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Michael Reactions of Titanium Enolates of Glycolic Acid Derivatives with the Weinreb and Morpholine Amides of Acrylic Acid

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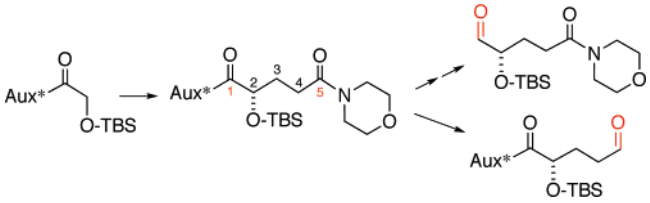
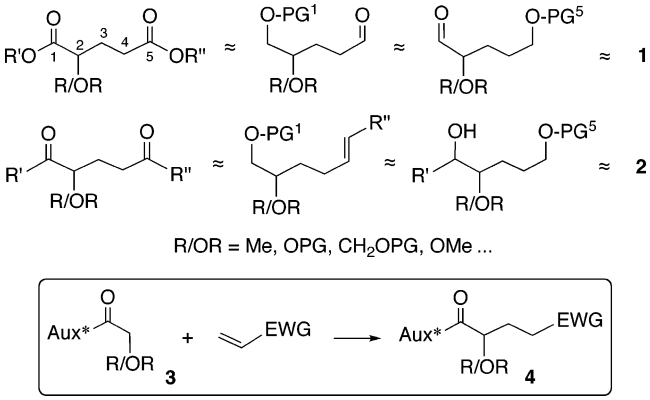


The conjugate additions of titanium enolates of glycolate-derived chiral oxazolidin-2-ones to various Michael acceptors have been evaluated as an entry to enantiopure 1,2,5-trioxygenated and related synthons. α,β-unsaturated Weinreb and morpholine amides do react under suitable conditions and their adducts can be converted to diverse C1−C5 chiral fragments.

Our ongoing studies toward the total syntheses of cytotoxic macrolides have required enantiopure C1−C5 building blocks of type **1** (and/or their C4-Me derivatives).[1] From synthons such as **1**, a diversity of fragments of structure **2** may be readily accessible. We have obtained some of these fragments from L-glutamic acid or its enantiomer, through its hydroxy analogues (butyrolactone derivatives).[1b] A more general approach involves a Michael reaction between compounds of type **3** and EWG-conjugated olefins. Alkaline enolates of type **3** decompose before reacting with $H_2C{=}CH{-}EWG$,[2,3] but Evans et al. found[3a] that Ti enolates of propanoyl oxazolidin-2-ones **3** (Aux* = L-Phe-derived auxiliary, R/OR = Me) reacted with alkyl acrylates and acrylonitrile to give the corresponding adducts of type **4** (Scheme 1) with high diastereoselection; methacrylate derivatives turned out to be more reluctant as Michael acceptors.[1a,3c]

SCHEME 1. Representative Series of C1−C5 Fragments Available from 3 and Michael Acceptors



In this context, we examined the reaction of **3**[4] with a set of acceptors for which there were no precedents. We report here the particular but representative case of **3** where Aux* is the 1,3-oxazolidin-2-one coming from D-Phe and R/OR is OTBS.[5] The main results can be summarized as follows.

When *N*-methoxy-*N*-methylpropenamide (the Weinreb amide of acrylic acid), prepared by treating free *N*,*O*-dimethylhydroxylamine with acryloyl chloride according to a reported procedure,[6] was added to titanium enolates[3a,7] of **3**, R/OR = OTBS, the yields of adduct **4a** were very poor with $TiCl_4$ as the Lewis acid (Table 1, entry 1) but improved up to 40−50% with a 75:25 $TiCl_4$−$Ti(O^iPr)_4$ mixture and increased up to 50−65% with 2 equiv of this mixture (Table 1).

When *N*-propenoylmorpholine, prepared from acryloyl chloride, morpholine, and diisopropylethylamine in CH_2Cl_2 in quantitative yield, was added to Ti enolates of **3** (R/OR = OTBS), the yields of the Michael adduct were 60−70%. When 2 equiv of $TiCl_3O^iPr$ were used (exactly 1.05 equiv in the enolization step and 1.10 equiv for the pre-complexation of the propenoylmorpholine), the yield went up to 86% (see Table 1, entry 2).

Although the electron-withdrawing character of $CONR_2$ and CON(OMe)Me groups was expected to be lower than that of CN and COOR groups, the fact was that the corresponding Michael adducts could be obtained in acceptable or good yields. In all cases, a single diastereomer was observed by ^1H NMR, in the crude product and after column chromatography; the

(1) (a) Mas, G.; González, L.; Vilarrasa, J. *Tetrahedron Lett.* **2003**, *44*, 8805 (amphidinolide K). (b) Andreou, T.; Costa, A. M.; Esteban, L.; González, L.; Mas, G.; Vilarrasa, J. *Org. Lett.* **2005**, *7*, 4083 (amphidinolide K). (c) Rodríguez-Escrich, C.; Olivella, A.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 989 (amphidinolide X/Y).

(2) Li and Na enolates of type **3**, when the temperature is raised up to −30 °C to increase the reaction rates, begin to decompose.

(3) (a) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961 (application to the total synthesis of calyculin). (c) Mas, G. Ph.D. Thesis, Universitat de Barcelona, 2000. (d) For the reaction of enolates of trisubstituted oxazolidinones with nitroalkenes, see: Brenner, M.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 2365. (e) For Michael additions of Li enolates to more reactive CF_3-substituted acrylates, see: Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363.

(4) In preliminary experiments, we had examined the reactions of Aux*COEt (**3**, Aux* = Evans L-Phe-derived auxiliary, R/OR = Me) with Michael acceptors such as $CH_2{=}CH{-}CON(OMe)Me$ and morpholine amide $CH_2{=}CH{-}CON(C_4H_8O)$. The results were parallel to those reported here.

(5) The TBS protecting group was chosen in view of its stability under the reaction conditions and the availability of specific cleavage methods. The OBn derivative decomposes before reacting, under similar conditions. The synthetic utility of the enolates of glycolate-derived oxazolidinones in other reactions, such as aldol reactions and alkylations, has been established: (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506. (b) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165.

(6) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735.

(7) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

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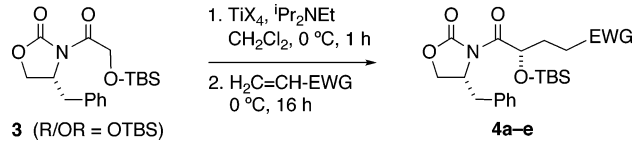
TABLE 1. Michael Additions of Ti Enolates of 3[a]



3 (R/OR = OTBS) **4a–e**

entry	EWG	yield (%) with $TiCl_4$	yield (%) with $TiCl_3O^iPr$	adduct
1	CON(OMe)Me	10	65[b]	**4a**
2	CON(C_4H_8O)[c]	61	86[b]	**4b**
3	$COSC_{12}H_{25}$	41	53	**4c**
4	COOMe	20	80	**4d**
5	COO^tBu		80	**4e**

[a] See the Experimental Section for details. [b] An extra amount of the Lewis acid (1.10 equiv) was added to the Michael acceptor solution before adding it via canula to the Ti enolate solution; when the extra amount of Lewis acid was 1.50 equiv, a slurry of difficult addition or transfer was formed (in practice, the isolated yields of the adducts diminished). [c] Morpholine amide.

HPLC analysis of the isolated compounds indicated a purity of 98−99%. Thus, the dr (≥98:2) turned out to be similar to those found in related Michael additions.[1c,3,4]

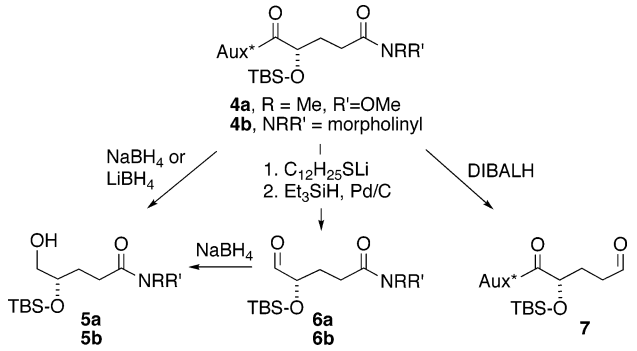
Reactions of **3**, R/OR = OTBS, with an unsaturated thiol ester and alkyl acrylates were also investigated (see Table 1, entries 3−5). With the thiol ester shown in entry 3 the addition did not reach completion even in the presence of an excess of Lewis acids; thus, we ruled out this adduct for subsequent manipulations. On the other hand, with methyl acrylate and *tert*-butyl acrylate (entries 4 and 5) the reactions with $TiCl_3O^iPr$ were quite efficient with only 1.05 equiv of this Lewis acid and did not improve with additional amounts. Again, only one diastereoisomer was detected in every case by ^1H NMR and by HPLC.

The configuration of **4d** was established by its hydrolysis to α-hydroxyglutaric acid, which after acidification and concentration gave the expected, known (+)-(*S*)-lactone-carboxylic acid. The configurations of the other adducts were assigned by analogy (NMR comparison with related Michael adducts of well-established absolute configurations).[1c,3a]

At this point, it was essential to distinguish one carboxyl group derivative from the other one of **4a** and **4b** for further chemical transformations of the C1−C5 fragment, according to our initial plans. Thus, we examined if the attack on the exocyclic CO group at C1 was feasible or not without touching the CO at C5, and vice versa. Attacks on the endocyclic CO group had to be avoided in all cases.

When **4a** was treated with $NaBH_4$[8] with a slight modification[8b] of the standard procedure, or with $LiBH_4$,[9] complete reduction to the expected hydroxy derivative (**5a**) took place (Scheme 2). Under identical conditions, **4b** gave **5b** in almost quantitative yield. By application of the cleavage method of Fukuyama et al.[10] to **4a** and **4b** (cleavage of Aux*−CO bonds with RSH under basic conditions, followed by the catalytic reduction of thioesters with Et_3SiH), the formyl group-containing compounds **6a** and **6b** were obtained, which were reduced in situ to (and stored as) **5a** and **5b**, respectively.

SCHEME 2. Chemoselective Transformations



On the other hand, reduction of the hydroxamate group of **4a** with DIBALH (1.5 equiv) in THF or Et_2O at −78 °C gave **7** in 95% yield,[11] without touching at all the acyl-oxazolidinone moiety.[12] This could be expected, but no examples have been reported so far.[11b]

Even more interesting, as there are no reports in the chemical literature about the chemoselective reduction of morpholine amides[13] in the presence of acyl-oxazolidinones or other acylated chiral auxiliaries, was the reduction of the morpholine amide group of **4b** with DIBALH (1.5 equiv, between −100 and −78 °C, in Et_2O or THF for a few minutes), which also gave rise to an oxo group at C5 (**7**) in 80% yield.[14]

Transformations of adducts **4d** and **4e** were also examined. The conditions of Fukuyama et al.[10] were useful to convert the Aux*CO moiety into a CHO group, without affecting the

(8) (a) Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067. (b) $NaBH_4$ was dissolved in phosphate-buffered water (pH 8); the reaction time was shortened to 30 min. Migration of the TBS group to the primary hydroxy group did not occur under these conditions.

(9) (a) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307. (b) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958. (c) Also see ref 1b for complex substrates where undesired conjugate additions can take place.

(10) (a) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477. (b) Fukuyama, T.; Tokuyama, H. *Aldrichim. Acta* **2004**, *37*, 87.

(11) The direct reduction of Weinreb amides to aldehydes is a standard. Since the pioneering work of Nahm and Weinreb (Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815), ca. 200 out of 500 papers have utilized DIBALH as the reducing agent, according to a SciFinder-based search. (b) Very often R*CO-Aux* are converted to R*CO-N(OMe)Me and then to R*CHO, but no examples are found of competition between the two first groups for nucleophiles.

(12) It is known that diisobutylaluminum hydride (DIBALH), in CH_2Cl_2 at −78 °C, attacks both the endo and exo CO groups of acylated oxazolidinones, whereas only the exocyclic CO reacts in the case of their 5,5-dimethyl analogues ("Super Quats"): (a) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3475. (b) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganese, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886. To favor the selective attack on the hydroxamate, we have utilized ethereal solvents.

(13) For the use of morpholine amides as an alternative to Weinreb amides, see: (a) Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414. (b) Kurosu, M.; Kishi, Y. *Tetrahedron Lett.* **1998**, *39*, 4793. (c) Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107. (d) Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37. (e) Jackson, M. M.; Leverett, C.; Toczko, J. F.; Roberts, J. C. *J. Org. Chem.* **2002**, *67*, 5032. (f) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G.; Torregiani, E.; Marcantoni, E. *J. Org. Chem.* **2002**, *67*, 8938. (g) Goodman, S. N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4703. (h) Clark, C. T.; Milgram, B. C.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 3977. (i) Tosaki, S.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem. Eur. J.* **2004**, *10*, 1527 and references cited therein. (j) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311. (k) Denmark, S. E.; Hemmstra, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1038. (l) Concellón, J. M.; Rodríguez-Solla, H.; Méjica, C.; Blanco, E. G. *Org. Lett.* **2007**, *9*, 2981.

ester groups. The reaction with $NaBH_4$ under pH-buffered conditions[8b] was also chemoselective, as only the Aux* group was removed. By sharp contrast, the reduction of **4d** with $LiBH_4$ led mainly to the diol (reduction of both the COOMe and COAux* groups, even with equimolar amounts of $LiBH_4$). Moreover, treatment of **4d** with DIBALH, under the smooth conditions indicated above (addition of 1.5 equiv of DIBALH in hexane at −100 °C to **4d** in THF at −100 °C, stirring for 15 min at −78 °C), afforded a 2:1 mixture of **4d** and **7**; with 2.2 equiv of DIBALH for 2 h at −78 °C, a 60:40 mixture of **7** and its alcohol (by reduction in situ of the formyl group of **7**) was obtained. Reduction of **4e** with DIBALH (1.5 equiv for 6 h at −78 °C) gave a 1.3:1 mixture of **4e** and **7**; with a larger excess of DIBALH (2.5 equiv, for 2 h at −78 °C) the ratio among **4e**, **7**, and the alcohol derived from the formyl group of **7** was 1:4:3. In other words, we were unable to find as large a range of reaction conditions allowing us to discriminate between COOR and COAux* as we were with CONRR′ and COAux*.

In summary, previous functionalization of the propenoic (acrylic) acid derivatives as hydroxamates or morpholine amides does not preclude their highly diastereoselective reactions with appropriate chiral Ti enolates. With the more stable morpholine amide, the yields of the Michael adducts are remarkable under the conditions reported here. These adducts may then be cleaved smoothly by attack of appropriate nucleophiles at either C1 or C5, with high chemoselectivity. The reaction of the morpholine amides[14b] with DIBALH (in the presence of *N*-acyl oxazolidinones), which are reported for the first time to the best of our knowledge, are interesting alternatives to the synthetic arsenal for the carboxyl-to-carbonyl conversions. Various enantiopure fragments of type **1** and **2** are accessible via this approach, bearing in mind that the formyl groups of **6** and **7** are amenable to single and double C−C bond-forming reactions.

Experimental Section

General Procedure (Michael Reaction). To 1.00 mmol of **3** (Aux*H = (*R*)-4-benzyloxazolidin-2-one, R/OR = OTBS) in 6 mL of CH_2Cl_2 at 0 °C were added 1.05 mmol of a previously prepared 0.5 M solution of TiX_4 in CH_2Cl_2 and then 1.05 mmol of $^iPr_2NEt$. Stirring for 1 h, addition of 1.50 mmol of the Michael acceptor (in 3 mL of CH_2Cl_2 via canula), stirring for a further 16 h, partitioning of the final mixture between aqueous $NaHCO_3$ and EtOAc, and purification by flash column chromatography gave the desired adducts.

In the case of entries 1 and 2, when 1.05 mmol of $TiCl_3O^iPr$ [from a 75:25 $TiCl_4$−$Ti(O^iPr)_4$ mixture in CH_2Cl_2] were employed in the enolization step, the Michael acceptor was pre-complexed with an additional 1.10 mmol of $TiCl_3O^iPr$.

4-[(*R*)-Benzyl]-1-[(*S*)-2-*tert*-butyldimethylsilyloxy-4-(*N*-methoxy-*N*-methylamino)carbonyl]butanoyl-1,3-oxazolidin-2-one, or 4-[(*S*)-*tert*-Butyldimethylsilyloxy]-5-[(*R*)-4-phenylmethyl-2-oxo-1,3-oxazolidin-3-yl]-*N*-methoxy-*N*-methyl-5-oxopentanamide (4a): colorless oil; R_f 0.52 (CH_2Cl_2/MeOH 98:2); $[\alpha]_D$ −52.9 (*c* 0.98, $CHCl_3$); t_R (HPLC) 8.0 min (4.6 mm × 250 cm silica gel column, 0.9 μL/min, 90:10 hexane−isopropanol); IR (film) 1779, 1713, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5 H), 5.39 (dd, *J* = 7.2, 4.0 Hz, 1 H), 4.73 (ddt, *J* = 10.2, 7.8, 3.6 Hz, 1 H), 4.25 (dd, *J* = 9.0, 7.8 Hz, 1 H), 4.19 (dd, *J* = 9.0, 3.6 Hz, 1 H), 3.69 (s, 3 H), 3.34 (dd, *J* = 13.4, 3.6 Hz, 1 H), 3.17 (s, 3 H), 2.72 (dd, *J* = 13.4, 10.2 Hz, 1 H), 2.8−2.6 (m, 2 H), 2.2−2.1 (m, 1 H), 2.05 (dddd, *J* = 13.6, 10.0, 7.2, 6.4 Hz, 1 H), 0.94 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.8 (C), 170.2 (C), 153.0 (C), 135.1 (C), 129.4 (CH), 129.0 (CH), 127.4 (CH), 70.6 (CH), 66.8 (CH_2), 61.2 (CH_3), 55.0 (CH), 37.9 (CH_2), 31.6 (CH_3), 29.9 (CH_2), 27.7 (CH_2), 25.7 (CH_3), 18.3 (C), −4.8 (CH_3), −5.3 (CH_3); HRMS (+ESI) calcd for $C_{23}H_{37}N_2O_6Si$ [M + H]$^+$ *m*/*z* 465.2415, found 465.2420.

1-[(*S*)-2-*tert*-Butyldimethylsilyloxy]-4-(4-morpholinylcarbonyl)butanoyl]-4-[(*R*)-phenylmethyl]-1,3-oxazolidin-2-one (4b): colorless oil; R_f 0.62 (CH_2Cl_2/MeOH 95:5); t_R (HPLC) 10.6 min (90:10 hexane−isopropanol, as above); $[\alpha]_D$ −37.7 (*c* 0.96, $CHCl_3$); IR (film) 1777, 1712, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5 H), 5.37 (dd, *J* = 6.8, 4.4 Hz, 1 H), 4.72 (ddt, *J* = 10.0, 8.0, 3.6 Hz, 1 H), 4.26 (t, *J* = 9.0 Hz, 1 H), 4.20 (dd, *J* = 9.0, 3.6 Hz, 1 H), 3.7−3.5 (m, 8 H), 3.32 (dd, *J* = 13.4, 3.6 Hz, 1 H), 2.73 (dd, *J* = 13.4, 10.0 Hz, 1 H), 2.6−2.4 (m, 2 H), 2.2−2.0 (m, 2 H), 0.93 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6 (C), 170.8 (C), 153.1 (C), 135.0 (C), 129.4 (CH), 129.0 (CH), 127.4 (CH), 70.5 (CH), 66.9 (CH_2), 66.8 (CH_2), 66.6 (CH_2), 55.0 (CH), 45.9 (CH_2), 41.9 (CH_2), 37.9 (CH_2), 30.6 (CH_2), 28.7 (CH_2), 25.7 (CH_3), 18.3 (C), −4.8 (CH_3), −5.2 (CH_3); HRMS (+ESI) calcd for $C_{25}H_{39}N_2O_6Si$ [M + H]$^+$ *m*/*z* 491.2572, found 491.2580.

Reduction Reactions. Reductions of **4a** and **4b** with $NaBH_4$ (400 mol %, phosphate-buffered water at pH 8, THF, rt, ca. 95% yields)[8] and with $LiBH_4$ (110 mol %, plus 110 mol % of MeOH, THF, 0 °C, 92−95% yields)[9] gave **5a** and **5b**, respectively; as soon as TLC indicated the disappearance of the starting compounds (ca. 30 min), the reactions were diluted with cold water, partially neutralized, and extracted with EtOAc. Alternatively, the two-step cleavage of the chiral auxiliary of **4a** and **4b** with $C_{12}H_{25}SH$ (3 equiv) and BuLi (0.3 equiv) in THF at 0 °C, followed by treatment with Et_3SiH and Pd/C in CH_2Cl_2 at rt,[10] gave crude products (identified and characterized by their CHO groups and by chromatography), which were immediately reduced in situ, with $NaBH_4$ at rt, to store them as the hydroxy derivatives, **5a** and **5b**, respectively. Reduction of Weinreb amide **4a** (0.50 mmol in 5 mL of THF) with DIBALH (750 μL of a 1.0 M hexane solution, 0.75 mmol, 1.5 equiv) at −78 °C for 15 min afforded the formyl derivative **7** (193 mg, 95% yield) after purification by column chromatography under N_2.

1-[(*S*)-2-*tert*-Butyldimethylsilyloxy-5-oxopentanoyl]-4-[(*R*)-phenylmethyl]-1,3-oxazolidin-2-one (7): colorless oil; R_f 0.37 (CH_2Cl_2); $[\alpha]_D$ −74.7 (*c* 0.96, $CHCl_3$); IR (film) 1779, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.2 Hz, 1 H), 7.4−7.2 (m, 5 H), 5.34 (dd, *J* = 7.4, 4.0 Hz, 1 H), 4.8−4.7 (m, 1 H), 4.28 (t, *J* = 9.0 Hz, 1 H), 4.22 (dd, *J* = 9.0, 3.6 Hz, 1 H), 3.30 (dd, *J* = 13.4, 3.4 Hz, 1 H), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1 H), 2.7−2.6 (m, 2 H), 2.2−2.1 (m, 1 H), 2.06 (quint, *J* = 7.4 Hz, 1 H), 0.93 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.5 (CH), 173.5 (C), 153.1 (C), 134.8 (C), 129.4 (CH), 129.0 (CH), 127.5 (CH), 70.3 (CH), 66.9 (CH_2), 55.0 (CH), 39.6 (CH_2), 37.9 (CH_2), 27.6 (CH_2), 25.7 (CH_3), 18.2 (C), −4.9 (CH_3), −5.3 (CH_3); HRMS (+ESI) calcd for $C_{21}H_{32}NO_5Si$ [M + H]$^+$ *m*/*z* 406.2044, found 406.2053.

Reduction of the Morpholine Amide with DIBALH. To a solution of **4b** (36 mg, 0.075 mmol) in anhydrous THF (280 μL) at −100 °C was added a hexane solution of DIBALH (112 μL, 1.0 M, 1.5 equiv) previously cooled also at −100 °C. After stirring for 15 min at −78 °C, dilution with a few milliliters of THF at −78 °C followed by a quick filtration through a pad of silica gel, with CH_2-

(14) (a) In our experiments with the morpholine amide (**4b**), which is less reactive than the Weinreb amide (**4a**), we preferred stopping the reactions at conversions of 80−90%, recovering the unreacted starting material, rather than adding larger amounts of DIBALH or increasing the reaction times, as byproducts coming from the attack on the other CO carbon atoms could appear. (b) Morpholine amide Aux*COCH(Me)CH_2CH_2CON(C_4H_8O), that is **3** (R/OR = Me), was also cleaved successfully, in the same way. Independent studies regarding the reduction of morpholine amides to aldehydes will be reported in due course.

Cl_2 as the eluent, gave a crude product that contained (NMR) only the desired compound, **7**, and ca. 10% of the starting material (**4b**). Purification by column chromatography (under N_2) gave pure **7** (24 mg, 80%).

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Supporting Information Available: Experimental details for **4c**, **4d**, **4e**, **5a**, and **5b** and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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