# Stereoselective Amination, Bisamination, and Amination/Esterification of Bis(trimethylsilyl)-1,2-bisketene Initiated by Chiral Amines

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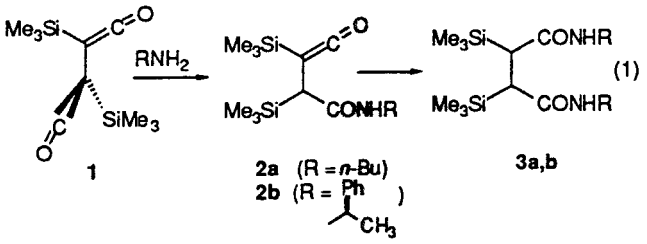
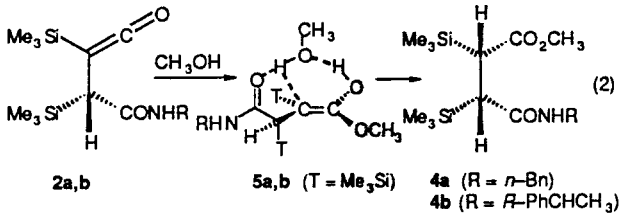
Recent studies[1] in our laboratory have demonstrated that the 1,2-bisketene **1** with 1 equiv of *n*-$BuNH_2$ or $PhCH_2NH_2$ (eq 1) gives rapid conversion to ketenyl



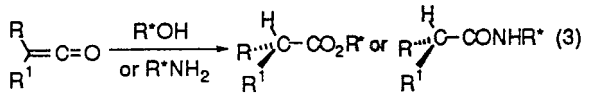

amides **2** as the only observable products, while reaction with 2 equiv of amine gave the succinamides **3**, with little selectivity in formation of *meso* and *dl* isomers. Kinetic studies showed there are different rate laws for the first and second steps, and for 0.020 M *n*-$BuNH_2$ the observed rate constant of the first step exceeded that of the second by a factor of $3.8 \times 10^4$.

In the reaction of **2a** (R = *n*-Bu) with $CH_3OH$ there was >9/1 selectivity for the *erythro* ester amide **4** (eq 2).[1]



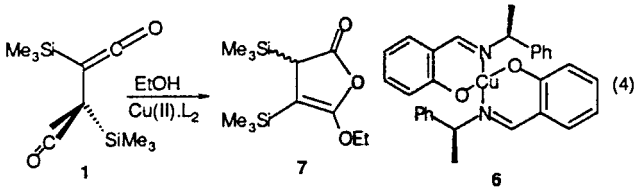

The product-determining step in this reaction is proton transfer to $C_\beta$ of an intermediate enol ester, and a model **5** was presented to explain the diastereoselectivity (eq 2).[1] This structure involves assistance by the amide carbonyl in proton transfer to $C_\beta$ in a conformation which minimizes the interaction between the bulky $Me_3Si$ groups.

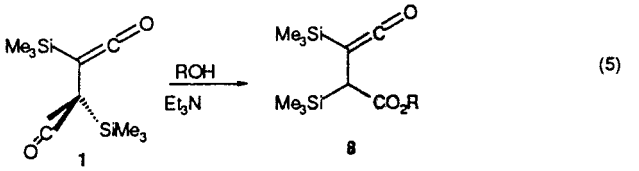
The demonstrated selectivity in the reaction of eq 2 invites questions as to other selectivity which might become manifest in such reactions. Thus the addition of chiral alcohols or amines to unsymmetrical ketenes $RR^1C{=}C{=}O$ forming esters or amides has been recognized since 1919[2] to provide the opportunity for stereoselectivity in the generation of the new stereocenter (eq 3). The first efforts to achieve this goal[2b] were not




successful,[2b,c] but in classic studies Pracejus et al.[3] demonstrated the feasibility of this process in both ester and amide formation. Further work in other laboratories has expanded the scope of this process.[4]

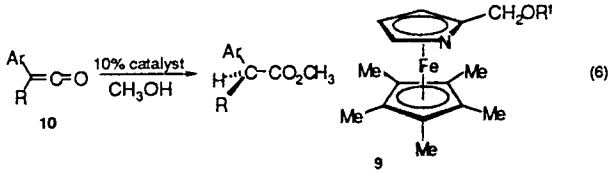
Recently Dejmek and Selke[4f,g] have studied the reactions of bisketene **1** with alcohols using copper(II) catalysts such as **6** with chiral bidentate ligands. Lactones **7** were formed (eq 4), but with no observed enantioselec-




tivity, a result attributed to racemization of the initial product.[4f,g] The reaction of **1** with alcohols catalyzed by *tertiary* amines gives ketenyl esters (eq 5).[5]

Fu et al.[4h] used the chiral azaferrocene **9** to catalyze the addition of $CH_3OH$ to arylalkylketenes **10** to give $\beta$-aryl propionates with 75−80% ee (eq 6). Chiral amino esters react with haloketenes forming amides with de up to 95%.[4i]




We have now examined the stereoselectivity in each step of eqs 1 and 2, initiated with chiral amines. Reaction of **1** with 1 equiv of *R*-(+)-1-phenylethylamine in acetone at −78 °C followed by removal of the solvent gave the

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(2) (a) For a recent thematic collection on diastereoselection, see: *Chem. Revs.* **1999**, *99*, 1067−1480. (b) Weiss, R. *Monatsch. Chem.* **1919**, *40*, 391−402. (c) McKenzie, A.; Christie, E. W. *J. Chem. Soc.* **1934**, 1070−1075.

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**Table 1. Solvent and Temperature Effects on the Diastereoselectivity in the Monoamination of Bisketene 1 with *R*-1-Phenylethylamine**

| solvent | temp (°C) | **2b** (*R*/*S*) | solvent | temp (°C) | **2b** (*R*/*S*) |
|---|---|---|---|---|---|
| pentane | −78 | 57/43 | $CS_2$[a] | −78 | 63/37 |
| toluene | −78 | 64/36 | THF | −78 | 33/67 |
| $CH_2Cl_2$ | 25 | 57/43 | $Et_2O$ | −78 | 42/58 |
| $CH_2Cl_2$ | −78 | 73/27 | EtOAc | −78 | 37/63 |
| $CH_3CN$ | −40 | 66/34 | acetone | −78 | 33/67 |
| $Et_3N$[a] | −78 | 58/42 | | | |

[a] Neat amine was added directly into 2 mL of reaction solvent.

ketenyl amide **2b** as a solid which by $^1$H NMR consisted of two diastereomers in a 67/33 ratio (eq 1). One recrystallization from ether at −20 °C gave the major isomer as a white crystalline solid in a 97.7/2.3 diastereomer ratio by $^1$H NMR, and dissolving this in $CH_3OH$ for 10 min followed by evaporation of the solvent gave the ester amides **4b** which by $^1$H NMR have a 97.6/2.4 *erythro*/*threo* selectivity for the configuration of the succinyl framework (eq 2).[6] The stereochemistry of *erythro*-**4b** was established by X-ray analysis as the 2*S*,3*R* arrangement shown, and this establishes the *S* configuration as shown for **2b**. Models predicting the stereochemistry of ketenyl amide **2b** analogous to those originally suggested by Pracejus[3] may be considered (see Supporting Information).

The effects of solvent and temperature on the selectivity of the formation **2b** are summarized in Table 1. It is striking that the configuration favored is reversed for the oxygen-containing solvents as compared to the others studied.

Reaction with *R*-(+)-1-phenylethylamine of recrystallized ketenyl amide **2b** with 97.7% *S*-configuration at −78 °C in $CH_2Cl_2$ gave two succinamides as identified by $^1$H NMR, namely *meso*-**3b** (2*S*,3*R*) and only one of the *d*,*l*-**3b** isomers, assigned as the 2*S*, 3*S* isomer,[6a] in relative yields of 27 and 73%, respectively. Thus there is a 73/27 preference for protonation of the enol amide to form succinamide in $CH_2Cl_2$ at −78 °C in both the first (Table 1) and second amination steps. The 2*S*,3*S* isomer **3b** was separated from the *meso* isomer by recrystallization from ether and fully characterized.

Reaction of bisketene **1** with 2 equiv of *R*-(+)-1-phenylethylamine in $CH_2Cl_2$ at −78 °C and analysis by $^1$H NMR revealed the presence of *meso*-**3b** (2*S*,3*R*), and the *d*,*l* (2*S*,3*S* and 2*R*,3*R*) isomers of **3b** in relative yields of 25, 20, and 55%, respectively. The 2*R*,3*R* isomer of **3b** was separated from this mixture by recrystallization, and its individual spectral properties were confirmed. The preference for the *R*,*R* product indicates that just as in the experiment with *S* ketenyl amide **2b** (vide supra) that the initial chiral center creates a preference for the same configuration in the second step, and the occurrence in the second step of the same 73/27 selectivity found above for the first addition starting with *S*-**2b** predicts the relative yields of the three stereoisomers to be 27, 20, and 53%, respectively, in good agreement with the observed results. That the selectivities are the same is coincidental, as the selectivity in the first step is governed by the configuration of the chiral amine, while in the second step the existing chiral center in the substrate is responsible.

**Table 2. Solvent and Temperature Effects on the Diastereoselectivity in the Monoamination of Bisketene 1 with *R*-PhCH($NH_2$)$CO_2CH_3$ and *S*-*t*-BuCH($NH_2$)$CO_2CH_3$**

| amine | solvent | temp (°C) | diastereomer ratio |
|---|---|---|---|
| *R*-PhCH($NH_2$)$CO_2CH_3$ | $CH_2Cl_2$ | 40 | 68/32 |
| | $CH_2Cl_2$ | 25 | 67/33 |
| | $CH_2Cl_2$ | 0 | 70/30 |
| | acetone | 0 | 66/34 |
| *S*-*t*-BuCH($NH_2$)$CO_2CH_3$ | $CH_2Cl_2$ | 40 | 55/45 |
| | $CH_2Cl_2$ | 25 | 57/43 |
| | $CH_2Cl_2$ | 0 | 55/45 |

In the addition of alcohols to bisketene **1** in pentane at 22 °C catalyzed by lithium alkoxides the *dl*/*meso* ratios of the product succinates were 18/82 (MeOH), 55/45 (EtOH), 57/43 (*i*-PrOH), and 92/8 (*t*-BuOH).[5a] The preference for the *dl* product with the larger *t*-BuOH parallels the preference for *dl* product in formation of **3b** and may reflect the same conformational preference previously suggested for the proton delivery step.[5a]

To compare the selectivities of other chiral amines the methyl esters of *R*-phenylglycine and *S*-*tert*-butylglycine were reacted with **1** giving the ketenylamides **2c,d**, respectively. Qualitatively these amines are less reactive than is *R*-1-phenylethylamine, in accord with the previously observed[7] dependence of amination reactivity on amine p$K_a$. The reactions are inordinately slow below 0 °C, and reliable results could not be obtained below this temperature. After evaporation of the solvent the products were analyzed directly by spectral means, and the presence of the two diastereomeric products was observed by $^1$H NMR, although the *R*/*S* configurations of the new chiral center at $C_2$ were not established. The selectivities of the reactions are reported in Table 2, but the highest de obtained of 39% and 13%, respectively, were not as high as those with *R*-1-phenethylamine (Table 1). Interestingly no improvement in selectivity was noticed at lower temperature, and the reversal in selectivity between $CH_2Cl_2$ and acetone found for *R*-1-phenylethylamine was not observed for **2c**.

In summary the first amination step of the reaction of bisketene **1** with *R*-(+)-1-phenylethylamine in $CH_2Cl_2$ at −78 °C proceeds with a 73/27 selectivity for proton transfer in the intermediate enol amides to form the *R* ketenyl amide **4b**. By contrast in oxygen-containing solvents the *S* configuration is favored. Further amination of ketenyl amide **2b** (either *R* or *S*) proceeds with a 73/27 preference for formation of *dl* bisamide **3b**. The major stereoisomeric ketenyl amide intermediate from the first amination may be purified by recrystallization and undergoes esterification with $CH_3OH$ to form the *erythro* ester amide **2b** with 95% de.

## Experimental Section

*R*-(+)-1-Phenylethylamine (Norse Laboratory, 95% ee), *R*-phenylglycine methyl ester hydrochloride (Aldrich, 99%), and *S*-*tert*-butylglycine methyl ester, also known as L-*tert*-leucine methyl ester (Aldrich, 99%), were used as received.

***N*-(*R*)-(1′-Phenylethyl)-(*S*)-2,3-bis(trimethylsilyl)-4-oxobut-3-enamide (*S*-2b).** To bisketene **1** (1.14 g, 5.04 mmol) in 50 mL of acetone stirred at −78 °C was added *R*-(+)-1-phenylethy-

(6) (a) The designations of *meso*- and *d*,*l* for **3b** and *erythro* for **4a,b** refer to the succinyl moiety. (b) $\delta$ 1.95 and 1.97 and $J = 0$ for *d*,*l*-**3b**; $\delta$ 2.22 and 2.27 and $J = 11$ Hz for *meso*-**3b**. The $^1$H NMR signals assigned to *erythro*-**4b** were confirmed by reacting **1** first with $CH_3OH$ to form the ketenyl ester and then with *R*-1-phenylethylamine to form all four stereoisomers of **4b** (2*S*,3*R*;2*R*,3*S*;2*S*,3*S*; 2*R*,3*R*) for which all the $^1$H NMR signals of the succinyl moiety could be assigned.

(7) Allen, A. D.; Tidwell, T. T. *J. Org. Chem.* **1999**, *64*, 266−271.

lamine (0.610 g, 5.04 mmol) in 10 mL of acetone. The solution was stirred 1 h at −78 °C, and the solvent was evaporated giving a solid which was washed with dry ether and recrystallized once from ether at −20 °C to give *S*-**2b** (0.263 g, 15%) as a white crystalline solid in 97.7% diastereomeric purity: mp 128−130 °C; $[\alpha]^{25}_D = +49.5$ ($c = 0.030$ in $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 0.127 (s, 9), 0.169 (s, 9), 1.49 (d, 3, $J = 7.0$ Hz), 1.87 (s, 1), 5.15 (m, 1), 5.98 (d, 1, $J = 7.8$ Hz), 7.27−7.37 (m, 5); $^{13}$C NMR ($CDCl_3$) $\delta$ −2.0, −1.0, 10.6, 21.6, 32.1, 48.8, 126.1, 127.3, 128.6, 143.2, 172.3, 179.7; IR ($CDCl_3$) 3415, 2081, 1646 cm$^{-1}$; EIMS *m*/*z* 347 ($M^+$, 18), 304 (12), 242 (100), 200 (14), 142 (22), 105 (38), 73 (78); HRMS *m*/*z* calcd for $C_{18}H_{29}NO_2Si_2$ 347.1737, found 347.1738. The $^1$H NMR of the crude reaction mixture displayed signals of *R*-**2b**: $\delta$ ($CDCl_3$) 0.08 (s, 9), 0.13 (s, 9), 1.496 (d, 3, $J = 6.8$ Hz), 1.85 (s, 1), 5.15 (m, l), 6.00 (bd, l, $J = 8.0$ Hz), 7.27−7.37 (m, 5).

**Reaction of Ketenylamide 2b with Methanol.** Methanol (10 mL) was added to solid *S*-**2b** (63.4 mg) at room temperature, and after 10 min the resulting solution was evaporated to give a gum which by $^1$H NMR consisted of 97.4% *erythro*-**4b** with 2.6% *threo*-**4b**. Recrystallization from pentane gave *erythro*-**4b**: mp 65−66 °C, $[\alpha]^{25}_D = +41.5$ ($c = 0.014$ in $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ −0.13 (s, 9), 0.03 (s, 9), 1.42 (d, 3, $J = 6.9$ Hz, $CH_3$), 2.18 (d, 1, $J = 11.6$ Hz), 2.57 (d, 1, $J = 11.7$ Hz), 3.52 (s, 3), 4.98 (m, 1), 5.42 (d, 1, $J = 7.4$ Hz), 7.20−7.40 (m, 5); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.8, −1.5, 21.6, 35.2, 37.2, 49.1, 50.9, 126.5, 127.4, 128.6, 143.1, 172.0, 175.6; IR ($CDCl_3$) 3439, 1706, 1654 cm$^{-1}$; EIMS *m*/*z* 379 ($M^+$, 19), 364 (52), 260 (47), 170 (35), 105 (100), 73 (74); HRMS *m*/*z* calcd for $C_{19}H_{33}NO_3Si_2$ 379.1999, found 379.2004.

**Reaction of Ketenylamide 2b with 1 equiv of *R*-1-Phenylethylamine.** To a solution of recrystallized 97.7% *S* ketenyl amide **2b** (21.8 mg, 0.063 mmol) in 5 mL of $CH_2Cl_2$ was added the amine (8.0 $\mu$L, 7.5 mg, 0.062 mmol) in 2 mL of $CH_2Cl_2$ in one portion at −78 °C. The reaction mixture was stirred 1 h at −78 °C, and evaporation of the solvent gave a white solid which by $^1$H NMR consisted of *meso*-**3b** and the 2*S*,3*S* *d*,*l* isomer of **3b** in a 27/73 ratio. Recrystallization from ether gave **3b** (2*S*,3*S*): mp 163−165 °C; $[\alpha]^{25}_D = +70.8$ ($c = 0.010$ in $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 0.04 (s, 18), 1.52 (d, 6, $J = 6.9$ Hz), 1.94 (s, 2), 5.10 (m, 2), 7.20−7.38 (m, 10), 7.63 (bd, 2, $J = 6.7$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.3, 21.8, 38.5, 49.1, 126.4, 127.1, 128.5, 143.7, 173.3; IR ($CDCl_3$) 3435, 1648, 1626 cm$^{-1}$; EIMS *m*/*z* 468 ($M^+$, 32), 453 (10), 363 (60), 259 (66), 235 (28), 105 (100), 73 (58); HRMS *m*/*z* calcd for $C_{26}H_{40}N_2O_2Si_2$ 468.2628, found 468.2632.

**Reaction of Bisketene 1 with 2 equiv of *R*-1-Phenylethylamine.** To a solution of bisketene **1** (83.9 mg, 0.37 mmol) in 5 mL of $CH_2Cl_2$ was added the amine (0.0954 g, 0.79 mmol) in 2 mL of $CH_2Cl_2$ in one portion at −78 °C. The reaction mixture was stirred 1 h at −78 °C, and the solvent was evaporated to give a white solid which by $^1$H NMR consisted of *meso*-**3b**,2*S*,3*S*-**3b**, and 2*R*,3*R*-**3b** in a ratio of 25/20/55. A 3-fold recrystallization from ether gave 2*R*,3*R*-**3b**: mp 167−168 °C; $^1$H NMR ($CDCl_3$) $\delta$ −0.04 (s, 18), 1.53 (d, 6, $J = 6.9$ Hz), 1.96 (s, 2), 5.14 (m, 2), 7.28−7.34 (m, 10), 7.57 (bd, 2, $J = 6.7$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.2, 22.0, 38.6, 49.0, 126.7, 127.2, 128.5, 143.1, 173.5; IR ($CDCl_3$) 3436, 1648, 1625 cm$^{-1}$; EIMS *m*/*z* 468 (34), 453 (11), 363 (68), 259 (69), 235 (27), 105 (100), 73 (54); HRMS *m*/*z* calcd for $C_{26}H_{40}N_2O_2Si_2$ 468.2628, found 468.2631.

In a similar experiment to a stirred solution of *R*-(+)-1-phenylethylamine (210 $\mu$L, 1.63 mmol) in 3 mL of $CH_2Cl_2$ at 25 °C was added in one portion bisketene **1** (184 mg, 0.814 mmol) in 3 mL of $CH_2Cl_2$. A momentary pink color was observed but disappeared within seconds. After 2 min of stirring the solvent was evaporated and the resulting white solid was shown by $^1$H NMR to consist of equal amounts of the *meso* and *d*,*l* diastereomers of **3b**, with a 66/34 preference for one of the *d*,*l*-isomers and with no significant impurities. Radial chromatography (2% MeOH/$CH_2Cl_2$) separated the *meso* isomer (97% pure by NMR) and the mixed *d* and *l* isomers, which were recrystallized from EtOH/$H_2O$. *meso*-**3b** (49 mg, 0.105 mmol, 13%): mp 140−142 °C, $^1$H NMR ($CDCl_3$) $\delta$ −0.21 (s, 9), 0.16 (s, 9), 1.48 (m, 6), 2.22 (d, 1, $J = 11$ Hz), 2.27 (d, 1, $J = 11$ Hz), 5.01 (m, 2), 5.57 (m), 7.3 (m, 10); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.5, −1.1, 21.7, 21.8, 37.4, 49.1, 49.2, 126.5, 126.6, 127.3, 127.4, 128.5, 128.6, 143.1, 172.6, 172.9; IR ($CDCl_3$) 3443, 1646, 1493 cm$^{-1}$; EIMS *m*/*z* 468 (11), 453 (9), 363 (26), 235 (48), 105 (100), 73 (68); HRMS *m*/*z* calcd for $C_{26}H_{40}N_2O_2Si_2$ 468.2628, found 468.2635. *d*-**3b** and *l*-**3b** (15 mg, 0.032 mmol, 4%): mp 152−155 °C; $^1$H NMR ($CDCl_3$) $\delta$ −0.033 (s, 18), 0.036 (s, 18), 1.51 (d, 6, $J = 7$ Hz), 1.53 (d, 6, $J = 7$ Hz), 1.95 (s, 2), 1.97 (s, 2), 5.1 (m, 4), 7.3 (m, 20), 7.6 (m, 4); $^{13}$C NMR ($CDCl_3$) $\delta$ −1.3, −1.2, 21.8, 22.0, 38.6, 38.7, 49.1, 49.15, 126.5, 126.7, 127.1, 127.2, 128.45, 128.5, 143.1, 143.8, 173.3, 173.5; IR ($CDCl_3$) $\delta$ 3455, 1650, 1627, 1493 cm$^{-1}$; EIMS *m*/*z* 468 (14), 453 (7), 259 (50), 105 (100), 73 (60); HRMS *m*/*z* calcd for $C_{26}H_{40}N_2O_2Si_2$ 468.2628, found 468.2629.

**Solvent and Temperature Effects on the Reaction between Bisketene 1 and *R*-1-Phenylethylamine.** To a solution of bisketene **1** (ca. 70−100 mg) in 5 mL of solvent was added ca. 0.9 equiv of amine in 2 mL of the same solvent. The solvent was removed, and the diastereoselectivity of the reactions was measured by $^1$H NMR.

***N*-(*R*)-(1′-Phenylcarbomethoxymethyl)-(*R*,*S*)-bis(trimethylsilyl)-4-oxobut-3-enamides (2c).** By an analogous procedure as for the solvent and temperature effects study of the preparation of **2b**, *R*-phenylglycine methyl ester (prepared from the hydrochloride by treatment with Amerlite IRA-900 $HCO_3^-$ form ion-exchange resin) and **1** were reacted to give after evaporation of the reaction solvent **2c**: $^1$H NMR ($CDCl_3$) $\delta$ (major isomer) 0.12 (s, 9), 0.17 (s, 9), 1.92 (s, 1), 3.72 (s, 3), 5.56 (d, 1, $J = 7.0$ Hz), 6.75 (bd, 1, $J = 7.0$ Hz), 7.34 (m, 5), (minor isomer) 0.10 (s, 9), 0.12 (s, 9), 1.89 (s, 1), 3.73 (s, 3), 5.58 (d, 1, $J = 6.6$ Hz), 6.61 (bd, 1, $J = 6.8$ Hz), 7.34 (m, 5); $^{13}$C NMR ($CDCl_3$) $\delta$ (major isomer only) −2.1, −1.0, 10.5, 32.0, 52.7, 56.6, 127.2, 128.5, 128.9, 136.7, 171.3, 172.7, 179.6; IR ($CDCl_3$) 3422, 2082, 1740, 1662 cm$^{-1}$; EIMS *m*/*z* 391 ($M^+$, 9), 290 (191), 242 (31), 73 (100). HREIMS *m*/*z* calcd for $C_{19}H_{29}NO_4Si_2$ 391.1635, found 391.1638.

***N*-(*S*)-(1′-*tert*-Butylcarbomethoxymethyl)-(*R*,*S*)-bis(trimethylsilyl)-4-oxo-3-enamides (2d).** By an analogous procedure as for the preparation of **2c** *S*-*tert*-butylglycine methyl ester and **1** gave **2d**: $^1$H NMR ($CDCl_3$) $\delta$ (major isomer) 0.164 (s, 9), 0.172 (s, 9), 0.98 (s, 9), 1.89 (s, 1), 3.70 (s, 3), 4.37 (d, 1, $J = 9.2$ Hz) 6.43 (bd, 1, $J = 9.0$ Hz), (minor isomer) 0.162 (s, 9), 0.174 (s, 9), 0.98 (s, 9), 1.88 (s, 1), 3.71 (s, 3), 4.38 (d, $J = 9.0$ Hz), 6.28 (bd, $J = 8.8$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ (major isomer) −1.9, −1.0, 10.6, 26.6, 31.1, 34.5, 51.6, 60.3, 172.0 (only one peak), 173.1, (minor isomer) −2.0, −1.1, 10.7, 26.6., 32.2, 34.4, 51.7, 60.7, 173.2; IR ($CDCl_3$) 3428, 2078, 1732, 1652 cm$^{-1}$; EIMS *m*/*z* 371 (36), 328 (19), 270 (68), 214 (30), 155 (31), 73 (100). HREIMS *m*/*z* calcd for $C_{17}H_{33}NO_4Si_2$ 371.1948, found 371.1940.

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**Supporting Information Available:** Further discussion, spectra, and an X-ray crystallographic file on *erythro*-**4b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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