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Highly Diastereoselective Cyanation of Methyl Ketimines Obtained from (*R*)-Glyceraldehyde

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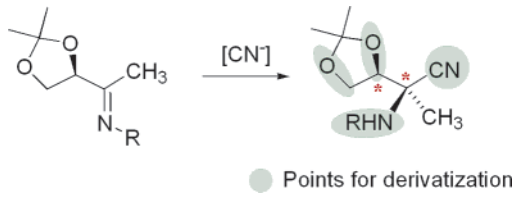

Addition of trimethylsilyl cyanide to ketimines derived from (*R*)-2,2-dimethyl-1,3-dioxolan-4-yl methyl ketone to generate a quaternary stereocenter has been achieved with high yields and excellent diastereoselectivity. The stereoselectivity was found to be temperature and solvent dependent. The *β*-hydroxy-α-amino nitrile of syn configuration was the major compound in kinetically controlled reactions, whereas the anti stereoisomer was obtained in excess in thermodynamically controlled reactions. Double stereodifferentiation under kinetic control conditions was successful, and the cyanation reaction occurred with complete syn diastereoselectivity using the matched pair. The versatility of the resulting amino nitrile as a synthetic intermediate was tested by performing the synthesis of orthogonally protected (*R*)-(2-aminomethyl)alanine.

α-Amino nitriles have proven to be versatile intermediates for a large number of synthetic applications.[1] In historical terms, the most important use of α-amino nitriles involves hydrolysis of the nitrile group to generate α-amino acids. It is also possible to reduce the nitrile group to prepare 1,2-diamines, which are employed as medicinal agents or chiral ligands.[2] The cyanation of imines offers a short route to α-amino nitriles, and there has been great interest in developing an asymmetric version of this process to obtain chiral α-amino nitriles for use as intermediates in the production of optically active α-amino acids. Of particular interest are nonproteinogenic α-amino acids,[3] which are often used as key building blocks in pharmaceuticals. Moreover, in recent years, several methods and strategies for the asymmetric synthesis of quaternary stereocenters have been developed and published[4] and the stereoselective Strecker reaction of ketimines is one of the most direct and practical methods for the synthesis of amino nitriles with quaternary stereocenters.

Reactions involving ketimines remain a great challenge because of their low reactivity and the difficulty in controlling facial stereoselectivity, and in this context, some research has been carried out in an attempt to overcome these difficulties. These efforts have recently culminated in efficient chiral catalysts for the cyanation of ketimines,[5] and these systems provide excellent enantioselectivities for aromatic ketimines. Nevertheless, the stereoselectivity is significantly lower when aliphatic ketimines are used as starting materials. Moreover, the cost and time involved in synthesizing these complex catalysts constitute a serious drawback for their applicability.

Most of the reported methods for the asymmetric cyanation of ketimines involve the use of stoichiometric chiral auxiliaries or optically active starting materials. Among the stoichiometric approaches, the addition of cyanide to ketimines using amines as chiral auxiliaries has already been investigated and applied to the stereoselective synthesis of α,α-dialkylamino acids.[6,7]

In contrast, Strecker-type reactions using ketimines in which the chiral matrix is the carbonyl moiety have been exploited to a much lesser extent. Indeed, most studies have been based on the use of chiral cyclic ketimines derived mainly from carbohydrates.[8] Approaches using acyclic ketimines derived from chiral ketones afford the corresponding α-amino nitriles in acceptable yields but, unfortunately, with modest or very low diastereoselectivities.[9]

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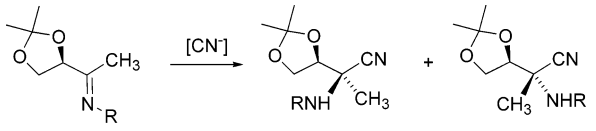
SCHEME 1



1a-c *syn* **2a-c** *anti* **2a-c**

a, R = $PhCH_2$
b, R = (*R*)-$Ph(CH_3)CH$
c, R = (*S*)-$Ph(CH_3)CH$

Bearing in mind the important role that α,α-dialkylamino acids with aliphatic side chains can play in the construction of novel peptidic sequences with tailor-made enhanced properties,[10] it is essential to carry out additional studies on the asymmetric cyanation of aliphatic acyclic ketimines.

We have previously reported the diastereoselective addition of cyanide to aldimines derived from conveniently protected (*R*)-glyceraldehyde as a novel approach to enantiomerically pure *β*-hydroxy-α-amino acids.[11] We wish to report here an extension of this methodology to *N*-benzyl ketimines derived from (*R*)-2,2-dimethyl-1,3-dioxolan-4-yl methyl ketone to afford dihydroxylated α-amino nitriles bearing a quaternary stereogenic center and a tertiary stereogenic center at consecutive positions. These compounds can be regarded as useful new building blocks because they have four possible points of derivatization in contiguous positions, namely cyano and amino groups at C_2 and hydroxy groups at C_3 and C_4 (Scheme 1).

(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl methyl ketone was easily obtained from (*R*)-2,3-*O*-isopropylideneglyceraldehyde following the procedure described by Leyes and Poulter.[12] Condensation of this ketone with benzylamines promoted by $TiCl_4$[13] yielded the *N*-benzyl ketimines **1a**−**c** employed in this study. The *E* stereochemistry of the C=N bond was assigned by selective ge-1D nuclear Overhauser enhancement spectroscopy (NOESY) experiments.

Crude ketimines were used in the subsequent cyanation reaction (Scheme 1), and chromatographic purification was not required. The results obtained in the cyanation reactions of compounds **1a**−**c** are collected in Table 1.

Initially, ketimine **1a** was allowed to react with trimethylsilyl cyanide (1.2 equiv) in dichloromethane at room temperature to afford a mixture of the corresponding amino nitriles **2a** in moderate yield and with high diastereoselectivity in favor of the amino nitrile of *R* configuration on the newly formed stereogenic center (relative configuration syn) (entry 1). In the presence of a Lewis acid such as zinc chloride or through the use of other cyanide sources such as diethylaluminum cyanide, the starting ketimine rapidly decomposed and a complex mixture of products that was difficult to purify was obtained. Fortunately, the use of a larger excess of trimethylsilyl cyanide (2 equiv) substantially improved the yield of the cyanation reaction (entry 2). We proceeded to investigate the influence of temperature and solvent on the reaction. By repeating the reaction at a lower temperature in dichloromethane or by using other aprotic solvents, we observed slight variations in chemical yield and diastereoselectivity (entries 3−8). The best results were obtained at −20 °C in dichloromethane or acetonitrile. On the other hand, the diastereofacial selectivity was found to be very sensitive to temperature changes by using the protic solvent 2-propanol (entries 9−11). For example, *syn*-**2a** was obtained preferentially at −20 °C whereas the anti diastereoisomer was obtained in excess at room temperature. Moreover, when the reaction time was increased from 3 to 12 h, the syn/anti ratio changed markedly to reach a maximum value of 34:66.

On the basis of the experimental data described above, we reasoned that the addition of trimethylsilyl cyanide to imine **1a** proceeded under kinetic control at −20 °C in CH_2Cl_2 and under thermodynamic control at room temperature in 2-propanol in conjunction with longer reaction times. In an effort to demonstrate this assumption, diastereomerically pure amino nitriles *syn*-**2a** and *anti*-**2a**, which were previously purified by column chromatography, were dissolved in CH_2Cl_2 and 2-propanol, respectively. The four resulting solutions were kept at room temperature for several days, and the syn/anti ratio was monitored by high-pressure liquid chromatography (HPLC). After 2 days, products dissolved in CH_2Cl_2 remained unaltered whereas solutions of both *syn*-**2a** and *anti*-**2a** in 2-propanol evolved to reach a thermodynamic ratio (syn/anti = 34:66).

The absolute configuration at the newly formed stereogenic center in the cyanation reaction was unambiguously determined by single-crystal X-ray diffraction analysis of compound *anti*-**2a**.

Finally, we studied the possibility of using ketimines derived from chiral amines as starting compounds to perform a double stereodifferentiation process. With this aim in mind, ketimines **1b** and **1c**, derived from (*R*)- and (*S*)-α-methylbenzylamines, respectively, were treated with trimethylsilyl cyanide under the optimal kinetic reaction conditions established previously, i.e., using dichloromethane as the solvent at −20 °C. Under these conditions, the corresponding cyanide addition products were obtained in high yields (entries 12 and 13). Asymmetric induction was not observed on starting with the ketimine derived from (*R*)-α-methylbenzylamine, and an almost equimolecular mixture of syn and anti adducts was obtained (mismatched pair). On the other hand, when the imine derived from (*S*)-α-methylbenzylamine was used as the substrate, the syn diastereoisomer was the only product detected by NMR (matched pair).

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TABLE 1. Stereoselective Addition of Cyanide to Ketimines 1a−c

entry	ketimine	[CN⁻] source (equiv)	solvent	*T* (°C)	reaction time (h)	product	yield[a] (%)	dr[b] syn/anti
1	**1a**	Me_3SiCN (1.2)	CH_2Cl_2	rt	3	**2a**	44	84/16
2	**1a**	Me_3SiCN (2)	CH_2Cl_2	rt	3	**2a**	79	83/17
3	**1a**	Me_3SiCN (2)	CH_2Cl_2	0	3	**2a**	84	81/19
4	**1a**	Me_3SiCN (2)	CH_2Cl_2	−20	3	**2a**	84	87/13
5	**1a**	Me_3SiCN (2)	CH_2Cl_2	−40	3	**2a**	72	79/21
6	**1a**	Me_3SiCN (2)	toluene	−20	3	**2a**	77	84/16
7	**1a**	Me_3SiCN (2)	THF	−20	3	**2a**	69	85/15
8	**1a**	Me_3SiCN (2)	MeCN	−20	3	**2a**	89	86/14
9	**1a**	Me_3SiCN (2)	^{i}PrOH	−20	3	**2a**	47	82/18
10	**1a**	Me_3SiCN (2)	^{i}PrOH	rt	3	**2a**	73	41/59
11	**1a**	Me_3SiCN (2)	^{i}PrOH	rt	12	**2a**	61	34/66
12	**1b**	Me_3SiCN (2)	CH_2Cl_2	−20	3	**2b**	79	50/50
13	**1c**	Me_3SiCN (2)	CH_2Cl_2	−20	3	**2c**	82	>98/2

[a] Isolated yield after chromatography on silica gel. [b] Ratio determined by ^{1}H NMR analysis of the crude reaction mixtures using C_6D_6 as solvent.

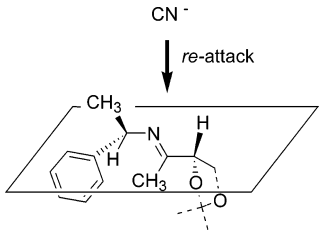


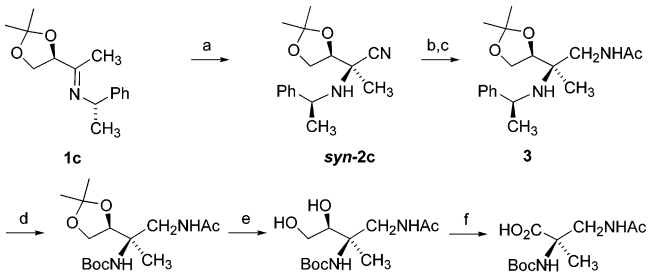
FIGURE 1.

We previously reported a model for the addition of trimethylsilyl cyanide to *N*-benzylimines derived from conveniently protected (*R*)-glyceraldehyde, and this model was supported by ab initio calculations.[11b] According to this model, the stereochemical course of the cyanation reaction of ketimine **1c** can be rationalized by assuming (i) that the trimethylsilyl moiety coordinates to the imine nitrogen, (ii) that the carbonyl moiety preferentially adopts an anti-Felkin−Anh conformation in which the α-C−OR bond is orthogonally oriented to the plane containing the imine group, and (iii) that the *N*-(*S*)-α-methylbenzyl group adopts a conformation in which the allylic 1,3 strain is minimized.[14] Attack of the cyanide from the *re* side accounts for the observed preferential production of the syn diastereoisomer (Figure 1).

Amino nitrile *syn*-**2c** can be used as a synthetic intermediate to prepare a wide variety of nitrogen-containing compounds with a chiral quaternary carbon atom, including amino alcohols, diamines, α-methyl-α-amino acids, etc., by the appropriate elaboration of the amino, the 2,2-dimethyl-1,3-dioxolan-4-yl, and/or the nitrile moieties. As an example, to demonstrate the versatility of this intermediate, the synthesis of orthogonally protected (*R*)-(2-aminomethyl)alanine was chosen. In our strategy, which is outlined in Scheme 2, the 2,2-dimethyl-1,3-dioxolan-4-yl moiety acts as the carboxylic acid precursor and the aminomethyl group is obtained from the nitrile group.

Reduction of amino nitrile *syn*-**2c** with lithium aluminum hydride provided the desired amine, which was isolated as the corresponding *N*-acetyl derivative **3**. Hydrogenolytic *N*-debenzylation of compound **3** in the presence of di-*tert*-butyl dicarbonate resulted in the formation of orthogonally protected diamine **4** in high yield. Deprotection of the acetal with trifluoroacetic acid afforded diol **5**, from which the (*R*)-(2-aminomethyl)-alanine derivative **6** was obtained by oxidative cleavage of the 1,2-diol moiety by treatment with excess sodium periodate in the presence of ruthenium trichloride.[15]

SCHEME 2[a]



[a] Reagents and conditions: (a) TMSCN, CH_2Cl_2, −20 °C, 6 h; (b) $LiAlH_4$, THF, 0 °C → room temperature, 3 h; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 2 h; (d) H_2 20% $Pd(OH)_2$/C, Boc_2O, EtOH, room temperature, 18 h; (e) CF_3CO_2H, 3:1 MeOH/H_2O, room temperature, 24 h; (f) $NaIO_4$, 2:2:3 CH_3CN/CCl_4/H_2O, room temperature, 5

In summary, the optimal conditions to carry out the cyanation of *N*-benzyl ketimines derived from (*R*)-2,2-dimethyl-1,3-dioxolan-4-yl methyl ketone have been identified and involve the use of trimethylsilyl cyanide in the absence of Lewis acid in dichloromethane at a low temperature. Under these conditions, the addition of cyanide to ketimines derived from (*S*)-α-methylbenzylamine exhibits a double stereodifferentiation process and the reaction takes place with complete control of stereoselectivity to afford the corresponding quaternary α-amino nitrile with the syn relative configuration. The resulting γ,β-dihydroxy-α-amino nitrile has four possible points for further derivatization and can presumably be used to prepare a wide variety of nitrogen-containing

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compounds. As an example, the 2,2-dimethyl-1,3-dioxolan-4-yl moiety has been transformed into a carboxylic acid group and the nitrile group has been reduced to an aminomethyl group to give a (*R*)-(2-aminomethyl)alanine derivative. Substitution of methylmagnesium bromide by different organomagnesium reagents[16] in the synthesis of the starting ketone would allow the preparation of a variety of alkyl ketimines, and this would extend the scope of the methodology described here. Research into this area is underway and will be published in due course.

Experimental Section

(*R*)-2-[(*S*)-1-Phenylethylamino]-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propane Nitrile (*syn*-2c). TMSCN (36.10 mmol) was added to a solution of crude imine **1c** (18.03 mmol) in dry CH_2Cl_2 (150 mL) at −20 °C under argon. The reaction mixture was kept at this temperature for 6 h and then quenched by adding saturated aqueous NH_4Cl (40 mL) and water (40 mL). The organic phase was washed successively with saturated aqueous $NaHCO_3$ and brine and then dried over anhydrous $MgSO_4$. Removal of the solvents in vacuo yielded 4.51 g of a crude product containing the corresponding amino nitrile *syn*-**2c**, which was used in the next step without further purification.

For characterization purposes, amino nitrile *syn*-**2c** was purified by flash chromatography on a silica gel column using hexane/ethyl acetate (3:1): $[\alpha]^{27}_D = -104.9$ (*c* 1.36, $CHCl_3$); IR absorption (pure) 3342, 2222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.05 (m, 5H), 4.17 (dd, 1H, J = 6.8 Hz, J = 6.8 Hz), 4.12 (dd, 1H, J = 8.0 Hz, J = 6.8 Hz), 4.10 (q, 1H, J = 6.8 Hz), 3.99 (dd, 1H, J = 8.0 Hz, J = 6.8 Hz), 1.95 (bs, 1H), 1.54 (s, 3H), 1.41 (s, 3H), 1.40 (d, 3H, J = 6.8 Hz), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 128.4, 127.0, 126.3, 121.3, 110.5, 80.2, 64.3, 57.6, 54.7, 26.5, 26.1, 24.9, 21.9; HRMS (FAB$^+$) calcd for $C_{15}H_{22}N_2O_2$ (M^+ − CN) 248.1650, found 248.1645.

(*R*)-*N*-Acetyl-2-[(*S*)-1-phenylethylamino]-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-propylamine (3). A 1 M solution of $LiAlH_4$ in THF (66 mmol) was added dropwise to a solution of the crude amino nitrile *syn*-**2c** (obtained in the previous step) in dry THF (200 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and then cooled to 0 °C. After the addition of CH_2Cl_2 (100 mL), the reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ (50 mL) and filtered through Celite. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvents were removed in vacuo. The residue was dissolved in dry CH_2Cl_2 (120 mL), and to the solution was added successively Et_3N (24.8 mmol), DMAP (0.86 mmol), and Ac_2O (19.81 mmol). The reaction mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and after removal of the solvent, the residue was chromatographed on silica gel (AcOEt) to give pure product **3** as a colorless oil (3.82 g, 66% from imine **1c**): $[\alpha]^{26}_D = -11.9$ (*c* 0.96, $CHCl_3$); IR absorption (pure) 3309, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.15 (m, 5H), 6.20 (bs, 1H), 4.08 (dd, 1H, J = 7.6 Hz, J = 7.6 Hz), 4.00 (dd, 1H, J = 6.4 Hz, J = 6.4 Hz), 3.94 (q, 1H, J = 6.8 Hz), 3.87 (dd, 1H, J = 7.6 Hz, J = 6.4 Hz), 3.80 (dd, 1H, J = 14.0 Hz, J = 8.8 Hz), 2.79 (dd, 1H, J = 14.0 Hz, J = 2.4 Hz), 2.05 (bs, 1H), 1.94 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.27 (d, 3H, J = 6.8 Hz), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 148.9, 128.2, 126.4, 126.2, 109.2, 82.3, 65.4, 55.7, 51.1, 44.9, 27.2, 26.3, 25.2, 23.3, 20.2; HRMS (FAB$^+$) calcd for $C_{18}H_{29}N_2O_3$ (MH^+) 321.2178, found 321.2187.

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(*R*)-*N*-Acetyl-2-(*tert*-butoxycarbonylamino)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-propylamine (4). To a solution of compound **3** (6.4 mmol) and Boc_2O (19.2 mmol) in absolute ethanol (75 mL) was added 20% $Pd(OH)_2/C$ (300 mg), and the mixture was hydrogenolysed with H_2 at 1 atm with shaking at room temperature for 18 h. After completion of the reaction, the mixture was filtered through Celite and concentrated in vacuo. The residue was purified by silica gel flash chromatography (1st eluent ether/hexane 1:1; 2nd eluent AcOEt) to give pure **4** as a colorless oil (1.85 g, 91%): $[\alpha]^{26}_D = -11.7$ (*c* 1.05, $CHCl_3$); IR absorption (pure) 3311, 1710, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (bs, 1H), 5.12 (bs, 1H), 4.19 (dd, 1H, J = 6.4 Hz, J = 6.4 Hz), 4.02 (dd, 1H, J = 9.2 Hz, J = 6.4 Hz), 3.88 (dd, 1H, J = 9.2 Hz, J = 6.4 Hz), 3.57 (dd, 1H, J = 14.0 Hz, J = 6.4 Hz), 3.40 (dd, 1H, J = 14.0 Hz, J = 5.6 Hz), 1.98 (s, 3H), 1.45 (s, 3H), 1.43 (s, 9H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 155.8, 109.6, 79.7, 79.4, 65.0, 56.6, 45.7, 28.3, 26.2, 24.5, 23.3, 21.7; HRMS (FAB$^+$) calcd for $C_{15}H_{29}N_2O_5$ (MH^+) 317.2076, found 317.2081.

(*R*)-4-Acetylamino-3-(*tert*-butoxycarbonylamino)-3-methyl-1,2-butanediol (5). A solution of compound **4** (1.90 mmol) in 3:1 MeOH/H_2O (8 mL) was treated with CF_3CO_2H (0.96 mmol), and the mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, and the residue was diluted with H_2O (5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (AcOEt/EtOH 7:1) to give pure **5** as a white solid (481 mg, 92%): mp = 131−132 °C; $[\alpha]^{24}_D$ = +8.9 (*c* 1.0, CH_3OH); IR absorption (KBr) 3535, 3442, 3327, 1710, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (bs, 1H), 5.29 (bs, 1H), 3.72 (dd, 1H, J = 11.2 Hz, J = 3.2 Hz), 3.64 (dd, 1H, J = 14.0 Hz, J = 6.8 Hz), 3.60 (dd, 1H, J = 11.2 Hz, J = 7.6 Hz), 3.51 (dd, 1H, J = 7.6 Hz, J = 3.2 Hz), 3.47 (dd, 1H, J = 14.0 Hz, J = 6.4 Hz), 2.01 (s, 3H), 1.41 (s, 9H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 156.3, 80.0, 74.5, 62.1, 57.6, 45.0, 28.3, 23.2, 20.3. Elemental Anal. Calcd (%) for $C_{12}H_{24}N_2O_5$: C, 52.16; H, 8.75; N, 10.14. Found: C, 52.58; H, 8.94; N, 10.23.

(*R*)-(2-Acetylaminomethyl)-*N*-(*tert*-butoxycarbonyl)alanine (6). Small portions of $NaIO_4$ (4.88 mmol) were added to a stirred solution of compound **5** (1.12 mmol) in $CH_3CN/CCl_4/H_2O$ (2:2:3, 30 mL). After being vigorously stirred for 5 min following completion of the addition, the mixture was treated with $RuCl_3$ (0.053 mmol) and stirring was continued for 2 h. CH_2Cl_2 was added (30 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by silica gel flash chromatography (AcOEt) to give pure product **6** as a colorless oil (180 mg, 62%): $[\alpha]^{25}_D = +40.5$ (*c* 1.0, $CHCl_3$); IR absorption (KBr) 3500−2500, 1710, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (bs, 1H), 6.27 (bs, 1H), 3.76 (dd, 1H, J = 14.0 Hz, J = 6.8 Hz), 3.54 (dd, 1H, J = 14.0 Hz, J = 5.6 Hz), 2.02 (s, 3H), 1.54 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 172.4, 157.5, 81.7, 61.5, 46.4, 28.3, 22.9, 21.3; HRMS (FAB$^+$) calcd for $C_{11}H_{21}N_2O_5$ (MH^+) 261.1450, found 261.1444.

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Supporting Information Available: General statement describing materials and methods, general experimental procedures, ^1H NMR, and ^{13}C NMR spectra for all compounds; thermal ellipsoid plot for compound *anti*-**2a**; and X-ray crystallographic data in CIF format for compound *anti*-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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