Notes on the directed aldol synthesis and reduction of some compounds related to cycloheximide

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Several *N*-phenylcycloheximide analogues were prepared by $TiCl_4$-promoted aldol condensation between trimethylsilyl enol ethers of cyclic ketones and (*N*-phenylglutarimide)-β-acetaldehyde. Favored stereoisomers were isolated in several instances and identified from nuclear magnetic resonance data. Only for the analogue from 4-*tert*-butylcyclohexanone was it possible to obtain both *erythro* and *threo* isomers. Catalytic reduction of the β-hydroxyketone system over PtO_2 gave dihydrocycloheximide analogues possessing an axial ring hydroxyl group. Reduction in glacial HOAc was noted as promoting fission of the glutarimide ring with formation of lactone amides and, in several instances, concomitant reduction of the phenyl ring to a cyclohexyl group.

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On a préparé plusieurs analogues de la *N*-phénylcycloheximide en procédant à la condensation aldolique, catalysée par le $TiCl_4$, d'éthers énoliques triméthylsilyles de cétones cycliques et de (*N*-phénylglutarimide)-β-acétaldéhyde. Dans plusieurs cas, on a isolé les stéréoisomères les plus favorisés et on les a caractérisés par la résonance magnétique nucléaire. L'analogue de la *tert*-butyl-4 cyclohexanone est le seul cas où l'on a pu isoler les isomères tant *érythro* que *thréo*. La réduction catalytique du système β-hydroxycétonique, à l'aide de PtO_2, conduit aux analogues dihydrocycloheximides possédant un groupement hydroxyle axial. On a noté que la réduction dans l'acide acétique glacial favorise une fission du noyau glutarimide qui conduit à la formation d'amides lactoniques et, dans plusieurs cas, à une réduction concomitante du noyau phényle en groupement cyclohexyle.

[Traduit par la revue]

Our prior work (1) with analogues of the antibiotic and DNA biosynthetic inhibitor cycloheximide **1***a* indicated that these compounds held some promise as potential anticonvulsants. A general synthetic procedure leading regio- and stereospecifically to the requisite β-hydroxyketone functionality was sought, since the previous methods we used were not as simple and direct as we had hoped. We began by examining the $TiCl_4$-promoted directed aldol condensation procedure, initially described by T. Mukaiyama *et al.* (2), to develop an efficient strategy for the synthesis of additional analogues whereby the cyclohexane ring substituents and (or) the imide ring portion of the molecule could be varied before introducing the β-hydroxyketone system. Recently, S. Kudo *et al.* (3, 4) used titanium and tin halide mediated methods to prepare optically active *trans*-cycloheximide isomers and chiral *cis*-cycloheximide isomers for antimicrobial activity studies. Thus, the method offered promise.

Our initial experience with the Mukaiyama procedure using the glutarimide-β-acetaldehyde (5) was unsatisfactory as we were unable to effect adequate protection of the imide group with benzyl chloride. Direct reaction of the imidealdehyde and 6-methyl-1-trimethylsiloxycyclohexene employing 2 equiv. of $TiCl_4$ to overcome its deactivation gave only a 3.3% yield of product **1***b*, isolated as the acetate.[2] The product was readily identified by its spectral data and contained an isomeric mixture as indicated by ^1H nmr doublets at δ 1.0 (J = 6.35) and 1.16 (J = 7.2) for the C-2 methyl group.

Studies were then continued with *N*-phenylglutarimide-β-acetaldehyde since the *N*-phenyl substituent should provide the necessary imide protection needed for the aldol condensation process. At the same time, this group should afford products containing a substituent that has been a feature of some biologically interesting glutarimides (6, 7). *N*-Phenylglutarimide-β-acetaldehyde was readily synthesized by starting with methanetriacetic acid (8) and one equivalent of aniline, converting the imideacid to the acid chloride, and then reducing the corresponding acid chloride by the Rosenmund procedure. The silylated enol ethers were available from the corresponding cyclohexanones and cyclopentanone by standard procedures (9), and their purity was established from nmr data.

The $TiCl_4$-promoted aldol condensation proceeded smoothly with the cyclohexanone enol ethers and the *N*-phenylglutarimide aldehyde at −78°C as described by Mukaiyama (2). The reaction mixtures crystallized upon standing and the products were recrystallized to afford purified materials (see Table 1). Although the quantity of recovered crystalline product was not high, overall yields averaged 60–70%, as tlc of the mother liquors often indicated only a single material with an R_f value identical to the recrystallized material. The products were generally characterized by three distinct ir carbonyl absorptions at about 1725, 1700, and 1680 cm^{-1} for the ketone and cyclic imide moieties as well as bands at 3555–3510 cm^{-1} for the hydroxy group. Also, two nmr multiplets at δ 7.1 and 7.4, equal to two and three protons in area, respectively, represented the aromatic ring protons as influenced by the proximity of the imide carbonyl groups. Further analysis of the nmr spectra of the crude products in many cases indicated the presence of isomers, as evidenced by two signals (about δ 4.2 and 3.85) for the carbinol proton and by more than one methyl doublet, for products originating from methylcyclohexanones. Attempts to effect a separation and isolation of individual isomers were not successful although recrystallization did result in the isolation of a single racemic isomer in some instances and in two separate *tert*-butyl analogue isomers **2***a*,*b*. The latter isomers nevertheless had tlc R_f values identical with one another and with the crude reaction product. This latter reaction also led to a small amount of an anhydro product **3**, which might be expected from dehydration of the aldol product.

The lack of high stereoselectivity was not surprising since

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[2]During this project we became aware of the work by S. Kudo *et al.* (refs. 3 and 4), in which they used the unprotected imidealdehyde with the *trans* and *cis* forms of 4,6-dimethyl-1-trimethylsiloxycyclohexene to achieve condensation yields of 18.3 and 10.8%, respectively.

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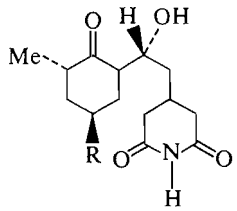
TABLE 1. Data for the products from $TiCl_4$-promoted aldol condensations

Compound	Melting point (°C)	Yield[a] (%)	Formula	Analyses (C, H, N) Calcd.	Found	Infrared (cm^{-1})	^1H nuclear magnetic resonance (δ)
2-Methyl **2***c*	148–150	25[b]	$C_{20}H_{25}NO_4$	69.95 7.34 4.08	70.16 7.82 4.31	3520, 1725 1700, 1670 1590, 1490	7.39 (m, 3H), 7.13 (m, 2H), 3.85 (m, 1H), 3.1–1.3 (16H), 1.19 (d, J = 7.2), 1.03 (d, J = 5.9)
2-Methyl[c] **2***f*	138–141.5	6.6[d]	$C_{22}H_{27}NO_5$	68.55 7.06 3.64	68.56 7.17 3.64	1735, 1715 1680, 1235	7.4 (m, 3H), 7.1 (m, 2H), 5.35 (m, 1H), 3.2–1.3 (14H), 2.07 (s, 3H), 1.0 (d, 3H, J = 6.2); in C_6D_6 δ 5.42 (m, 1H)
4-Methyl **2***d*	152.5–154	20.6[d]	$C_{20}H_{25}NO_4$	69.95 7.34 4.08	69.67 7.53 4.54	3520, 1730 1705, 1665 1590, 1490	7.39 (m, 3H), 7.09 (m, 2H), 3.85 (br, 1H), 3.2–1.5 (16H), 1.19 (d, 3H, J = 6.7)
3,5-Dimethyl **2***e*	153–156	19.5[e]	$C_{21}H_{27}NO_4$	70.56 7.62 3.92	70.11 7.72 3.90	3510, 1725 1700, 1675 1590, 1490	7.4 (m, 3H), 7.08 (m, 2H), 3.9 + 3.8 (m, 1H), 3.2–1.5 (15H), 1.12 (d, 3H, J = 8.2), 1.04 (d, 3H, J = 4.8)
2,4-Dimethyl **2***g*	158.5–159.5	29.9[b]	$C_{21}H_{27}NO_4$	70.56 7.62	70.73 7.93	3525, 1720 1700, 1667 1590, 1490	7.39 (m, 3H), 7.09 (m, 2H), 3.15–1.5 (15H), 1.08 (d, 3H), J = 6), 1.0 (d, 3H, J = 5), 4.0 (m, 1H)
Normethyl **2***h*	149.5–151.5	28.7[b]	$C_{19}H_{23}NO_4$	69.28 7.04 4.25	68.97 7.27 4.01	3520, 1725 1705, 1678 1590, 1490	7.4 (m, 3H), 7.1 (m, 2H), 3.85 (br, 1H), 4.2 (d, 1H, J = 9), 3.3–1.2 (16H)

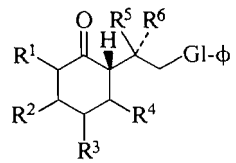
[a]No attempt was made to effect complete recovery of all isomers owing to similar tlc properties.
[b]From CH_2Cl_2–ether.
[c]Isolated only after extensive chromatography of the acetylated crude reaction mixture.
[d]From CH_2Cl_2.
[e]From acetone.

Mukaiyama *et al.* (2) and Heathcock *et al.* (10) have reported Lewis acid catalyzed aldol condensations to give poor diastereoselectivity. Nonetheless, the preferential formation of some isomers might ensue (2) when steric hindrance is encountered between the trimethylsiloxy group of the cyclohexene and a substituent at position 6. Kudo *et al.* (3, 4), for example, found a favored isomer to prevail in their work on 4,6-dimethyl-1-trimethylsiloxycyclohexenes.

Stereochemical identification of the isolated compounds was established through ^1H nmr data for the carbinol proton and for the cyclohexane ring methyl groups. For 1-methyl **2***c*, 4-methyl **2***d*, and 3,5-dimethyl **2***e* aldol products a multiplet at ca. δ 3.9 established a *threo* relationship between the glutarimide side chain attachment and the alcohol. Because of its bulk, the side chain was assumed to orient itself in the equatorial conformation on the cyclohexanone ring. Analysis of the methyl group signals for **2***c* revealed equatorial and axial epimers from two doublets at δ 1.03 and 1.19. Acetylation of crude product from the C-2 methyl reaction permitted the isolation of a *threo* product **2***f* with an equatorial methyl, albeit in poor yield. The C-4 methyl product **2***d* exhibited only one methyl doublet at δ 1.19 (J = 6.7) indicative of an axial configuration (the axial C-4 methyl of cycloheximide is found at δ 1.25 with J = 6.9), and, as expected, the 3,5-dimethyl analogue **2***e* had two separate doublets at δ 1.04 and 1.12 for various combinations of methyl group orientations.



1*a* R = Me
b R = H



2*a* $R^1 = R^2 = R^4 = R^5 = H$; R^3 = eq CMe_3; R^6 = OH
b $R^1 = R^2 = R^4 = R^6 = H$; R^3 = eq CMe_3; R^5 = OH
c R^1 = ax/eq Me; $R^2 = R^3 = R^4 = R^6 = H$; R^5 = OH
d $R^1 = R^2 = R^4 = R^6 = H$; R^3 = ax Me; R^5 = OH
e $R^1 = R^3 = R^6 = H$; $R^2 = R^4$ = ax/eq Me; R^5 = OH
f R^1 = eq Me; $R^2 = R^3 = R^4 = R^6 = H$; R^5 = OAc
g $R^1 = R^3$ = eq Me; $R^2 = R^4 = H$; R^5/R^6 = H/OH
h $R^1 = R^2 = R^3 = R^4 = H$; R^5/R^6 = H/OH

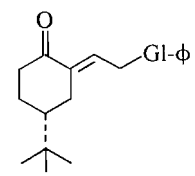


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TABLE 2. Data for the *N*-phenyldihydroxycycloheximides

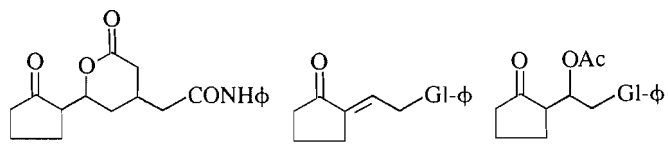
Compound	Melting point (°C)	Yield (%)	Formula	Analyses (C, H, N) Calcd.	Found	Infrared (cm^{-1})	^1H nuclear magnetic resonance (δ)
2-Methyl **7***a*	173–175	44.3	$C_{20}H_{27}NO_4$	69.54 7.88 4.05	69.53 7.92 3.95	3470, 1726 1665	7.4 (m, 3H), 7.1 (m, 2H), 4.1 (m, 1H), 3.8 (br, 1H), 3.3–1.2 (17H), 0.99 (d, 3H, J = 5)
4-Methyl **7***b*	155–158	51.8	$C_{20}H_{27}NO_4$	69.54 7.88 4.05	69.60 7.81 4.05	3535, 3400 1730, 1670	7.4 (m, 3H), 7.1 (m, 2H), 4.1 (m, 1H), 3.65 (m, 1H), 3.2–1.2 (17H), 1.01 (d, 3H, J = 7.2)
3,5-Dimethyl **7***c*	175–177.5	29.3[a]	$C_{21}H_{29}NO_4$	70.17 8.13 3.90	70.10 8.29 3.84	3500, 3380 1725, 1673	7.4 (m, 3H), 7.1 (m, 2H), 4.0 (d, 2H), 3.15–1.2 (16H), 1.0 (d, 3H, J = 8.5), 0.89 (d, 3H, J = 6.35)
Normethyl **7***e*	150–152	53.7	$C_{19}H_{25}NO_4$	68.86 7.61 4.23	68.75 7.75 4.35	3410, 3310 1720, 1660	7.4 (m, 3H), 7.1 (m, 2H), 4.3 (m, 1H), 3.7 (m, 1H), 3.2–1.1 (18H)
tert-Butyl (er) **7***f*	189–192	85.5	$C_{23}H_{33}NO_4$	71.29 8.58 3.61	71.43 8.56 3.62	3380, 1738 1665	7.4 (m, 3H), 7.1 (m, 2H), 4.0 (d, 1H), 4.1 (m, 1H), 3.2–1.1 (17H), 0.91 (s, 9H)
tert-Butyl (th) **7***g*	155–160	74.6	$C_{23}H_{33}NO_4$	71.29 8.58 3.61	71.01 8.19 3.55	3360, 1725 1675	7.4 (m, 3H), 7.1 (m, 2H), 4.3 (m, 1H), 3.7 (br, 1H), 3.2–1.1 (17H), 0.89 (s, 9H)

[a]This product was recrystallized from acetone, while EtOAc was used for all others.

Proton nmr data for the 2,4-dimethyl analogue **2***g* fit best with a *cis* dimethyl configuration (δ 1.0 and 1.08) for the cyclohexane ring methyls (4) and with an unassigned hydroxyl group orientation owing to a broad signal at δ 4.0. Without a methyl group on the cyclohexane ring to influence the course of the reaction as in the normethyl product **2***h*, stereospecificity should be lost and an equimolar mixture of isomers would be expected. The crystalline product, however, was a mixture of *threo* and *erythro* isomers in a 1:3 ratio, as determined from integration of the nmr multiplet at δ 3.85 for the *threo* isomer and the doublet at δ 4.2 for the *erythro* form.

In the case of the two separate *tert*-butyl analogue isomers, the *erythro* form **2***a* was readily ascertained by observation of a doublet at δ 4.25 for the proton on the carbinol carbon and the *threo* product **2***b* by a multiplet centered at δ 3.82. These assignments were supported by ^{13}C nmr spectra in which the hydroxyl carbon was at δ 66.77 for **2***a* and at δ 69.23 for **2***b*. Cycloheximide with its *erythro* configuration has this carbon atom absorption (11) at δ 66.5. In addition, ^1H nmr spectra of the corresponding acetates recorded first in $CDCl_3$, then C_6D_6, revealed an upfield shift from δ 5.35 to 5.29 for the *erythro* **2***a* acetate similar to the shift for cycloheximide acetate (δ 5.34 to 5.30), while a downfield shift from δ 5.39 to 5.41 was observed for the *threo* **2***b* acetate.

Use of cyclopentanone, the only non-cyclohexane type ketone employed, gave a crude product with a significant nmr signal at δ 6.5 indicative of a vinylic proton. Acetylation and tlc separation of the mixture led to three distinct compounds. The least mobile was identified as lactone amide **4**, primarily from ir bands at 3350 cm^{-1} for the NH, at 1680 and 1540 cm^{-1} for the amide I and II absorptions, and at 1725 cm^{-1} for the lactone carbonyl. Lactones of this type have been reported (12) to arise from glutarimide antibiotics under strongly acidic or basic conditions, and we encountered the same in our prior

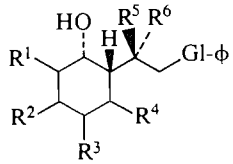


4 **5** **6**

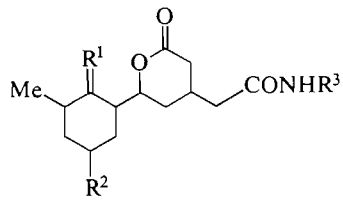
work (1). The second compound was the unsaturated ketone **5**, characterized by ir peaks at 1730, 1710, 1689, and 1645 cm^{-1}, a uv maximum at 242 nm, and an nmr signal at δ 6.5 (m, 1H) for the vinylic proton. The most mobile compound on tlc was the anticipated product **6**. Major ir absorptions were evident at 1735, 1705, 1670, and 1250 cm^{-1} while nmr signals were seen at δ 5.96 (t, 1H) and 2.04 (s, 3H), supporting this assignment. The acetoxy moiety was found to eliminate readily, making isolation difficult.

To provide dihydrocycloheximide analogues, the aldol condensation products were reduced catalytically, essentially as before (1), except 5–10% HOAc–EtOAc was substituted for the glacial HOAc solvent to avoid appreciable glutarimide ring fission. The diols normally crystallized from the reaction mixture in an average yield of 60% and were characterized by their differences in the hydroxyl group region of the infrared, and by nmr signals at δ 4.0–4.3 for the proton on the ring hydroxyl carbon and at δ 3.4–3.8 for the proton on the side chain hydroxyl carbon (see Table 2). From the former nmr absorptions the ring hydroxyl group is considered to be axial, in agreement with previous stereochemical studies (13) on the reduction of cycloheximide and with our observations (1) on the reduction of dehydrocycloheximide compounds.

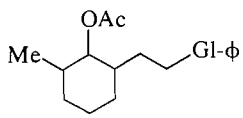
Analysis of the nmr signals for the methyl groups indicated that the 2-methyl diol **7***a* had an equatorial methyl, a result different from the parent compound in which both equatorial and axial methyl signals were observed. This orientation is

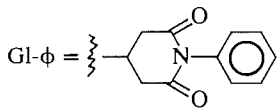


7*a* R^1 = ax/eq Me; $R^2 = R^3 = R^4 = R^6$ = H; R^5 = OH
b $R^1 = R^2 = R^4 = R^6$ = H; R^3 = ax Me; R^5 = OH
c $R^1 = R^3 = R^6$ = H; $R^2 = R^4$ = ax/eq Me; R^5 = OH
d $R^1 = R^3$ = eq Me; $R^2 = R^4$ = H; R^5/R^6 = H/OH
e $R^1 = R^2 = R^3 = R^4$ = H; R^5/R^6 = H/OH
f $R^1 = R^2 = R^4 = R^5$ = H; R^3 = eq CMe_3; R^6 = OH
g $R^1 = R^2 = R^4 = R^6$ = H; R^3 = eq CMe_3; R^5 = OH



8*a* R^1 = H, OH; R^2 = Me; R^3 = phenyl
b R^1 = O; R^2 = Me; R^3 = phenyl
c R^1 = H, OAc; R^2 = Me; R^3 = C_6H_{11}
d R^1 = H, OH; R^2 = H; R^3 = C_6H_{11}
e R^1 = H, OAc; R^2 = H; R^3 = C_6H_{11}





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probably a consequence of equilibration by an α-alkyl ketone in an acidic medium during a rather slow reduction. For the other diols the methyl group stereochemistry, as indicated by nmr, remained as observed in the aldol products, i.e., axial in the C-4 methyl diol **7***b*, a combination of both orientations in the 3,5-dimethyl analogue **7***c*, and diequatorial (*cis*) in the dihydrocycloheximide type compound **7***d*. For the *tert*-butyl analogues the reduction went smoothly and in good yield to afford the axial-*erythro* **7***f* and the axial-*threo* **7***g* diols with appropriate spectral characteristics.

Some unusual products, however, were obtained when the catalytic reductions were performed in glacial HOAc on material contained in the mother liquors, which were identical to crystalline material by tlc. These experiments prompted employment of a less acidic solvent for later reduction work. For example, the 2,4-methyl aldol product **2***g* mother liquors yielded the expected diol **7***d* but also hydroxy lactone **8***a* and keto lactone **8***b*. The acetoxy lactone **8***c*, characterized from the absence of aromatic proton signals in an nmr spectrum and correct C, H, N data, was not expected, however, since these hydrogenation conditions are not normally associated with reduction of an aromatic ring.

Hydrogenation of material from the 2-methyl aldol product **2***g* mother liquors under identical conditions, followed by acetylation to facilitate separation, also afforded similar aromatic ring reduced lactones **8***d* and **8***e*. Both were characterized from the absence of aromatic peaks in ir and nmr spectra and the presence of typical hydroxy, acetoxy, lactone, and amide ir bands, from analytical data, and from nmr proton integration. The acetoxy imide **9** was also isolated and was characterized from analytical and spectral data. This latter compound undoubtedly results from reduction of the α,β-unsaturated ketone (similar to **3**), which can be produced by acidic or basic dehydration of an aldol condensation product.

Experimental

Melting points were taken on a Fisher–Johns apparatus and are uncorrected. Infrared (ir) spectra were obtained with a Sargent–Welch 3-200 infrared spectrophotometer on solids incorporated into KBr wafers or on neat liquid samples. The nmr spectra were obtained on an IBM-NR 80 spectrometer on samples dissolved in $CDCl_3$ containing TMS as internal standard, unless otherwise noted. Ultraviolet spectra were recorded with a Varian 2290 spectrophotometer.

Precoated thin-layer chromatography (tlc) sheets of silica gel 60 F_{254} from EM Reagents were used for qualitative tlc, while preparative tlc was performed on 0.5-mm plates of silica gel PF_{254}.

N-*Phenyl-4-carboxymethyl-2,6-piperidinedione*

A solution of methanetriacetic acid (8) (8.87 g; 4.56 mmol), water (2 mL), and aniline (4.46 mL; 1 equiv.; distilled from zinc) was slowly heated to 180–200°C, then maintained at that tempeature for 1 h. The liquid materials were removed at 170°C/0.3 Torr (1 Torr = 133.3 Pa) and the residue was taken up in EtOAc and filtered. Concentration of the filtrate gave crystals, which were recrystallized to afford 8.54 g (81%); mp 200–201.5°C; ir: 3500–2600, 1730, 1670, 1600, 1490 cm^{-1}; nmr δ: 7.4 (m, 3H), 7.2 (m, 2H). *Anal.* calcd. for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.66; found: C 63.24, H 5.31, N 5.82.

N-*Phenyl-4-carbonylmethyl-2,6-piperidinedione*

The *N*-phenylimidyl acid (5.92 g) and $SOCl_2$ (59 mL) were heated at reflux for 0.5 h until the solids dissolved, then the excess $SOCl_2$ was removed *in vacuo*. The resultant crystals were washed with dry benzene to afford 5.53 g (86.9%) of intermediate acid chloride; mp 115–117°C; ir: 1810, 1730, 1675 cm^{-1}.

The acid chloride, dry toluene (280 mL), and 5% $Pd/BaSO_4$ (2.24 g) were placed into a flask, hydrogen was introduced into the solution through a gas diffusion tube, and the mixture was heated to reflux. The excess H_2 and other gases were passed through a standardized NaOH solution until the evolution of HCl essentially stopped (5 h; 82.5% of theoretical). Removal of the catalyst and concentration of the filtrate yielded 4.01 g (83.2%) of crystals. Recrystallization from $CHCl_3$ gave colorless crystals (3.64 g; 75.7%) of the desired *N*-phenylimidyl aldehyde; mp 113–115°C; ir: 2850, 2745, 1730, 1710 cm^{-1}; nmr δ: 9.8 (s, 1H), 7.4 (m, 3H), 7.01 (m, 2H), 3.1–2.5 (7H). *Anal.* calcd. for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.05; found: C 67.80, H 5.84, N 5.95.

Preparation of N-*phenylcycloheximide analogues*

In a typical experiment, a solution of the *N*-phenylimidyl aldehyde (1 g, 4.32 mmol) in CH_2Cl_2 (20 mL) at −78°C was treated with $TiCl_4$ (0.48 mL; 1 equiv.). The trimethylsilyl enol ether of 4-*tert*-butylcyclohexanone (1 equiv.) was added slowly, and the reaction was stirred at −78°C for 3 h, then at ambient temperature for 3 h. An ice–water mixture was used to quench the reaction, and the product was isolated by extraction with ether. Fractional recrystallization of the ether residue from acetone yielded first the *erythro tert*-butyl analogue **2***a* (310 mg; 18.7%); mp 184.5–187°C; ir: 3555, 1732, 1700, 1678, 1590, 1490 cm^{-1}; nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 4.25 (d, 1H, J = 10.9), 3.2–1.4 (16H), 0.95 (s, 9H); ^{13}C nmr δ: 66.77 (*C*HOH). *Anal.* calcd. for $C_{23}H_{31}NO_4$: C 71.66, H 8.11, N 3.63; found: C 71.52, H 8.15, N 3.85.

The *threo* analogue **2***b* was then isolated as colorless crystals (174 mg; 10.5%); mp 178–180.5°C; ir: 3540, 1730, 1700, 1680, 1590, 1490 cm^{-1}; ^1H nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 3.82 (br m, 1H), 3.2–1.3 (16H), 0.95 (s, 3H); ^{13}C nmr δ: 69.23 (*C*HOH). *Anal.* found: C 71.84, H 8.28, N 3.91.

Chromatography of the mother liquors by preparative tlc (50% EtOAc–hexane) gave 100 mg (6.0%) of anhydro compound **3**; mp 144–146°C; uv_{max}: 243 (ε 7680), sh 280–286 nm; ir: 1734, 1700, 1680, 1600 cm^{-1}; ^1H nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 6.58 (t, 1H),

3.1–1.25 (14H), 0.96 (s, 9H). *Anal.* calcd. for $C_{23}H_{29}NO_4$: C 75.17, H 7.95, N 3.81; found: C 74.86, H 8.11, N 3.78.

Each of the isomers was acetylated by acetic anhydride – pyridine to afford the corresponding acetate, which was recrystallized from EtOAc.

Erythro **2***a* acetate: mp 142.5–144°C; ir: 1740, 1710, 1678, 1240 cm^{-1}; ^1H nmr δ: 7.4 (m, 3H), 7.15 (m, 2H), 5.35 (m, 1H), 2.08 (s, 3H), 0.93 (s, 9H); ^1H nmr (C_6D_6) δ: 5.29 (m, 1H), 1.83 (s, 3H), 0.79 (s). *Anal.* calcd. for $C_{25}H_{33}NO_5$: N 3.28; found: N 2.95.

Threo **2***b* acetate: mp 131–132.5°C; ir: 1735, 1710, 1680, 1235 cm^{-1}; ^1H nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 5.39 (m, 1H), 2.09 (s, 3H), 0.95 (s, 9H); ^1H nmr (C_6D_6) δ: 5.41 (m, 1H), 1.8 (s, 3H), 0.78 (s). *Anal.* found: N 3.61.

Data for other aldol condensation products are in Table 1.

Directed aldol condensation with cyclopentanone enol ether

The *N*-phenylglutarimidyl aldehyde (0.76 g; 3.3 mmol) in CH_2Cl_2 (20 mL) at −78°C was treated with $TiCl_4$ (0.36 mL; 1 equiv.), then with 1-trimethylsilyloxycyclopentene (0.54 g; 1 equiv.). After the reaction mixture was stirred for 3 h, it was stirred at room temperature for another 3 h. Extraction with ether following ice–water quenching gave a crude oil (0.61 g), which was acetylated by acetic anhydride – pyridine and separated by preparative tlc (5% MeOH–$CHCl_3$) into three fractions.

The least mobile fraction (R_f 0.11) was determined to be amide lactone **4** (0.1 g); ir: 3350, 1725, 1715, 1680, 1545 cm^{-1}; nmr δ: 7.4, 7.1, 6.5, 5.3.

The next fraction (R_f 0.23) was recrystallized from ether–CH_2Cl_2 to yield pure unsaturated ketone **5** (0.12 g); mp 138–139°C; uv_{max}: 242 (ε 13 200), sh 275 nm; ir: 1730, 1710, 1689, 1645 cm^{-1}; nmr δ: 7.47 (m, 3H), 7.02 (m, 2H), 6.5 (m, 1H). *Anal.* calcd. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71; found: C 72.58, H 6.44, N 4.99.

The most mobile material (R_f 0.38) was the acetylated aldol product **6**, which crystallized from ether to give 0.02 g; mp 108–109.5°C; ir: 1735, 1705, 1670, 1250 cm^{-1}; nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 5.96 (m, 1H), 2.04 (s, 3H). *Anal.* calcd. for $C_{20}H_{23}NO_5$: N 3.92; found: N 4.35. The product lost the acetate moiety readily.

Reduction of aldol condensation products

In a typical experiment a mixture of the 2,4-dimethyl analogue **2***g* (40 mg), PtO_2 (50 mg), and 10% HOAc–EtOAc (20 mL) was shaken under 50 psi (1 psi = 6.9 kPa) of H_2 for 26 h. Fresh catalyst was added (50 mg) and shaking was continued for 16 h. The catalyst was collected on Celite, and the filtrate was washed with dilute $NaHCO_3$, then with water, and dried. Removal of the EtOAc gave an oil (42 mg) that crystallized upon standing. Recrystallization from EtOAc yielded 19.1 mg (47.5%) of diol **7***d*; mp 130–135°C; ir: 3500, 3380, 1725, 1675 cm^{-1}; nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 4.18 (br m, 1H), 3.48 (br, 1H), 1.01 (d, 3H, J = 6.35), 0.84 (d, 3H, J = 6.4). *Anal.* calcd. for $C_{21}H_{29}NO_4$: C 70.17, H 8.13, N 3.90; found: C 69.81, H 8.47, N 3.73.

Data for other diols are given in Table 2.

Reduction of N*-phenyl-2,4-dimethyl analogue* **2***g mother liquors in HOAc*

A mixture of the mother liquor (0.41 g), (identical to crystalline material by tlc) from the condensation reaction leading to **2***g*, PtO_2 (55 mg), and glacial HOAc (15 mL) was stirred under H_2 (44 psi) for 22 h. The catalyst was removed and the filtrate was diluted with EtOAc, then washed with dilute $NaHCO_3$ and water. The crude product (0.42 g) was purified by flash chromatography into three fractions. The least polar fraction (9 mg) was determined to be diol **7***d* by comparative spectral data.

The second fraction was separated into two lactones by preparative tlc (40% EtOAc–hexane; two dips). The more polar fraction gave hydroxy lactone **8***a* as colorless crystals from $CHCl_3$ (13.7 mg); mp 165–167°C; ir: 3500, 3320, 1720, 1662, 1525 cm^{-1}; nmr δ: 7.4 (m, 3H), 7.1 (m, 2H), 4.37 (br, 1H), 3.73 (m, 1H), 0.96 (d, 3H, J = 2.8), 0.92 (d, 3H, J = 3.4). *Anal.* calcd. for $C_{21}H_{29}NO_4$: C 70.17, H 8.13, N 3.90; found: C 69.95, H 8.46, N 3.95.

The less polar lactone was keto lactone **8***b* (13.2 mg); mp 164–170°C; ir: 3300, 1720, 1700, 1655, 1535 cm^{-1}; nmr δ: 7.5 (m, 3H), 7.3 (m, 2H), 4.7 (br m, 1H), 3.35 (d, 1H), 3–1.4 (14H), 1.0 (d, 6H, J = 6.35). *Anal.* calcd. for $C_{21}H_{27}NO_4$: C 70.56, H 7.62, N 3.92; found: C 70.61, H 7.52, N 4.05.

A third column fraction furnished acetoxy lactone **8***c* (10 mg); mp 160.5–163°C; ir: 3280, 1730, 1710, 1675, 1630 cm^{-1}; nmr δ: 5.5 (br, 1H), 4.6 (br, 1H), 3.75 (br, 1H), 2.01 (s, 3H), 2.8–1.2 (28H), 1.0 (d, 6H, J = 4.1). *Anal.* calcd. for $C_{23}H_{37}NO_5$: C 67.78, H 9.15, N 3.44; found: C 67.55, H 9.45, N 3.95.

Reduction of 2-methyl analogue **2***c mother liquors in HOAc*

Mother liquors from preparation of 2-methylcycloheximide analogue **2***c* (0.67 g), which were identical by tlc to crystalline material, were reduced over PtO_2 (100 mg) in glacial HOAc (20 mL) as above. The crude product was acetylated by Ac_2O–pyridine as usual and then separated by preparative tlc (3% MeOH–$CHCl_3$; two dips) into five fractions. Three fractions crystallized and were identified.

The least mobile fraction gave hydroxy lactone **8***d* (11 mg); mp 167–169.5°C; ir: 3460, 3330, 1715, 1655, 1530 cm^{-1}; nmr δ: 5.4 (br, 1H, lost with D_2O), 4.45 (br, 1H), 3.74 (m, 1H), 2.8–1.2 (27H), 0.96 (d, 3H, J = 5.7). *Anal.* calcd. for $C_{20}H_{33}NO_4$: C 68.34, H 9.45, N 3.98; found: C 68.55, H 9.54, N 4.18.

The second fraction was identified as acetoxy lactone **8***e* (10 mg); mp 175–176°C; ir: 3330, 1725, 1645, 1530, 1245 cm^{-1}; nmr δ: 5.4 (m, 1H), 4.2 (m, 1H), 3.7 (m, 1H), 2.07 (s, 3H), 2.7–1.0 (29H), 0.85 (d, 3H, J = 6.1). *Anal.* calcd. for $C_{22}H_{35}NO_5$: C 67.14, H 8.97, N 3.56; found: C 67.08, H 9.11, N 3.56.

The most mobile fraction (82 mg) gave 12 mg of acetoxy imide **9** from EtOAc; mp 149–150°C; ir: 1725, 1680, 1250 cm^{-1}; nmr δ: 7.4 (m, 3H), 7.2 (m, 2H), 5.13 (m, 1H), 2.09 (s, 3H), 3.1–1.1 (17H), 0.85 (d, 3H, J = 5.4). *Anal.* calcd. for $C_{22}H_{29}NO_4$: C 71.13, H 7.87, N 3.77; found: C 71.16, H 8.18, N 3.88.

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