On the Stereochemical Divergence in the Conjugate Addition of Lithium Dimethylcuprate/Trimethylsilyl Chloride to γ-Alkoxy and γ-Ureido α,β-Unsaturated Esters

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Dedicated to Professor H. Bestmann in recognition of his achievements as Executive Editor of Synthesis

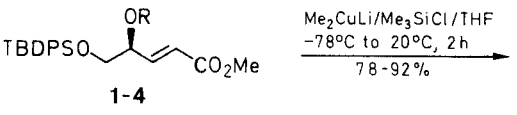
A comparative study was made of the reaction of chiral non-racemic γ-alkoxy and γ-ureido-α,β-unsaturated esters with lithium dimethylcuprate in the presence of trimethylsilyl chloride. The possible origins of the *anti*- and *syn*-additions respectively are discussed and rationalized.

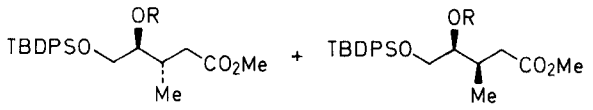
The conjugate addition of organocopper reagents to enones is a classical reaction in today's repertoire of stereocontrolled C–C bond forming reactions.[1] In contrast, the reaction with α,β-unsaturated esters had remained less exploited until Yamamoto and co-workers[2] demonstrated the utility of $MeCu \cdot BF_3$ in such reactions.[3,4] More recently a number of interesting conjugate additions to γ-substituted α,β-unsaturated esters have been reported, with pronounced stereoselectivity being observed when γ-alkoxy,[5] γ-tertiary amino,[6] and related groups[7,8] are present. Yamamoto and co-workers[9] have further shown that the γ,δ-dialkoxy α,β-unsaturated esters and related compounds react with organocopper-Lewis acidic reagents with 1,3-chirality transfer, resulting in double bond transposition and α-alkylation with excellent stereoselectivity.

The inclusion of trimethylsilyl chloride as a reagent in conjugate additions of organocopper reagents onto enones and enals[10,11] has a dramatically beneficial effect which has been studied by several other groups.[12,13] Conjugate addition of organocuprates to α,β-unsaturated esters in the presence of trimethylsilyl chloride leads to faster reaction times and higher yields.[14] While the preparative utility of such conjugate additions is uncontested, the stereochemical results in a number of systems are difficult to rationalize based on a unified mechanism. For example, there are conflicting reports on the dependence or non-dependence of the double-bond geometry on the stereochemical outcome of conjugate additions in γ-alkoxy α,β-unsaturated esters.[2,5] From independent reports[2–8] it appears that γ-alkoxy and γ-amino groups exert oppositing stereodirecting effects in conjugate additions of organocuprates, albeit in structurally different substrates and in different solvents.

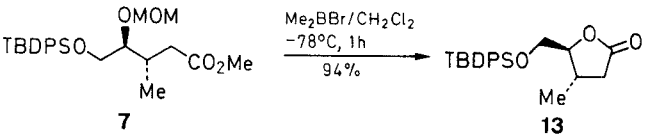
In connection with our interest in hetero-atom assisted displacements of tosyloxy groups with organocuprates,[15] we initiated a study aimed at comparing the stereochemical outcome of the reaction of lithium dimethylcuprate with γ-alkoxy and γ-ureido α,β-unsaturated esters within a structurally related series, and under a standard set of conditions.

Scheme **1** illustrates the results for a series of γ-alkoxy ethers of methyl (4*S*,*E*)-4,5-dihydroxy-2-pentenoates. Treatment of the MOM ether **2** with lithium dimethylcuprate in THF or diethyl ether or with $MeCu \cdot BF_3$ resulted in the recovery of starting material or decomposition (in diethyl ether as solvent). Eventually, when the reaction was carried out with 6 equivalents of each of





Substrate	R	Product	Ratio
1	BOM	**5/6**	14:1
2	MOM	**7/8**	11:1
3	MTM	**9/10**	9.8:1
4	Me	**11/12**	9.9:1



Scheme **1**

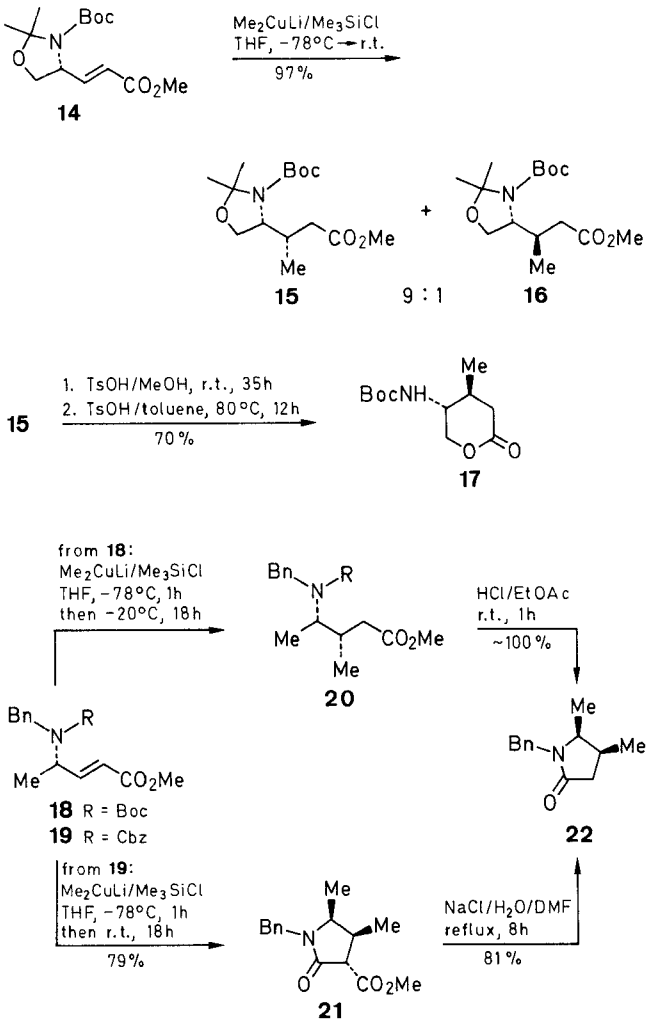
lithium dimethylcuprate and trimethylsilyl chloride in THF (–78 °C → –20 °C) conjugate addition took place in excellent yield to give a high preponderance of the *anti* (3*S*)-methyl products in each series. The highest stereoselection was observed for the BOM ether **1** where the *anti*/*syn* ratio was 14:1. In order to secure the configurational identity of the major isomer, the ether group in **7** was cleaved in the presence of dimethylboron bromide,[16] and the product was transformed into the known lactone **13**.[17]

Unfortunately when the reaction was extended to other cuprates such as lithium diphenylcuprate and lithium diallylcuprate, low to poor selectivity was observed (4.5:1 and 1.8:1 respectively, R = MOM), although the yields approached 80% in both cases. The degree of selectivity was also dependent on the size of the δ-substituent, since the *anti*/*syn* ratio dropped to 2:1 when the *tert*-butyldiphenylsiloxy group in **1** was replaced by a methyl group.

We then turned our attention to the γ-amino series and studied the conjugate addition of lithium dimethylcuprate in the presence of trimethylsilyl chloride to the esters **14**,[7] **18**, and **19** as shown in Scheme **2**.

The readily available oxazolidine derivative **14**[7] led to the *C*-methyl derivatives in excellent yield and with a high preponderance of the *syn*-isomer **15** (> 9:1). Interestingly, the *Z*-isomer corresponding to **14** gave **15** and **16** in a ratio of 2:1 (87%). The stereochemical identity of **15** was secured by hydrolysis and conversion to the δ-lactone

derivative **17** (which was subjected to an X-ray analysis).[18] The *N*-benzylurethane derivatives **18** and **19** underwent smooth conjugate addition under the same conditions as previously to give in each case, compounds **20** and **21** respectively as virtually single isomers (300 MHz NMR) and in high yields. In the case of **19**, the reaction led directly to the *N*-benzyl lactam derivative **21** as a result of a stereoselective conjugate addition followed by an intramolecular cyclization of the enolate with expulsion of the benzyloxy group from the *N*-benzyloxycarbonyl moiety.



Scheme 2

While our studies were in progress Reetz and Röhrig[6] reported on related conjugate additions in THF with the *N,N*-dibenzyl derivative of **18** where *syn*/*anti* ratios of > 94:6 were observed. It is of interest that high selectivity is maintained when the amino substituent is a carbamoyl group such as in **18** and **19**. Wermuth and coworkers[7] have recently reported conjugate additions of lithium dimethylcuprate to the oxazolidine derivative **14** (and its *Z*-isomer) *in diethyl ether as solvent* to give **15** and **16** in ratios of 70:30 (and 81:19 respectively). The somewhat lower selectivity for **14** and the higher selectivity for the *Z*-isomer compared to our results could be ascribed to the nature of the solvent (Et_2O versus THF).

As in the γ-alkoxy series, reaction of **14,18** and **19** with lithium dimethylcuprate or with $MeCu \cdot BF_3$ led to the recovery of unreacted starting material. The des-*N*-benzyl derivative of **18** was not a suitable substrate for conjugate addition, which points to the necessity to work with *N,N*-disubstituted[5] derivatives in this series. When the terminal carbon atom in **18** contained a phenyl group or a *tert*-butyldiphenylsiloxy group, no conjugate addition could be observed due to unreactivity (phenyl) and attack on the siloxy group respectively.

Discussion

As previously mentioned, the mechanism of organocopper conjugate additions to α,β-unsaturated carbonyl compounds is a subject of continuing debate.[10] Although there is good evidence for the initial formation of metastable $\delta\pi$[19] complexes with enones,[10] the presence of γ-alkoxy or amide substituents lead to more complex reactivity patterns.[20] In the case of a model cyclic enone, the addition of Me_3SiCl to the reaction mixture caused a reversal in the original stereochemical outcome (*trans* > *cis* adduct).[10] The acyclic γ-substituted α,β-unsaturated esters, **1,14,18** and **19** undergo conjugate addition only in the presence of Me_3SiCl, since in its absence no reaction took place. The reversal in stereoselectivity from *anti* to *syn* addition in going from γ-alkoxy (ex. **1**) to γ-ureido derivatives (ex. **14,18,19**) as observed here, is not entirely clear. The *anti* selectivity in the addition of $MeCu \cdot BF_3$ and lithium dialkyl cuprates[5a] to γ-alkoxy(*E*)-α,β-unsaturated esters has been explained based on a modified Felkin–Anh (OR-inside), and Felkin–Anh (OR-*anti*)[21] conformations respectively. Yamamoto and co-workers[2c] have proposed an OR-inside orientation in a ground state conformation, where a favorable interaction between the *p*-orbital of the double bond and the lone pair electrons on the alkoxy oxygen atom can be operative,[22] as suggested by Stork and Kahn[23] in another context. In fact, the O-inside conformation has also been suggested by Dorigo and Morokuma[24] based on ab initio MO studies relating to the stereoselectivity of the nucleophilic addition of organocopper reagents to α,β-unsaturated carbonyl compounds, including those with γ-alkoxy groups. The "O-inside alkoxy" effect has also been discussed by Houk and co-workers.[25]

In our system, there is a critical dependence on the presence of Me_3SiCl which ensures efficient addition, as well, as on the nature and size of the δ-substituent and the protective group on the γ-oxygen atom. Figure 1 shows three possible conformations that can lead to the observed *anti*-addition product.

Conformation A (OR-outside) is clearly disfavored for steric reasons involving the approach of the nucleophile. Moreover, this conformer can only be stabilized by the C–H bond[26] while the σ* C–Cu orbital is developing. Conformations **B** and **C** can involve prior coordination with the organocuprate to different extents,[24] and they could each account for the observed *anti*-product. Conformation **B** (Felkin–Ahn, OR-*anti*) is favored due to the

presence of the electron-withdrawing γ-alkoxy group in a preferred orientation vis-a-vis the π-system, where better mixing of the HOMO of the nucleophile and the σ*COR orbital can be expected.[10] This will also deplete electrons from the α,β-unsaturated system, thus minimizing chelation to the ester carbonyl oxygen. This conformation does not benefit from a stabilization of the incipient σ*C–Cu orbital in the transition state (TS) since the parallel sigma bond involves the electronegative alkoxy group.[24] 1,2-Allylic strain seems also to be a factor (R′ and H).[27] Conformation **C** (OR-inside), which agrees with Morokuma's model,[24] and Yamamoto's proposed conformer,[2c] has a number of positive features in its favor. It allows a faborable interaction of the alkoxy group with the π-system through a two-electrons (*p*) and a four-electron (π) interaction[22,23] in the ground state. In addition the high-lying σR′-C orbital can interact with the low-lying π* orbital thus stabilizing the α,β-unsaturated fragment, and rendering the carbonyl of the ester a better chelation site. The *anti*-orientation of the R′ group in conformer **C** may also stabilize the incipient σ*C–Cu orbital in the *d*,π* complex-β-cuprio(III) adduct, through sigma bond donation.[24] Conformation **C** is free of 1,2-allylic strain. As R′ becomes smaller (Me instead of $CH_2OTBDPS$), the energy difference between conformers **B** and/or **C**, and other conformers (ex. **D**,**E**) is diminished, and the proportion of *syn*-adduct may increase. The same applies to the change of the alkoxy substituent.

The reversal of selectivity in the conjugate addition from *anti* to *syn* when the γ-substituent is a nitrogen atom (ex. **14**–**18**, **19** is of interest. To the best of our knowledge there are two recent examples of such additions. Reetz and Röhrig[6] attributed the *syn*-selectivity with the *N*,*N*-dibenzyl analog of **18** to the absence of 1,2-allylic strain in a preferred conformation. According to Wermuth and co-workers,[7] *syn*-attack was "expected" for the major isomer **15** in the conjugate additions of organocuprates to **14**, but no definitive evidence for the stereochemical identity of the products (70:30, inseparable) was provided. The higher preponderance of the *syn*-isomer (81:19) with the *cis*-olefin corresponding to **14** was observed by the same workers using diethyl ether as solvent.[7] In our studies with **14**, the major isomer formed was found to be **15** (> 9:1, *syn*/*anti*). The *syn*-stereochemistry of **15** was unequivocally established based on an X-ray crystal structure of the lactone **17**. As previously mentioned, conjugate addition of lithium dimethylcuprate to **18** and **19** also gave *syn*-products.

Of the six possible relative conformations for **14** or **18**, the N-inside conformation **A** can be excluded based on steric grounds. Figure 2 conformer **B** (N-*anti*, R-inside) has a favorable orientation of the electronegative group with regard to the double bond and the incoming nucleophile. 1,2-Allylic strain[6] is also minimized in this conformation. Conformation C (N-outside, R-*anti*) offers stabilization in the TS due to the electron-donating character of the alkyl group R, and the parallel orientation of the σ C–R with regard to the incipient σ*C–Cu orbital. The possibility of chelation (ester and carbamate) in conformation C, may override the 1,2-allylic strain, as well as the bulk of the γ-substituent. Other conformations, which would lead to a product with *anti*-stereochemistry are evidently not favored. The formation of the lactam **21** from the reaction of **19** with lithium dimethylcuprate/Me_3SiCl may reflect the preference for conformer **B** in which the carbonyl group of the *N*-benzyloxycarbonyl group is favorably aligned vis-a-vis the enolate. In this case, intramolecular nucleophilic attack must precede the formation of a trimethylsilylketene acetal.

It is difficult to delineate the precise sequence of events (chelation, etc.), hence the factors that may contribute to the relative importance of ground state or TS conform-

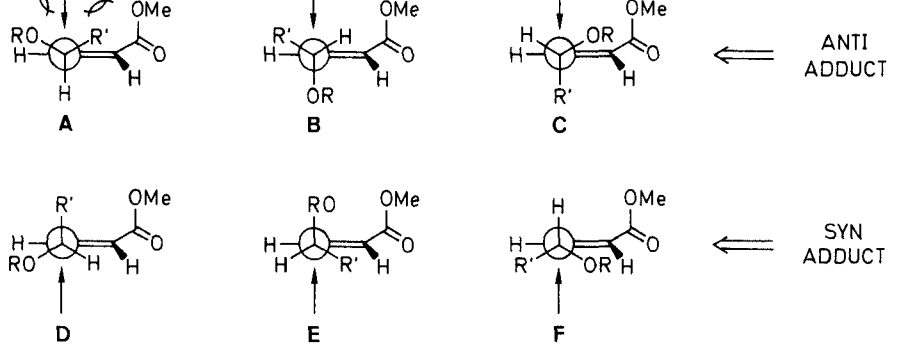


Figure 1

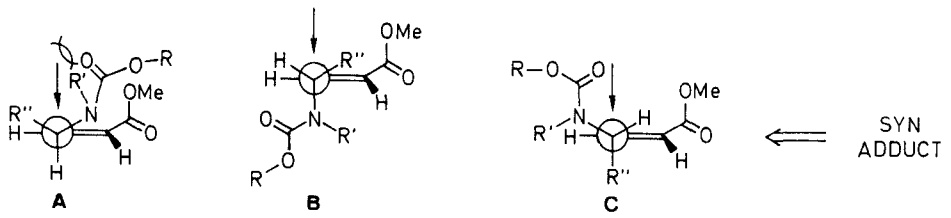


Figure 2

ations in determining the most favorable pathway in these conjugate additions. We have briefly discussed the different roles of electron-withdrawing (alkoxy) and electron-donating (alkyl) group in conformations in which an orthogonal orientation vis-a-vis the α,β-unsaturated system exits. Although each could lead to the observed *anti*-selectivity based on plausible stereoelectronic arguments, there is no compelling evidence to favor one conformer over the other. We therefore join others,[2,10,24] in the continuing quest for a definitive answer to this question.

We have shown that under controlled conditions, structurally related γ-alkoxy and γ-ureido α,β-substituted esters undergo highly stereocontrolled *anti*- or *syn*- conjugate additions respectively, with lithium dimethylcuprate and trimethylsilyl chloride in THF. We have also offered some mechanistic insights and provided some guidelines for future work in this area. The enantiomerically enriched or pure β-methyl acyclic and cyclic derivatives prepared in this study could be useful chirons in projects dealing with total synthesis and as unnatural amino acids in peptide chemistry.

Methyl (4*S*,*E*)-5-*tert*-Butyldiphenylsiloxy-4-hydroxy-2-pentenoate:
To a solution of methyl (4*S*,*E*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate[28] (1 g, 5.38 mmol) in H_2O (5 mL) at r.t. was added AcOH (18 mL). The solution was stirred at r.t. for 19 h. After several coevaporations with toluene (30 mL × 4), the residue was dissolved in DMF (5 mL), DMAP (6.6 mg, 0.54 mmol), imidazole (402 mg, 5.9/mmol) and *tert*-butyl(chloro)diphenylsilane (1.63 g, 5.91 mmol) were added at 0 °C. The solution was stirred at r.t. for 16 h. The mixture was poured into water and extracted with CH_2Cl_2 (15 mL). The organic layer was washed with brine, dried ($MgSO_4$). After filtration and evaporation, the residue was purified by flash column chromatography (solvent, EtOAc/hexane 1:4) to give the product (1.51 g, 73% yield).

^{1}H-NMR ($CDCl_3$): δ = 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 6.85 (dd, J = 4.2, 15.6 Hz, 1H), 6.14 (dd, J = 1.8, 15.6 Hz, 1H), 4.4–4.5 (m, 1H), 3.77 (dd, J = 3.9, 10.3 Hz, 1H), 3.74 (s, 3H), 3.57 (dd, J = 7.1, 10.3 Hz, 1H), 1.07 (s, 9H).

Methyl (4*S*,*E*)-4-(Benzyloxymethoxy)-5-(*tert*-butyldiphenylsiloxy)-2-pentenoate (1):
To a solution of methyl (4*S*,*E*)-5-*tert*-butyldiphenylsiloxy-4-hydroxy-2-pentenoate (95 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added *i*-Pr_2NH (320 mg, 2.47 mmol) and benzyloxymethyl chloride (194 mg, 1.24 mmol) at 0 °C. After stirring at r.t. for 18 h, *i*-Pr_2EtN (320 mg, 2.47 mmol) and benzyloxymethyl chloride (194 mg, 1.24 mmol) were added at 0 °C. The mixture was stirred at r.t. for 36 h, then poured into aq NH_4Cl and extracted with Et_2O (15 mL). The organic layer was washed with brine, dried ($MgSO_4$). After filtration and evaporation, the residue was purified by flash chromatography (solvent: EtOAc/hexane 1:9) to give compound **1** (118 mg, 94% yield), $[\alpha]_D^{25}$ + 21.5° (c = 1.1, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 7.8–7.6 (m, 4H), 7.2–7.5 (m, 11H), 6.94 (dd, J = 5.7, 15.8 Hz, 1H), 6.12 (dd, J = 1.5, 15.8 Hz, 1H), 4.87 (d, J = 7.0 Hz, 1H), 4.80 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.48 (ddd, J = 1.5, 5.3, 5.7, 6.4 Hz, 1H), 3.80 (dd, J = 6.4, 0.6 Hz, 1H), 3.71 (dd, J = 5.3, 10.6 Hz, 1H), 3.76 (s, 3H), 1.084 (s, 9H).

IR ($CHCl_3$): ν = 2930, 1725, 1120 cm^{-1}.

MS: m/z = 447 (M–C_4H_9), 417, 249, 135.

HRMS: m/z calc. for $C_{26}H_{27}O_5Si$, 447.1628, found 447.1588.

Methyl (4*S*,*E*)-5-*tert*-Butyldiphenylsiloxy-4-methoxymethoxy-2-pentenoate (2):
Prepared as described above for **1** using methoxymethyl chloride (79%); $[\alpha]_D^{25}$ + 11.9° (c = 1.1, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 6.89 (dd, J = 5.5, 15.8 Hz, 1H), 6.08 (dd, J = 1.5, 15.8 Hz, 14), 4.70 (d, J = 6.7 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 4.36 (dddd, J = 1.5, 5.3, 5.5, 6.4 Hz, 1H), 3.75 (s, 3H), 3.75 (dd, J = 6.4, 10.7 Hz, 1H), 3.68 (dd, J = 5.3, 10.7 Hz, 1H), 3.35 (s, 3H), 1.06 (s, 9H).

IR ($CHCl_3$): ν = 2930, 1730, 1120 cm^{-1}.

MS: m/z = 371 (M-C_4H_9), 341, 213, 135, 91.

HRMS m/z calc. for $C_{20}H_{23}O_5Si$ 371.1325, found 371.1315.

Methyl (4*S*,*E*)-5-*tert*-Butyldiphenylsiloxy-4-methoxy-2-pentenoate (4):
Prepared as described for **1** using MeI (63%); $[\alpha]_D^{25}$ − 4.1° (c = 0.8, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 6.87 (dd, J = 5.6, 15.8 Hz, 1H), 6.06 (dd, J = 1.5, 15.8 Hz, 14), 3.89 (dddd, J = 1.4, 1H), 3.76 (s, 3H), 3.76 (dd, J = 6.0, 10.5 Hz, 1H), 3.66 (dd, J = 5.4, 10.5 Hz, 14), 3.36 (s, 3H), 1.07 (s, 9H).

IR ($CHCl_3$). ν = 2930, 1725, 1120 cm^{-1}.

MS: m/z = 341 (M-C_4H_9), 213, 199, 183, 135.

HRMS: m/z calc. for $C_{19}H_{21}O_4Si$ 341.1209, found 341.1233.

Methyl (4*S*,*E*)-5-*tert*-Butyldiphenylsiloxy-4-(methylthiomethoxy)-2-pentenoate (3):
To a mixture of methyl (4*S*,*E*)-5-*tert*-butyldiphenylsiloxy-4-hydroxy-2-pentenoate (500 mg, 1.30 mmol) and dimethyl sulfide (645 mg, 10.4 mmol) was added benzoyl peroxide[29] (1.26 g, 5.21 mmol) portionwise over 60 min. The mixture was stirred at 0 °C for 1 h and poured into 1 N NaOH. Et_2O (50 mL) was added and the organic layer separated and washed with brine. Drying (Na_2SO_4) followed by concentration and flash chromatography on silica gel (eluant, hexane/EtOAc 9:1) gave the MTM ether **3** (156 mg, 27% yield); $[\alpha]_D^{25}$ + 32.1° (c = 1.1, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 6.86 dd, J = 5.6, 15.8 Hz, 1H), 6.07 (dd, J = 1.5, 15.8 Hz, 1H), 4.74 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.48 (dddd, J = 1.5, 5.3, 5.6, 6.9 Hz, 1H), 3.75 (s, 3H), 3.75 (dd, J = 6.4, 10.7 Hz, 1H), 3.70 (dd, J = 5.3, 10.7 Hz, 1H), 2.13 (s, 3H), 1.06 (s, 9H).

IR ($CHCl_3$): ν = 2920, 1725, 1120 cm^{-1}.

MS: m/z = 387 (M-C_4H_9), 325, 295, 199, 135.

HRMS: m/z calc. for $C_{20}H_{23}O_4SSi$ 387.1087, found 387.1080.

Methyl (4*S*,*E*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]-2-pentenoate (18):
To a suspension of L-alanine ethyl ester hydrochloride (2.50 g, 16.3 mmol) in Et_2O (20 mL) were added BnBr (2.80 g, 16.3 mmol) and Et_3N (3.30 g, 32.5 mmol) at 0 °C. The mixture was stirred at r.t. for 15 h. Concentration and column chromatography on silica gel (eluant; EtOAc/hexane 1:3) gave *N*-benzyl-L-alanine ethyl ester (1.72 g, 50%). To a solution of this ester (828 mg, 4.0 mmol) were added DMAP (49 mg, 0.4 mmol) and di-*tert*-butyl dicarbonate (1.05 g, 4.8 mmol) at r.t. The mixture was stirred at r.t. for 36 h, then poured into aq $NaHCO_3$, CH_2Cl_2 (100 mL) was added and the organic layer separated and washed with brine. Drying (Na_2SO_4) followed by concentration and flash chromatography on silica gel (eluant; EtOAc/hexane 1:4) gave *N*-benzyl-*N*-*tert*-butoxycarbonyl-L-alanine ethyl ester (894 mg, 73%). To a solution of *N*-benzyl-*N*-*tert*-butoxycarbonyl-L-alanine ethyl ester (800 mg, 2.61 mmol) in toluene (5 mL) was added DIBAL-H (1 M in toluene, 4.4 mg, 4.43 mmol) dropwise for 15 min at − 78 °C. The mixture was stirred at − 78 °C for 2 h. The cold solution was then transferred into a rapidly stirring solution of 1 N hydrochloric acid. The mixture was extracted with EtOAc (75 mL) and the organic phases were dried ($MgSO_4$) and evaporated to dryness. To the solution of the crude aldehyde in MeCN (7 mL) was added methyl (triphenylphosphoranylidene)acetate (958 mg, 2.87 mmol) at r.t. After stirring at r.t. for 16 h, evaporation and column chromatography (eluant, EtOAc/hexane 1:9), **18** was obtained as colorless oil (764 mg, 92% yield); $[\alpha]_D^{25}$ − 46.8° (c = 1.2, $CHCl_3$).

$C_{18}H_{25}NO_4$	calc.	C 67.69	H 7.89	N 4.39
(319.4)	found	67.41	7.59	4.14

^{1}H-NMR ($CDCl_3$): δ = 7.4–7.1 (m, 5H), 6.91 (dd, J = 4.8, 15.9 Hz, 1H), 5.79 (br d, J = 15.9 Hz, 1H), 4.6–4.4 (m, 2H), 4.21 (br d, J = 15.3 Hz, 1H), 3.73 (s, 3H), 1.42 (br s, 9H), 1.26 (d, J = 7.1 Hz, 3H).

IR ($CHCl_3$): ν = 2980, 1735, 1680, 1165 cm^{-1}.

MS: m/z = 263 (M-C_4H_8), 204, 150, 91.

HRMS: m/z calc. for $C_{14}H_{17}O_4N$ 263.1158, found 263.1161.

Methyl (4*S*,*E*)-4-[Benzyl(benzyloxycarbonyl)amino]-2-pentenoate (19):

To a solution of *N*-benzyl-L-alanine ethyl ester (556 mg, 2.69 mmol) in CH_2Cl_2 (15 mL) were added sat. $NaHCO_3$ (15 mL) and benzyl chloroformte (504 mg, 2.95 mmol) at r.t. The mixture was stirred at r.t. for 15 h then extracted with CH_2Cl_2 (50 mL) and the organic layer was separated and washed with brine. Drying (Na_2SO_4) followed by concentration and flash chromatography on silica gel (eluant; EtOAc/hexane 1:4) gave *N*-benzyl-*N*-benzyloxycarbonyl-L-alanine ethyl ester (861 mg, 94%). Treatment with DIBAL-H followed by a Wittig reaction as described for **18** gave the product **19** in 92% yield; $[\alpha]_D^{25}$ −40.4° (c = 0.8, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 7.4–7.1 (m, 10H), 6.90 (br d, J = 14.9 Hz, 1H), 5.9–5.7 (m, 1H), 5.17 (s, 2H), 5.0–4.8 (m, 1H), 4.58 (br d, J = 16.1 Hz, 1H), 4.30 (br d, J = 16.1 Hz, 1H), 3.72 (s, 3H), 1.27 (d, J = 7.1 Hz, 3H).

IR ($CHCl_3$): ν = 2940, 1725, 1700 cm^{-1}.

MS: m/z = 353 (M^+), 294, 262, 218, 91.

HRMS: m/z calc. for $C_{21}H_{23}O_4N$ 353.1628, found 353.1633.

Methyl (3*S*,4*S*)- and (3*R*,4*S*)-4-(Benzyloxymethoxy)-5-tert-butyldiphenylsiloxy-3-methylpentanoate (5 and 6); Typical Procedure:

A solution of Me_2CuLi (0.70 mmol) [prepared by adding MeLi · LiBr (1.5 M in Et_2O, 1.40 mmol, 0.74 mL) to a suspension of CuI (134 mg, 0.70 mmol) in dry THF (1 mL) at 0°C and subsequent stirring for 15 min at −78°C] at −78°C was treated with Me_3SiCl (76 mg, 0.70 mmol) and **1** (59 mg, 0.12 mmol) dissolved in dry THF (1.5 mL). The temperature was allowed to rise to −20°C gradually over 2 h. The mixture was treated with an NH_4OH/NH_4Cl pH 8 buffer solution and then stirred at r.t. for 15 min. After extraction with Et_2O (2 × 20 mL), the organic layers were dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure. The crude products were purified by flash chromatography (EtOAc/hexane 1:9) and gave a mixture of **5** and **6** (53 mg, 87% yield):

^{1}H-NMR ($CDCl_3$) *for the major isomer* **5**: δ = 7.8–7.6 (m, 4H), 7.5–7.2 (m, 11H), 4.87 (d, J = 1.0 Hz, 1H), 4.65 (d, J = 11.9 Hz, 1H), 4.53 (d, J = 11.9 Hz, 1H), 3.67 (s, 3H), 3.8–3.77 (dd, J = 5.8, 11.0 Hz, 1H), 3.70 (dd, J = 4.7, 11.0 Hz, 1H), 3.61 (q, J = 5.1 Hz, 1H), 2.57 (dd, J = 4.8, 14.8 Hz, 1H), 3.5–3.3 (m, 1H), 2.18 (dd, J = 8.4, 14.8 Hz, 1H), 1.07 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H); *minor isomer* **6**, 0.92 (d, J = 6.9 Hz, 3H).

MS: m/z = 463 (M-C_4H_9), 311, 265, 91.

HRMS: m/z calc. for $C_{27}H_{31}O_5Si$ 463.1941, found 463.1855.

Methyl (3S,4S)- and (3R,4S)-5-tert-Butyldiphenylsiloxy-4-methoxymethoxy-3-methylpentanoate (**7** *and* **8**): Yield 92%.

^{1}H-NMR ($CDCl_3$) *for the major isomer* **7**: δ = 7.8–7.6 (m, 4H), 7.5–7.3 (m, 6H), 4.74 (d, J = 6.7 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 3.8–3.6 (m, 2H), 3.71 (dd, J = 5.8, 10.8 Hz, 1H), 3.68 (dd, J = 4.7, 10.8 Hz, 1H), 3.67 (s, 3H), 3.51 (q, J = 5.3, 1H), 3.34 (s, 3H), 2.53 (dd, J = 4.4, 15.0 Hz, 1H), 2.5–2.3 (m, 1H), 2.15 (dd, J = 9.3, 15.0 Hz, 1H), 1.06 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H); *minor isomer* **8**, 0.89 (d, J = 6.9 Hz).

MS: m/z = 387 (M-C_4H_9), 325, 311, 213, 91.

HRMS: m/z calc. for $C_{21}H_{27}O_5Si$ 387.1628, found 387.1631.

Methyl (3S,4S)- and (3R,4S)-5-tert-Butyldiphenylsiloxy-3-methyl-4-(methylthiomethoxy)pentanoate (**9**) *and* **10**): yield 78%.

^{1}H-NMR ($CDCl_3$) *for the major isomer* **9**: δ = 7.8–7.6 (m, 4H), 7.5–7.3 (m, 6H), 4.72 (d, J = 11.5 Hz, 1H), 3.73 (dd, J = 5.6, 10.2 Hz, 1H), 3.69 (dd, J = 4.6, 10.2 Hz, 1H), 3.57 (q, J = 4.6 Hz, 1H), 2.54 (dd, J = 4.3, 15.1 Hz, 1H), 2.2–2.4 (m, 1H), 2.15 (dd, J = 9.2, 15.1 Hz, 1H), 2.14 (s, 3H), 1.06 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H); *minor isomer* **10**, 0.88 (d, J = 6.9 Hz).

MS: m/z = 403 (M-C_4H_9), 341, 311, 265, 199.

HRMS: m/z calc. for $C_{21}H_{27}O_4SSi$ 403.140, found 403.1408.

Methyl (3S,4S)- and (3R,4S)-5-tert-Butyldiphenylsiloxy-4-methoxy-3-methylpentanoate (**11** *and* **12**): yield 88%.

^{1}H-NMR ($CDCl_3$) *for the major isomer* **10**: δ = 7.8–7.6 (m, 4H), 7.5–7.3 (m, 6H), 3.72 (dd, J = 4.4, 9.7 Hz, 1H), 3.69 (dd, J = 5.0, 9.7 Hz, 1H), 3.66 (s, 3H), 3.36 (s, 3H), 3.04 (q, J = 6.2 Hz, 1H), 2.48 (dd, J = 4.8, 14.8 Hz, 1H), 2.4–2.2 (m, 1H), 2.17 (dd, J = 8.4, 14.8 Hz, 1H), 1.07 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H); *minor isomer* **12** 0.87 (d, J = 6.8 Hz).

MS: m/z = 357 (M-C_4H_9), 325, 213, 183.

HRMS: m/z calc. for $C_{20}H_{25}O_4Si$ 357.1522, found 357.1502.

Conversion of 7 to (3*S*,4*S*)-5-*tert*-Butyldiphenylsiloxy-3-methyl-4-pentanolide (13):

To a solution of **7** (44 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added Me_2BBr (1.6 M in CH_2Cl_2, 0.3 mmol, 186 µl) at −78°C. After 1 h at −78°C, THF (1 mL) and sat. aq $NaHCO_3$ (0.5 mL) were added at −78°C. The reaction mixture was warmed to r.t. and then diluted with Et_2O (20 mL), and the organic layer was separated and washed with aq NH_4Cl and brine. After drying (Na_2SO_4) and concentration of organic layers, the residue was purified by flash chromatography on silica gel (EtOAc/hexane 1:4) to give lactone **13** (34 mg, 94% yield), identical in all respects to authentic material.[17]

Methyl (*S*)- and (*R*)-3-[(*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]butanoate (15 and 16):

A solution of Me_2CuLi (10.53 mmol) [prepared by adding MeLi · LiBr (1.5 M in Et_2O, 21.05 mmol, 14 mL) to a suspension of CuI (2.00 g, 10.53 mmol) in dry THF (20 mL) at 0°C and subsequent stirring for 15 min at −78°C] was treated with Me_3SiCl (1.14 g, 10.53 mmol) and **14**[7] (500 mg, 1.75 mmol), dissolved in dry THF (30 mL). The temperature was allowed to reach r.t. gradually. The mixture was treated with an NH_4OH/NH_4Cl pH 8 buffer solution and then stirred at r.t. for 15 min. After extraction with Et_2O (100 mL), the organic layers were dried (Na_2SO_4) and filtered. After evaporation, the residue was purified by flash chromatography (EtOAc/hexane 1:4) to give the mixture of **15** and **16** (510 mg, 97% yield > 9:1 *syn*/*anti*).

^{1}H-NMR ($CDCl_3$): δ = 4.0–3.7 (m, 3H), 3.66 (s, 3H), 2.6–2.4 (m, 1H), 2.51 (dd, J = 3.7, 15.6 Hz, 1H), 2.07 (dd, J = 11.2, 15.6 Hz, 1H), 1.7–1.5 (br s, 3H), 1.47 (s, 12H), 0.93 (d, J = 7.1 Hz, 3H).

^{13}C-NMR/DEPT ($CDCl_3$): δ = 172.66 (0), 152.10 (0), 93.46 (0), 179.26 (0), 63.65 (−), 60.50 (+), 50.67 (+), 35.7 (−), 32.05 (+), 75 (+), 26.01 (+), 23.44 (+), 16.02 (+).

(3*S*,4*R*)-4-*tert*-Butoxycarbonylamino-3-methyl-5-pentanolide (17):

To a solution of **15** (251 mg, 0.83 mmol) in MeOH (4 mL) was added TsOH · H_2O (8 mg, 0.04 mmol) at r.t. After stirring for 35 h at r.t., the mixture was diluted with EtOAc (35 mL) and washed with aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated to give the crude alcohol (233 mg). A portion (51 mg) was treated TsOH · H_2O (2 mg) at r.t. in toluene (2 mL) and subsequently warmed to 80°C for 12 h. Then the mixture was diluted with EtOAc (30 mL) and aq $NaHCO_3$ was added. The organic layer was separated, dried ($MgSO_4$), evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane 1:9) to give lactone **17** (29 mg, 70% from **15**): mp 123–124°C; $[\alpha]_D^{25}$ +48.8° (c = 0.8, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 4.60 (br s, 1H), 4.40 (dd, J = 4.4, 6.6 Hz, 1H), 4.07 (dd, J = 6.6, 11.5 Hz, 1H), 3.8–3.6 (m, 1H), 2.73 (dd, J = 6.0, 17.0 Hz, 1H), 2.25 (dd, J = 9.9, 17.0 Hz, 1H), 1.98 (dddq, J = 6.0, 7.5, 9.9, 6.7 Hz, 1H), 1.46 (s, 9H), 1.15 (d, J = 6.7 Hz, 3H).

IR (KBr): ν = 2920, 1745, 1680, 1520 cm^{-1}.

MS: m/z = 229 (M^+), 173, 156.

HRMS: m/z calc. for $C_{11}H_{19}O_4N$ 229.1315, found 229.1325.

(3*R*,4*R*,5*S*)-1-Benzyl-3-methoxycarbonyl-4,5-dimethyl-2-pyrrolidinone (21):

A solution of Me_2CuLi (2.04 mmol) [prepared by adding MeLi · LiBr (1.5 N in Et_2O, 4.08 mmol, 2.7 mL) to a suspension of CuI (388 mg, 2.04 mmol) in dry THF (6 mL) at 0 °C and subsequent stirring for 15 min at − 78 °C] at − 78 °C was treated with Me_3SiCl (222 mg, 2.04 mmol) and **18** (120 mg, 0.34 mmol) dissolved in dry THF (9 mL). After stirring at − 78 °C for 1 h, the temperature was allowed to rise to r.t. and the mixture was stirred at r.t. for 18 h. After same work up as for **15**, the residue was purified by flash chromatography (EtOAc/hexane 1:2 → 1:1) to give **21** (70 mg, 79% yield); $[\alpha]_D^{25}$ − 143.2° (*c* = 1.1, $CHCl_3$).

$C_{15}H_{19}NO_3$ (261.3) calc. C 68.94 H 7.33 N 5.36
found 68.77 7.21 5.48

^{1}H-NMR ($CDCl_3$): δ = 7.4–7.2 (m, 5H), 5.01 (d, *J* = 15.1 Hz, 1H), 3.97 (d, *J* = 15.1, 1H), 3.82 (s, 3H), 3.57 (dq, *J* = 7.5, 6.5 Hz, 1H), 3.21 (d, *J* = 9.7 Hz, 1H), 2.79 (ddq, *J* = 7.5, 9.7, 7.0 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR/DEPT ($CDCl_3$): δ = 170.19 (0), 169.15 (0), 136.08 (0), 128.52 (+), 127.69 (+), 127.41 (+), 54.37 (+), 54.26 (+), 52.40 (+), 44.32 (−), 35.46 (+), 13.72 (+), 13.21 (+).

IR ($CHCl_3$): ν = 2960, 1740, 1690, 1160 cm^{-1}.

MS: *m/z*: 261 (M^+), 202, 146, 138, 91.

HRMS: *m/z* calc. for $C_{15}H_{19}O_3N$ 261.1365, found 261.1361.

Methyl (3*S*,4*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]-3-methylpentanoate (20):

A solution of Me_2CuLi (0.62 mmol) [prepared by adding MeLi · LiBr (0.9 N in Et_2O, 1.25 mmol, 1.4 mL) to a suspension of CuI (119 mg, 0.62 mmol) in dry THF (2 mL) at 0 °C and subsequent stirring for 15 min at − 78 °C] was treated with Me_3SiCl (68 mg, 0.62 mmol) and **19** (40 mg, 0.13 mmol) dissolved in dry THF (1.5 mL). After stirring at − 78 °C for 1 h, the temperature was allowed to rise to − 20 °C and the mixture was stirred at − 20 °C for 18 h. The cold mixture was treated with an NH_4OH/NH_4Cl pH 8 buffer solution and then stirred at r.t. for 15 min. After extraction with Et_2O (35 mL), the organic layers were separated and dried (Na_2SO_4) and filtered. After evaporation, the crude residue was purified by flash chromatography (EtOAc/hexane 1:2) to give **20** (34 mg, 81% yield); $[\alpha]_D^{25}$ − 13.2° (*c* = 1.4, $CHCl_3$).

$C_{19}H_{29}NO_4$ (335.4) calc. C 68.03 H 8.71 N 4.18
found 68.21 8.53 4.02

^{1}H-NMR ($CDCl_3$): δ = 4.43 (d, *J* = 5.9 Hz, 1H), 4.3–3.9 (m, 1H), 3.67 (s, 3H), 3.62 (d, *J* = 5.9 Hz, 1H), 2.5–2.0 (m, 3H), 1.7–1.2 (m, 9H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.90 (br d, *J* = 5.8 Hz, 3H).

IR ($CHCl_3$): ν = 2980, 1740, 1690, 1165 cm^{-1}.

MS: *m/z* = 335 (M^+), 279, 234, 178, 134, 91.

HRMS: *m/z* calc. for $C_{19}H_{29}O_4N$ 335.2097, found 335.2128.

(4*R*,5*S*)-1-Benzyl-4,5-dimethyl-2-pyrrolidinone (22):

From **20**: Treatment of **20** with hydrogen chloride in EtOAc (10 mL) at r.t. for 1 h gave **22** quantitatively as a syrup; $[\alpha]_D^{25}$ − 76.9° (*c* = 0.8, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 7.4–7.2 (m, 5H), 5.00 (d, *J* = 15.2 Hz, 1H), 3.93 (d, *J* = 15.2 Hz, 1H), 3.49 (dq, *J* = 6.8, 7.0 Hz, 1H), 2.51 (dd, *J* = 7.9, 15.4 Hz, 1H), 2.44 (dddq, *J* = 6.8, 7.7, 7.19, 7.3 Hz, 1H), 2.15 (dd, *J* = 7.9, 15.4 Hz, 1H).

IR ($CHCl_3$): ν = 2690, 1690 cm.

MS: *m/z* = 203 (M^+), 188, 146, 91.

HRMS: *m/z* calc. for $C_{13}H_{17}ON$ 203.1310, found 203.131.

From **21**: A mixture of **21** (20 mg, 0.097 mmol), NaCl (4.5 mg, 0.077 mmol) and H_2O (3 mg, 0.15 mmol) in DMF (1 mL) was refluxed for 8 h.[30] The cooled reaction mixture was diluted with H_2O and extracted with EtOAc (20 mL). The combined extracts were washed with brine and dried (Na_2SO_4) concentration and preparative TLC (EtOAc/hexane 1:1) provided **22** (13 mg, 81% yield).

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