at 0 °C was added $Zn(BH_4)_2$ (12 mL of a 0.15 M solution in ether;[1] 1.8 mmol) with stirring. After 3 h, excess hydride was destroyed by careful addition of H_2O and then 2 N

(16) Flynn, E. H.; Sigal, M. V., Jr.; Wiley, P. F.; Gerzon, K. *J. Am. Chem. Soc.* **1954**, *76*, 3121.

(17) For previous syntheses of mycarose, cladinose, and related branched chain sugars, see: Yoshimura, J. In *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69.

HCl. The resulting mixture was extracted twice with ether; the combined organic phase was dried (Na_2SO_4), filtered, and evaporated. A small portion was purified via chromatography (EtOAc/hexane, 1:3) to give **7**, which had the following spectral characteristics. NMR: δ 4.19 (dd, J = 2, 7 Hz, 1 H), 4.08 (d, J = 7 Hz, 1 H), 3.62 (s, 1 H), 3.57–3.25 (m, 2 H), 3.24–3.0 (m, 3 H), 1.81–1.48 (m, 2 H), 1.05 (t, J = 7 Hz, 1 H), 1.0 (t, J =7 Hz, 1 H), 0.93 (d, J = 7 Hz, 1 H), 0.75 (d, J = 7 Hz, 3 H), 0.69 (d, J = 7 Hz, 3 H). IR ($CHCl_3$): 3500, 3380, 1630 cm^{-1}. MS, chemical ionization m/e (rel intensity): 232 (M + 1, 100), 214 (36), 196 (15), 131 (10). The crude diol was stirred rapidly with 10 mL of ether and 3 mL of 5 M aqueous H_2SO_4 for 6 h. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated. Chromatography of the residue (ethyl acetate/hexane, 1:3) afforded 0.276 g (76%) of **8**. IR and 200-MHz ^1H NMR spectra were in full agreement with those previously reported.[11]

(+)- and (−)-3(*R)-Hydroxy-4(*R**)-phenoxy-3,5(*R**)-dimethyltetrahydrofuran-2-one ((±)-11).** Aldol product **6c** (2.96 g, 9.3 mmol) in 10 mL of dry THF was added dropwise to a solution of methylmagnesium chloride (23.5 mmol, 7.8 mL of 3 M solution) in 40 mL of THF at −78 °C under N_2 with stirring. After 30 min the reaction mixture was warmed to 0 °C and quenched by addition of 2 N HCl. After the usual extractive workup, the reaction mixture (crude diol **9b**) was dried, filtered, evaporated, taken up in 20 mL of ether, and stirred vigorously for 16 h with 5 mL of 2:1 concentrated H_2SO_4/H_2O. Flash chromatography of the residue obtained on evaporation of the organic phase (ethyl acetate/hexane, 1:5) yielded 1.0 g (50%) of lactone **11**, mp 74–76 °C. IR ($CHCl_3$): 3600–3200, 2970, 1770, 1240, 1100 cm^{-1}. NMR: δ 7.39–7.20 (m, 2 H), 7.02 (t, J = 6 Hz, 1 H), 6.90 (d, J = 6 Hz, 2 H), 4.62 (dq, J = 3.64, 6.7 Hz, 1 H), 4.30 (d, J = 3.64 Hz, 1 H), 3.29 (s, O*H*), 1.59 (s, 3 H), 1.52 (d, J = 6.7 Hz, 3 H). MS, chemical ionization m/e (rel intensity): 223 (M^+ + 1, 13), 205 (1), 179 (1), 133 (1).

Resolution of (±)-11. Racemic **11** (1.8 g, 8.4 mmol) was combined with 4 mL of (*R*)-(+)-α-methylbenzylamine and heated under N_2 at 80 °C for 12 h. The mixture was partitioned between 2 N HCl and ether, washed with water, dried (Na_2SO_4), and evaporated to afford a semisolid residue. The crude product was taken up in hot hexane/ethyl acetate (2:1) and cooled slowly. Seeding with a pure sample of **12b** (obtained by preparative TLC) led to the crystallization of 1.08 g of **12b**, mp 138–140 °C. The mother liquor was evaporated and subjected to flash chromatography (ethyl acetate/hexane, 1:2), yielding, in order of elution, 1.12 g of **12a**, mp 109–110 °C, and 0.06 g of **12b** (combined yield, 80%). The infrared spectra ($CHCl_3$) of the two diastereomers were virtually identical, with absorbances at 3590, 3405, 2990, 1650, 1590, 1490, 1445, and 1225 cm^{-1}. **12a**: NMR δ 7.40–7.21 (m, 6 H), 7.10–6.91 (m, 4 H), 5.11–4.96 (m, 1 H), 4.56 (d, J = 5.7 Hz, 1 H), 4.35 (s, 1 H), 4.22–4.05 (m, 1 H), 3.00 (d, J = 3 Hz, 1 H), 1.68 ns, 1 H), 1.49 (s, 3 H), 1.36 (d, J = 7 Hz, 3 H), 1.10 (d, J = 7, 3 Hz). MS, chemical ionization m/e (rel intensity): 344 (M^+ + 1, 100), 326 (5), 281 (9), 105 (20). **12b**: NMR δ 7.36–6.92 (m, 10 H), 5.15–4.97 (m, 1 H), 4.64 (d, J = 5.0 Hz, 1 H), 4.30–4.12 (m, 2 H), 2.95 (d, J = 5 Hz, 1 H), 1.70 (s, 1 H), 1.49 (d, J = 7 Hz, 3 H), 1.43 (s, 3 H), 1.27 (d, J = 7 Hz, 3 H), MS, chemical ionization, m/e (rel intensity): 341 (M^+ + 1, 100), 326 (6), 281 (7), 250 (17), 240 (21), 105 (86). **12b** (1.0 g, 2.9 mmol) in 100 mL of 1:1 ether/methylene chloride was stirred for 3 h with 5 mL of 2:1 H_2SO_4/H_2O. Extractive workup and chromatography as in the preparation of racemic **11** gave (+)-**11** (0.573 g, 89%), $[\alpha]^{22}D$ = +72.6° (c = 0.8, CH_3OH).

(3*S*,4*S*,5*S*)-4-Phenoxy-3,5-dimethyl-2,3-dihydroxytetrahydrofuran. Diisobutylaluminum hydride (8.8 mmol, 8.8 mL of 1 M solution in toluene) was added dropwise to (+)-**11** (0.97 g, 4.4 mmol) in 30 mL of ether with stirring at −78 °C under an atmosphere of N_2. The reaction mixture was held at this temperature for 30 min, then warmed to 0 °C, and quenched by careful addition of 1 N H_2SO_4. Flash chromatography of the residue obtained after drying and evaporation of the organic phase (3:2 hexane/ethyl acetate) gave the title compound (0.935 g, 95%), $[\alpha]^{22}D$ = +57°, C = 0.8 in ethyl acetate. IR (CCl_4): 3600, 3140, 3050, 2980, 1585, 1485, 1230, 1040, 690 cm^{-1}. NMR δ 7.30 nt, J = 6 Hz, 2 H), 7.06–7.86 (m, 3 H), 5.03 (br s, 1 H), 4.40–4.22 (m, 2 H), 3.96 (d, J = 5 Hz, 1 H), 3.42 (s, 1 H), 1.42 (s, 3 H), 1.30 (d, J = 7 Hz, 3 H). MS, chemical ionization m/e (rel intensity): 225 (M^+ + 1, 0.9), 207 (5), 189 (100), 161 (23), 94 (22).

(3*R*,4*S*,5*S*)-1-Methoxy-3-methyl-4-phenoxy-3,5-dihydroxyhex-1-ene (13). The above lactol (1.0 g, 4.5 mmol) in 4 mL of THF was added to a suspension of KH (8.9 mmol, 1.0 g of 35% dispersion in oil) in 10 mL of THF with stirring at 0 °C under N_2. In a separate flask, 7.5 mmol of lithium (methoxymethyl)diphenylphosphine oxide was prepared at 0 °C under N_2 in 10 mL of THF from 7.5 mmol of LDA (3.0 mL of 2.5 M BuLi plus 1.26 mL of diisopropylamine) and (methoxymethyl)-diphenylphosphine oxide (7.8 mmol, 1.92 g). The red lithio phosphine oxide solution was transferred via syringe into the flask containing the potassium alkoxide, and the resultant mixture was allowed to stir at 25 °C for 24 h. The reaction mixture was partitioned between ether and 1 N HCl, washed with water, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography of the residue (ethyl acetate/hexane, 1:2) afforded 0.87 g (77%) of **13** as a 3:2 Z/E mixture, $[\alpha]^{22}D$ = −13.5° (c = 1, EtOAc). IR (CCl_4): 3620–3160, 3040, 2940, 1650, 1585, 1490, 1230, 1095, 1045, 690 cm^{-1}. NMR: 7.35–7.19 (m, 2 H), 7.05–6.85 (m, 3 H), 6.60 (d, J = 14 Hz, 0.4 H), 5.79 (d, J = 6 Hz, 0.6 H), 4.80 (d, J = 14 Hz, 0.4 H), 4.56 (d, J = 6 Hz, 0.6 H), 4.45–4.0 (m, 3 H), 3.66 (s, 1.8 H), 3.30 (s, 1.2 H), 1.42, 1.46 (s, 1.8 and 1.2 H), 1.27, 1.20 (d, J = 6 Hz, 1.2 and 1.8 H). MS, chemical ionization m/e (rel intensity): 253 (M^+ + 1, 2), 191 (100), 189 (51), 159 (16).

β-Methyl 4-*O*-Phenylmycaroside (14). A 1.5:1 Z:E mixture of enol ether **13** (0.41 g, 1.63 mmol) was dissolved in 4 mL of THF at 25 °C under N_2. With stirring, a solution of $Hg(OAc)_2$ (3.58 mmol, 1.14 g) in 15 mL of THF was added and the resultant mixture was stirred for 100 min. Most of the solvent was removed in vacuo, the residue was taken up in dry methanol (10 mL) and added slowly to a solution of $NaBH_4$ (0.2 g, 5 mmol) in 10 mL of methanol at 0 °C with stirring. After 20 min the mixture was partitioned between ether and H_2O, washed with $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (ethyl acetate/hexane, 1:9) afforded 0.36 g (88%) of **14** as an oil, $[\alpha]^{24}D$ = +3.0° (c = 1, EtOAc). A sample of racemic material melted at 68 °C. IR (CCl_4): 3580 (sharp), 3040, 2985, 1590, 1490, 1230, 1160, 1080, 1035 cm^{-1}. NMR: δ 7.29 (t, J = 7 Hz, 2 H), 7.02–6.90 (m, 3 H), 4.68 (dd, J = 2, 10 Hz, 1 H), 4.00–3.92 (m, 2 H), 3.51 (s, 3 H), 2.39 (d, J = 2 Hz, O*H*), 2.08 (dd, J = 2, 14 Hz, 1 H), 1.61 (ddd, J = 2, 10, 14 Hz, 1 H), 1.22 (d, J = 7 Hz, 3 H), 1.20 (s, 3 H). MS, chemical ionization m/e (rel intensity): 253 (M^+ + 1, 3), 221 (48), 203 (55), 191 (100), 159 (62).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.46; H, 8.19. Equilibration (TsOH, CH_3OH, 25 °C, 24 h) followed by chromatography allowed for isolation of a small amount of the α-anomer. NMR: δ 7.26 (t, J = 7 Hz, 2 H), 7.02–6.88 (m, 3 H), 4.82 (d, J = 3.5 Hz, 1 H), 4.15 (dq, J = 5, 7 Hz, 1 H), 3.95 (d, J = 5 Hz, 1 H), 3.38 (s, 3 H), 2.10 (d, J = 14 Hz, 1 H), 1.91 (dd, J = 5, 14 Hz, 1 H), 1.24 (d, J = 7 Hz, 3 H), 1.21 (s, 3 H), (O*H* not observed).

β-Methyl 4-*O*-Phenylcladinoside (15). Alcohol **14** (0.3 g, 1.2 mmol) was added to a suspension of KH (0.15 g of 35% oil dispersion, 1.32 mmol) in 3 mL of THF at 25 °C. Dimethyl sulfate (0.14 mL, 1.44 mmol) was added and the mixture was stirred at 25 °C for 2 h and then poured into H_2O/ether. Flash chromatography (ether/hexane, 1:20 → 1:4) gave the title compound (0.306 g, 96%), $[\alpha]^{25}_D$ = +7.75° (c = 2, in ethyl acetate). IR (CCl_4): 3050, 2960, 1585, 1390, 1230, 1160, 1045, 990 cm^{-1}. NMR: 7.28 (t, J = 7 Hz, 2 H), 7.01–6.95 (m, 3 H), 4.68 (dd, J = 2, 10.5 Hz, 1 H), 4.13 (dq, J = 8, 7 Hz, 1 H), 3.94 (d, J = 8, 1 H), 3.50 (s, 3 H), 3.39 (s, 3 H), 2.25 (dd, J = 2, 14 Hz, 1 H), 1.50 (dd, J = 7, 14 Hz, 1 H), 1.23 (d, J = 7 Hz, 3 H), 1.23 (s, 3 H). MS, chemical ionization m/e (M^+): 267 (M^+ + 1, 1), 235 (2), 164 (9), 134 (100).

(−)-β-Methyl Cladinoside (16). Phenyl ether **15** (0.107 g, 0.4 mmol) was dissolved in 6 mL of THF and 2.25 mL of t-BuOH in a flash equipped with a stirring bar and dry ice condenser and protected from moisture by a KOH drying tube. Ammonia (25 mL) was condensed into the apparatus, and Li (0.112 g, 18 mmol) was added in small pieces with stirring. After 80 min the ammonia was evaporated, and the reaction was partitioned between ether and water. The residue obtained after drying and evaporating the organic phase was taken up in 3 mL of dry methanol and treated with 20 mg of pyridinium tosylate. After 24 h the solvent was removed in vacuo and the residue flash chromatographed

(ether/hexane, 1:5), affording 66 mg (87%) of the title compound, $[\alpha]^{23}_D$ = -20.1° (c = 1, EtOAc). That obtained from (-)-erythromycin[16] had $[\alpha]^{23}_D$ = -26.0° (c = 1, EtOAc). IR ($CHCl_3$): 3600-3350, 2980, 2940, 2840, 1450, 1370, 1160, 1055, 1000, 920 cm^{-1}. NMR: δ 4.48 (dd, J = 2, 10 Hz, 1 H), 3.58 (dq, J = 9, 7 Hz, 1 H), 3.36 (s, 3 H), 3.23 (s, 3 H), 2.95 (dd, J = 9, 9 Hz, 1 H), 2.23 (dd, J = 2, 14 Hz, 1 H), 2.10 (d, J = 9 Hz, OH), 1.36 (dd, J = 10, 14 Hz, 1 H), 1.30 (d, J = 7, 3 H), 1.21 (s, 3 H). MS, chemical ionization m/e (rel intensity): 191 (M^+ + 1, 11), 159 (100), 127 (20), 109 (4).

(-)-β-Methyl Mycaroside (17). (-)-14 (0.27 g, 1.1 mmol) prepared from 11 was reduced (75 mL of liquid NH_3, 0.3 g of Li, 6 mL of t-BuOH, 20 mL of THF) and acidified (CH_3OH, PPTS) as described in the preparation of methyl (-)-cladinoside to yield 0.16 g (82%) of 17, $[\alpha]^{25}_D$ = -52.8° (c = 1, $CHCl_3$) (lit.[18] +54° for naturally derived material). NMR: δ 4.62 (dd, J = 2.1, 9.4 Hz, 1 H), 3.58 (dq, J = 9, 7 Hz, 1 H), 3.42 (s, 3 H), 3.02 (br d, J = 9 Hz, 1 H), 2.50, 2.30 (br s, OH), 1.96 (dd, J = 2.1, 14 Hz, 1 H), 1.55 (dd, J = 9.4, 14 Hz, 1 H), 1.30 (d, J = 7 Hz, 1 H), 1.24 (s, 3 H).

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Registry No. **1a**, 69016-02-0; **1b**, 120313-15-7; **2a**, 120313-17-9; **2b**, 120313-18-0; **2c**, 120313-19-1; **2d**, 120313-20-4; **3d**, 120313-21-5; **4a**, 120313-16-8; **4b**, 120313-14-6; **5a**, 120313-22-6; **5b**, 120313-24-8; **6a**, 120313-23-7; **6b**, 120313-25-9; **6c**, 120313-26-0; **6d**, 120313-27-1; **7**, 120313-28-2; **8**, 106470-99-9; **9a**, 120313-31-7; **9b**, 120313-29-3; **10a**, 120313-32-8; (±)-**11**, 120313-30-6; (+)-**11**, 120313-35-1; (+)-**11** aldose derivative, 120313-36-2; **12a**, 120313-34-0; **12b**, 120313-33-9; (*E*)-**13**, 120313-38-4; (*Z*)-**13**, 120313-37-3; **14**, 120313-39-5; (-)-**14**, 120313-41-9; **15**, 120313-40-8; **16**, 57794-93-1; **17**, 38411-52-8; PhCHO, 100-52-7; $(CH_3)_2CHCHO$, 78-84-2; CH_3CHO, 75-07-0; *trans*-$CH_3CH{=}CHCHO$, 123-73-9; $CH_2{=}CHCHO$, 107-02-8; $Ph_2POCHLiOMe$, 83532-12-1; phenoxyacetic acid, 122-59-8; *N,N*-diisopropyloxamate, 120313-13-5; 2-furancarboxaldehyde, 98-01-1.

Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for **9a** (11 pages). Ordering information is given on any current masthead page.

Synthesis of Peptides Containing *S*-(*N*-Alkylcarbamoyl)cysteine Residues, Metabolites of *N*-Alkylformamides in Rodents and in Humans

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Hydrochloride salts of *S*-(*N*-methylcarbamoyl), *S*-(*N*-ethylcarbamoyl), and *S*-(*N,N*-dimethylcarbamoyl) derivatives of cysteine, *N*-acetylcysteine, and cysteinylglycine have been prepared. *S*-(*N*-Methylcarbamoyl)glutathione hydrochloride has also been synthesized. Protecting groups for amino and carboxylic acid functions were selected for their ability to solubilize the peptides in dichloromethane in which solvent the thiols were treated with alkyl isocyanates and with *N,N*-dimethylcarbamoyl chloride. Removal of *S*-(amidomethyl) protecting groups using mercury(II) acetate was found to cause some loss of *N*-(*tert*-butoxycarbonyl) groups. Elimination of disulfide was evident during coupling of disulfide derivatives of cysteine using mixed anhydride methods but not with a carbodiimide coupling agent. Mixed disulfide protections were reductively cleaved by propane-1,3-dithiol. Many of the deprotected *S*-carbamoyl amino acids and peptides are metabolites of the corresponding *N*-alkylformamides in rodents and in humans.

N-Substituted formamides have a variety of biological activities, both beneficial and adverse. *N*-Methylformamide (NMF; **1a**) has been found to be an antitumor agent in experimental systems[2] and also to be an hepatotoxin,[3,4] whereas *N*-ethylformamide (**1b**) has little or no anticancer activity[2] but is also toxic to the liver.[5] *N,N*-Dimethylformamide (DMF; **1c**), however, displays both of these effects only weakly in rodents.[2,5,7] We have recently shown that the two secondary amides are metabolized to the corresponding mercapturic acids **5a,b** in mice[8] and that this metabolic pathway (Scheme I) is implicated[5,8,9] in the hepatotoxicity of **1a,b**. A mass spectrometric study[9] has also enabled the characterization of the glutathione derivative **2a** as a metabolite of **1a** in mice. *N*-Acetyl-*S*-(*N*-methylcarbamoyl)cysteine (**5a**) has also been detected[7] in the urine of mice and humans exposed to **1c**, with an apparent parallel between the amount excreted and the extent of hepatotoxicity. Selective oxidation of the formyl group of *N*-methylformamide has been reported rarely in

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