JOC Article

Lewis Acid-Promoted Synthesis and Reactivity of *β*-*O*-Benzylhydroxylamino Imides Derived from D-Glyceraldehyde

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This paper describes the synthesis and use of *β*-hydroxylamino imides derived from D-glyceraldehyde possessing a number of reactive sites that operate synergistically or alternatively to bring about highly regio- and diastereoselective transformations to give an optically pure aziridine-2-imide, a dihydro pyrimidine-2,4-dione, or a lactone. Both the syntheses, via the diastereoselective 1,4-conjugate addition of *O*-benzyl hydroxylamine to α,*β*-unsaturated imides, and transformations can be simply tuned by choosing between different Lewis acids.

Introduction

Among the nonproteinogenic amino acids, polyhydroxylated amino acids are interesting due to their presence in natural and synthetic compounds with diverse biological activities, such as nucleoside antibiotics.[1] In addition, they give access to alkaloids, azasugars, enzyme inhibitors, anticancer and antiviral compounds, etc.[2] Polyhydroxylated *β*-amino acids are much rarer in the literature then their α counterparts,[3] and a few syntheses of these compounds have been reported so far.[4] A practical methodology involves the 1,4-addition of a nitrogen nucleophile to an α,*β*-unsaturated carbonyl compound,[5] and particularly one containing the 1,3-dioxolan-4-yl moiety derived from D-glyceraldehyde.[2b,6] This residue typically favors a syn selectivity, ranging from good to moderate for *Z*- and *E*-isomers, respectively.

The use of hydroxylamines as nitrogen nucleophiles is of particular interest due to their high reactivity and the possibility of modifying the resulting 1,4-adducts.[6a,7] For example, the 1,4-adducts resulting from *O*-benzyl hydroxylamine and *N*,*O*-bis-TMS hydroxylamine turned out to be aziridine precursors, by way of the intramolecular cyclization of an intermediate enolate.[8] Aziridines can be considered versatile precursors of α- or *β*-amino acids,[9] and they have also been used in the synthesis of polyhydroxylated amino acids, such as polyoxamic acid[10] and 3-amino 3-deoxy D-xylonic acid ethyl ester.[11]

In this paper, we describe the conjugate addition of *O*-benzyl hydroxylamine to α,*β*-unsaturated imides **5** and **6** promoted by catalytic Lewis acids.[12] Recently, various research groups, including ours, have examined the role of Lewis acids in highly diastereo-[13] or enantioselective[14] conjugate additions of hydroxylamine derivatives. In some cases, stereochemical tuning was observed, depending on the Lewis acid selected. To improve the reactivity, we introduced an oxazolidin-2-one substituent to **5** and **6**, and used different Lewis acids in only small (5%) amounts. The addition of *O*-benzyl hydroxylamine gave *β*-hydroxylamino imides **7** and **8** with different yields and selectivity. We also report the synthesis of the *γ*,*δ*-dihydroxylated *β*-amino acid ester **13**.[15] Moreover, the presence of oxazolidin-2-one permitted the stereoselective cyclization of optically pure **7** to *trans*-aziridine **15** via titanium enolate.[8] We also found an intriguing oxazolidinone incorporation, which gave the unprecedented

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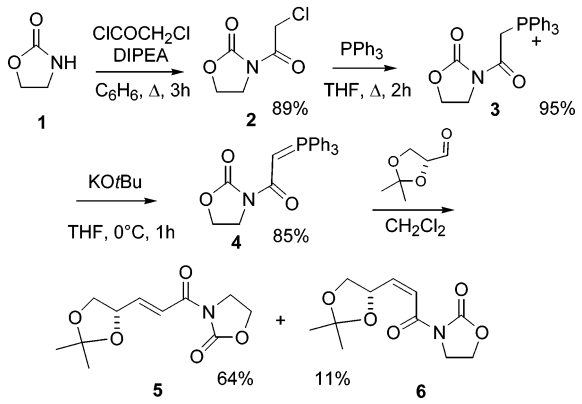
SCHEME 1



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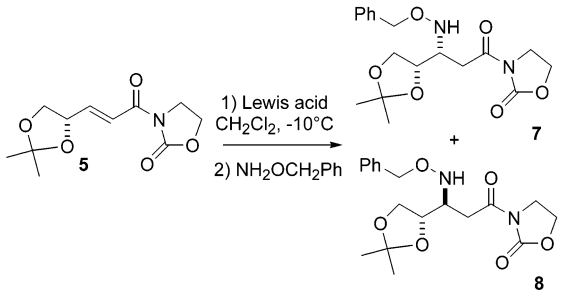

dihydro pyrimidine-2,4-dione **16**. Dihydro uracils[16] are present in fungicides, herbicides, hormone analogues, and unusual nucleotides or peptidyl nucleotides.[17] Finally, we describe the cyclization to lactone **18**, a precursor of 3-amino-2,3-dideoxy pentose,[2b,15a] by way of diol deprotection and lactonization under very mild conditions.

Results and Discussion

To prepare α,*β*-unsaturated compounds carrying an oxazolidinone moiety, we performed a standard Wittig olefination with D-glyceraldehyde[18] and the proper ylide **4** (Scheme 1). The synthesis of **4** required the treatment of **1** with chloroacetyl chloride at reflux in the presence of diisopropylethylamine, and the resulting **2**, purified by flash chromatography over silica gel, was transformed into the phosphonium salt **3** with triphenyl phosphine. Treatment of **3** with potassium *tert*-butoxide gave ylide **4**, which was isolated after recrystallization from ether. Finally, Wittig reaction of D-glyceraldehyde and **4** in CH_2Cl_2 gave a 6:1 mixture of (*E*)-**5** and (*Z*)-**6**, which were isolated by flash chromatography.

The conjugate addition of *O*-benzyl hydroxylamine to *trans*-**5** without a Lewis acid gave no trace of any product. On the other hand, in the presence of Lewis acids, a mixture of diastereomeric products **7** and **8** was obtained, with varying yields and stereoselectivity (Scheme 2, Table 1).

The use of 5% catalytic amounts of $Sc(OTf)_3$ and $MgBr_2 \cdot Et_2O$ (Entries 1 and 2) gave approximately 1:1 mixtures of **7** and **8**, although with excellent yields and without any byproduct. The use of $Yb(OTf)_3$ (Entry 3) gave the products in quantitative yields and with slightly better selectivity, while Bu_2BOTf (Entry 4) gave the products only in trace amounts. With $CeCl_3 \cdot 7H_2O$,[19] however, a 1:2 mixture of **7** and **8** was obtained in good yield (Entry 6).

It has been reported that the conjugate addition of *O*-benzyl hydroxylamine to α,*β*-unsaturated compounds carrying a chiral imidazolidin-2-one gave good diastereoselectivity in the formation of a planar chelate involving aluminum and the two carbonyls.[20] On the contrary, the reaction of *O*-benzyl hydroxylamine and *trans*-**5** in the presence of 1.5 equiv of $AlMe_2Cl$ at low temperature (Entry 6) for 1 h gave **7** and **8** in a moderate yield and selectivity, accompanied by a mixture of compounds derived from 1,2-addition.

Although diastereoselectivity was generally moderate, an interesting Lewis acid dependence was observed. While *syn*-**7** predominated with boron and ytterbium Lewis acids, *anti*-**8** was obtained as the major compound with aluminum and cerium salts.

To improve the **7**/**8** ratio, we turned our attention to *cis*-**6**. The literature generally showed a much higher selectivity for cis-unsaturated esters derived from glyceraldehyde than for trans-unsaturated esters.[5−7] (*Z*)-Methyl-4,5-isopropylidendioxy-2-pentenoate, easily prepared according to the literature,[21] was hydrolyzed with LiOH[22] to the corresponding acid **9**,[23] which was in turn transformed into the mixed anhydride **10** (Scheme 3). The reaction of **10** with the magnesium salt **11**, obtained by treatment of **1** with isopropylmagnesium chloride in THF, gave the desired **6** in almost an 80% yield with respect to the reagent ester.

The reaction of *O*-benzyl hydroxylamine and *cis*-**6** was performed in the presence of diverse Lewis acids (Table 2). Under the same reaction conditions reported for *trans*-**5**, the reaction rates were notably slower. In the presence of $AlMe_2Cl$ (Entry 1), after 2 h we obtained a 40/60 mixture of **7** and **8** in low yield. With $Yb(OTf)_3$, the reaction proceeded quantitatively in 18 h and with an opposite selectivity (**7**/**8** = 71/29) (Entry 2). A careful analysis of the reaction mixture in the presence of ytterbium triflate after 6 h (Entry 3) revealed an excellent stereoselectivity and the presence of *trans*-**5**, probably derived from the isomerization of *cis*-**6**. Therefore, the modest stereoselectivity observed in the presence of $AlMe_2Cl$ and $Yb(OTf)_3$ could be attributed to the addition of *O*-benzyl hydroxylamine to **5**, based on the higher reactivity displayed with respect to **6** (Table 1). We sought to identify the most appropriate Lewis acid for minimizing cis−trans isomerization. The reaction was

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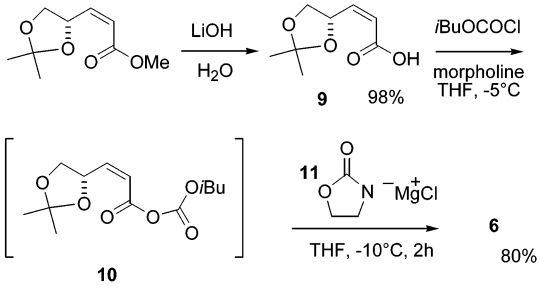
TABLE 1. 1,4-Addition of *O*-benzyl Hydroxylamine to *trans*-5 in the Presence of 0.05 equiv of Lewis Acid

entry	Lewis acid	solvent[a]	temp (°C)	time (h)	**7** + **8** (%)[b]	**7**/**8** (%)[c]
1	$Sc(OTf)_3$	CH_2Cl_2	−10	6	90	50/50
2	$MgBr_2{\cdot}Et_2O$	2/1 CH_2Cl_2/THF	−10	4	>98	50/50
3	$Yb(OTf)_3$	CH_2Cl_2	−10	4	>98	60/40
4	Bu_2BOTf	CH_2Cl_2	−10	12	20	67/33
5	$CeCl_3{\cdot}7H_2O$	THF	−10	6	90	32/68
6	$AlMe_2Cl$[d]	CH_2Cl_2	−60	1	60[e]	39/61

[a] Solvents were varied depending on the solubility of the Lewis acid. [b] After isolation. [c] Calculated according to ^{1}H NMR analysis of the reaction mixture. [d] 1.5 equiv. [e] The rest was starting material **5** (20%), and 1,2-addition products (20%).

SCHEME 3



attempted with $ZnCl_2$ (Entry 4) and, interestingly, the reaction mixture showed a single diastereoisomer, albeit in low yield.

Repetition of the reaction with $CeCl_3{\cdot}7H_2O$ gave both good stereoselectivity and yield, suggesting a slower isomerization rate (Entry 5). Finally, the use of $Cu(OTf)_2$ (Entry 6) or $MgBr_2.Et_2O$ (Entry 7) gave **7** in a good and an excellent yield, respectively, as a single stereoisomer.

The *β-O*-benzyl hydroxylamine imides **7** and **8** were readily purified by flash chromatography over silica gel. Compound **7** underwent highly regio- and diastereoselective transformations in the presence of diverse Lewis acids.

A first Lewis acid-induced transformation allowed the efficient removal of oxazolidin-2-one. Treatment of **7** with a mixture of methanol and toluene at 80 °C in the presence of 20% $MgBr_2$, according to a procedure recently reported by Orita et al.,[24] quantitatively gave the transesterification product **12** in 2 h (Scheme 5).

Hydrogenation of **12** in the presence of Pd/C[25] gave *β*-amino ester **13** in a satisfactory yield. This procedure also allowed us to confirm the stereochemistry of **7** and **8**, by comparison of the analytical data of **13** with the data in the literature.[15a]

Oxazolidin-2-one was also removed under Evans' basic conditions. Treatment of **6** with LiOOH in a mixture of THF and H_2O (Scheme 6)[26] afforded the *β*-benzyl hydroxylamino acid **14**. Treatment of **14** with a solution of diazomethane in ether gave methyl ester **12**. Despite the high yields obtained in each step, the overall procedure was around 15% less efficient than the one-step procedure depicted in Scheme 5.

The synthetic value of oxazolidin-2-one **1** as an enolate promoter[8] was applied to the synthesis of aziridine **15**. A solution of **7** in CH_2Cl_2 was treated with 1 equiv of $TiCl_4$, and after 5 min this mixture was transferred via a cannula to a solution of 2 equiv of TEA in CH_2Cl_2. A dark-red color appeared within a few seconds, indicating the formation of a titanium enolate, and after 10 min the reddish color turned brown, suggesting a fast enolate reaction.^{1}H NMR analysis of the reaction mixture revealed the presence of aziridine **15** as a single diastereoisomer with a relative trans configuration, according to the H_2-H_3 coupling constant (H_2, 3.62 ppm; H^3, 2.36 ppm; $J_{2-3} = 2.9$ Hz).[8,27] Purification by flash chromatography gave **15** in a moderate yield, and the rest was a complex mixture of byproducts arising from aziridine ring opening, acetonide deprotection, and/or imidazolidinone cleavage.

To improve the protocol described above, we attempted the ring-closure of **7** to aziridine via aluminum enolate.[8] A solution of **7** in CH_2Cl_2 was treated with 1 equiv of $AlMe_2Cl$, the mixture was transferred to a solution of 2 equiv of TEA in CH_2Cl_2, and the resulting pale yellow mixture was quenched after 10 min. Analysis of the reaction mixture revealed no trace of aziridine, but the new dihydro pyrimidine-2,4-dione **16**, derived from the intramolecular attack of oxazolidinone carbonyl by hydroxylamine, was obtained pure in 50% yield after flash chromatography. The use of 2 equiv of $AlMe_2Cl$ and 4 equiv of diisopropylethylamine instead of TEA increased the yield up to 85% after purification. The presence of a good base seemed to be important for the reaction. Indeed, treatment of **7** with $AlMe_2Cl$ alone gave an approximately 8/2 mixture of diol-deprotected **17** and lactone **18**, with almost complete conversion, as revealed by ^{1}H NMR analysis of the reaction mixture. The mixture of **17** and **18** was subjected to flash chromatography over silica gel. However, after elution only **18** and **1** were obtained, due to the intramolecular removal of oxazolidinone induced by the acidity of the silica gel. The ease of the lactonization confirmed the strong tendency displayed by **1** toward displacement by a hydroxy group in the presence of Lewis acids.[24] The relative stereochemistry of **18** was determined by measuring the H_4-H_5 coupling constant by ^{1}H NMR analysis. The direct determination of J_{4-5} was troublesome, since H_4 resonance appeared as a broad multiplet at 4.00−4.19 ppm, and H_5 appeared as a pseudoquintet at 4.62 ppm, J = 3.6 Hz. Decoupling of the doublet NH signal at 6.17 ppm with J = 6.0 Hz simplified the H_4 signal to a pseudoquartet with J = 7.5 Hz, and decoupling of the CH_2OH region at 3.66−3.82 ppm transformed the H_5 signal into a doublet, with a residual J_{4-5} = 7.4 Hz. These values

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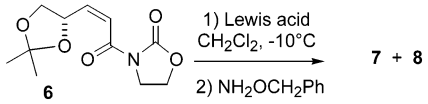
TABLE 2. 1,4-Addition of *O*-Benzyl Hydroxylamine to *cis*-6 in CH_2Cl_2 in the Presence of 0.05 equiv of Lewis Acid

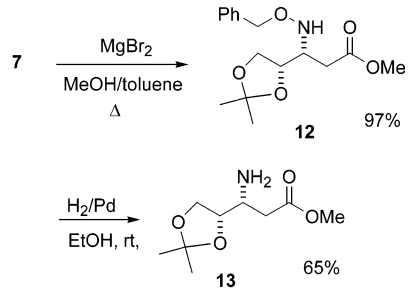
entry	Lewis acid	solvent[a]	temp (°C)	time (h)	**7** + **8** (%)[b]	**7**/**8** (%)[c]
1	$AlMe_2Cl$[d]	CH_2Cl_2	−60	2	35[e]	40/60
2	$Yb(OTf)_3$	CH_2Cl_2	−10	18	>98	71/29
3	$Yb(OTf)_3$	CH_2Cl_2	−10	6	25[f]	>99/1
4	$ZnCl_2$	2/1 CH_2Cl_2/THF	−10	24	10	>99/1
5	$CeCl_3 \cdot 7H_2O$	THF	−10	18	95	91/9
6	$Cu(OTf)_2$	2/1 CH_2Cl_2/THF	−10	24	75	>99/1
7	$MgBr_2 \cdot Et_2O$	2/1 CH_2Cl_2/THF	−10	18	>98	>99/1

[a] Solvents were varied depending on the solubility of the Lewis acid. [b] After isolation. [c] Calculated according to ^1H NMR analysis of the reaction mixture. [d] 1.5 equiv. [e] The rest was *trans*-**5** (15%) and 1,2-addition products (50%). [f] The rest was *trans*-**5** (20%) and *cis*-**6** (55%).

SCHEME 4



SCHEME 5



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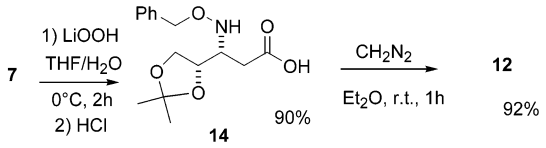

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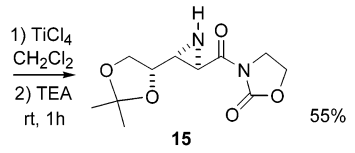

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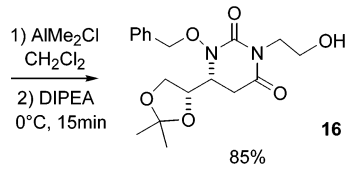
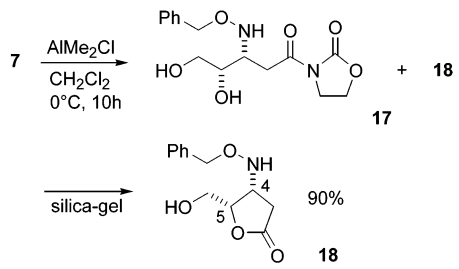


agree with those reported in the literature by Sewald for *cis*-lactones (J_{4-5} = 7.3−7.4 Hz) and *trans*-lactones (J_{4-5} = 4.9 Hz).[2b]

Conclusions

We studied simple molecular systems that showed a strong sensitivity toward Lewis acid activation. In the 1,4-addition of *O*-benzyl hydroxylamine to the *cis*-α,*β*-unsaturated imide derived from glyceraldehyde **6** in the presence of catalytic Lewis acids, the yield and selectivity were strongly dependent on the Lewis acid, and both were excellent with $CeCl_3$, $Cu(OTf)_2$, and $MgBr_2$. The same reaction with *trans*-**5** was less stereoselective, but it was possible to steer the reaction toward a predominance of syn or anti adducts with $Yb(OTf)_3$, or either $AlMe_2Cl$ or $CeCl_3$, respectively. The resulting *β*-hydroxylamino imide **7** showed a number of alternative reaction pathways, managed by different Lewis acids, which selectively activated different reaction sites. Thus, treatment with $MgBr_2$/MeOH gave rise to ester **12**, $TiCl_4$/TEA gave cyclization to *trans*-aziridine **15**, $AlMe_2Cl$/DIPEA gave dihydro uracil **16**, $AlMe_2Cl$/silica gel gave lactone **18**.

SCHEME 9



Experimental Section

General Remarks. Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. *O*-Benzylhydroxylamine was used as a 0.5 M solution in CH_2Cl_2, stored over activated molecular sieves. The solution was obtained by treatment of *O*-benzylhydroxylamine hydrochloride (2.00 g, 12.5 mmol) with aqueous NaOH (0.75 g, 18.8 mmol), followed by three extractions with CH_2Cl_2, then the organic layers were dried over Na_2SO_4. The final volume was adjusted to 25 mL. Et_2O was distilled from $CaCl_2$. D-Glyceraldehyde was obtained by oxidation of protected D-mannitol,[18] and used without prior distillation. To a mechanically stirred mixture of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (3.00 g, 11.4) and $NaHCO_3$ (2.50 g, 29.7 mmol) in CH_2Cl_2 (30 mL) and water (15 mL) was slowly added $NaIO_4$ (3.16 g, 14.8 mmol) portion-wise at 0 °C, than the mixture was allowed to react at rt for 3 h. The mixture was transferred into a separating funnel, the organic layer was separated, and water layer was extracted twice with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4, then solvent was evaporated at reduced pressure. The residue (2.40 g, 80%) was used without further purification. CH_2Cl_2 was distilled from P_2O_5. Toluene was distilled from molecular sieves. THF was distilled from sodium benzophenone ketyl. Flash chromatography was performed on silica gel (230−400 mesh), and solvents were simply distilled. Triethylamine (TEA) and diisopropylethylamine (DIPEA) were simply stored over KOH. TLC were performed on fluorescent silica gel plates. NMR spectra were recorded at 300 (^1H NMR) and at 75 MHz (^{13}C NMR). GC-MS analyses were performed with a capillary column HP 5−5% Ph-Me-Si, 30 m, 0.25 *μ*m, ID 0.25 mm.

3-(2-Chloroacetyl)oxazolidin-2-one (2). To a stirred solution of oxazolidin-2-one **1** (1.50 g, 17.2 mmol) and DIPEA (6.00

mL, 34.4 mmol) in $CHCl_3$ (30 mL) was added a solution of chloroacethyl chloride (2.70 mL, 34.4 mmol) in $CHCl_3$ (10 mL) drop by drop at −5 °C. When the addition was complete, the mixture was allowed to reach rt, then it was slowly heated to 80 °C. After 4 h the mixture was cooled to rt, and the solvent was evaporated at reduced pressure. The residue was quenched with saturated Na_2CO_3 (10 mL) and the mixture was extracted three times with EtOAc. The organic layers were collected and dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The residue was purified by by flash chromatography over silica gel (eluant EtOAc:cyclohexan 1:4) giving **2** (2.50 g, 89%, purity 94% by GC analysis). IR (Nujol) ν 2952, 1758, 1678, 1660, 1401 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (t, J = 11.4 Hz, 2 H), 4.49 (t, J = 11.4 Hz, 2 H), 4.74 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 45.3, 46.1, 64.3, 151.7, 165.5; GC-MS *m*/*z* (%) 163, and 165 (49, and 17, respectively, M^+), 135 (19), 114 (5), 88 (95), 77 (89), 70 (100).

(4″*S*)-(*E*)-3-[3′-(2″,2″-Dimethyl[1″,3″]dioxolan-4″-yl)propenoyl]oxazolidin-2-one (5). A stirred solution of **2** (2.50 g, 15.3 mmol) and triphenyl phosphine (4.80 g, 18.4 mmol) in THF (60 mL) was heated at reflux for 2 h. The mixture was cooled to rt, then it was allowed to stand for 3 h at 0 °C. The precipitated crude 3-(triphenylphosphonium-methylcarbonyl)-oxazolidin-2-one chloride (**3**) (6.20 g, 95%) was filtered and used without further purification. ^1H NMR ($CDCl_3$) δ 3.32 (d, J = 13.5 Hz, 1H), 4.02 (t, J = 8.1 Hz, 2H), 4.45 (t, J = 8.1 Hz, 2H), 6.17 (d, J = 13.5 Hz, 1H), 7.61−7.94 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 165.3, 165.1, 155.0, 132.8, 131.8, 128.7, 127.2, 126.0, 61.1, 42.8, 39.3, 37.7.

The phosphonium salt **3** (6.20 g, 14.6 mmol) was suspended in THF (50 mL), and potassium *tert*-butoxyde (1.64 g, 14.6 mmol) was slowly added portion-wise at −5 °C. After 1 h the suspension was completely dissolved, and the solvent was evaporated at reduced pressure. The mixture was dissolved in hot ether, than it was cooled at −15 °C, and after 3 h the precipitated solid was filtered, giving crude 3-(triphenylphosphonio-methylcarbonyl)oxazolidin-2-one (**4**) (4.82 g, 85%), which was used without further purification. ^1H NMR ($CDCl_3$) δ 4.01 (t, J = 8.5 Hz, 2H), 4.27 (t, J = 8.5 Hz, 2H), 4.73 (d, J = 23.2 Hz, 1H), 7.38−7.83 (m, 15H).

Ylide **4** (2.41 g, 6.20 mmol) was suspended in CH_2Cl_2 (40 mL), D-glyceraldehyde (1.61 g, 12.4 mmol) was added, and the mixture was stirred overnight at 0 °C. The reaction was quenched with H_2O, the mixture was filtered over Celite, and the solid was washed with CH_2Cl_2. The filtrate was transferred into a separating funnel, the organic layer was separated, and the water was extracted three times with CH_2Cl_2. The organic layers were collected and dried over Na_2SO_4. After solvent evaporation at reduced pressure, the residue was purified by flash chromatography over silica gel (eluant EtOAc:cyclohexane 1:4), giving (*E*)-**5** (0.96 g, 64%) and (*Z*)-**6** (0.16 g, 11%) as waxy solids.

(*E*)-5: IR (Nujol) ν 2962, 1775, 1677, 1634, 1379, 1209, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.46 (s, 3 H), 3.70 (dd, J = 6.9, 8.4 Hz, 1 H), 4.08 (t, J = 7.2 Hz, 2 H), 4.19 (dd, J = 6.9, 8.1 Hz, 1 H), 4.43 (t, J = 7.2 Hz, 2 H), 4.73 (q, J = 6.6 Hz, 1 H), 7.05 (dd, J = 6.0, 15.3 Hz, 1 H), 7.48 (d, J = 15.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.5, 26.6, 42.6, 62.1, 66.7, 68.7, 110.3, 120.9, 146.6, 164.5, 196.9; GC-MS *m*/*z* (%) 241 (M^+, 0.5), 226 (14), 211 (3), 166 (100), 153 (81), 122 (42), 97 (36); $[\alpha]_D^{20}$ +22.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.80; H, 6.27; N, 5.79.

(4″*S*)-3-[3′-Benzyloxyamino-3′-(2″,2″-dimethyl[1″,3″]-dioxolan-4″-yl)propanoyl]oxazolidin-2-one (7, 8). To a stirred solution of **5** or **6** (0.10 g, 0.41 mmol) in the solvent of choice (15 mL, Tables 1 and 2) in a two-nec, round-bottom flask was added a Lewis acid (5% mol, 0.021 mmol, Tables 1 and 2) under inert atmosphere at −10 °C. After 20 min, *O*-benzyl hydroxylamine (0.5 M in CH_2Cl_2, 0.90 mL, 0.45 mmol) was added drop by drop. After the scheduled time, the reaction was quenched with 5 mL of saturated Na_2CO_3 and the mixture was extracted twice with CH_2Cl_2. The organic layers were collected and dried over Na_2SO_4. After the solvent evaporation at reduced pressure, the residue was purified by flash chromatography over silica gel (eluant EtOAc:cyclohexane 1:4), giving **7** alone or a mixture of **7** and **8** (see Tables 1 and 2).

(3′*R*)-7: IR (Nujol) ν 2988, 1776, 1687, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.42 (s, 3 H), 2.88 (dd, J = 3.5, 16.2 Hz, 1 H), 3.27 (dd, J = 9.3, 16.2 Hz, 1 H), 3.56 (ddd, J = 3.5, 6.6, 9.3 Hz, 1 H), 3.78−3.92 (m, 3 H), 4.03 (dd, J = 6.2, 8.4 Hz, 1 H), 4.22−4.32 (m, 3 H), 4.63 (d, J = 12.0 Hz, 1 H), 4.68 (d, J = 12.0 Hz, 1 H), 7.20−7.49 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.0, 35.2, 42.9, 59.6, 62.5, 66.9, 75.9, 76.7, 109.9, 128.3, 128.5, 128.8, 129.1, 129.2, 138.0, 154.0, 171.9; GC-MS *m*/*z* (%) 349 (4), 263 (20), 215 (3), 176 (15), 128 (6), 101 (10), 91 (100); $[\alpha]_D^{20}$ +9.8 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.34; H, 6.65; N, 7.68.

(3′*S*)-8: IR (Nujol) ν 2985, 1779, 1692, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.45 (s, 3 H), 3.17 (dd, J = 2.7, 17.1 Hz, 1 H), 3.34 (dd, J = 9.9, 17.1 Hz, 1 H), 3.38−3.45 (m, 1 H), 3.83−3.93 (m, 3 H), 4.01 (dd, J = 6.6, 8.7 Hz, 1 H), 4.27−4.36 (m, 2 H), 4.61 (s, 2 H), 7.18−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.5, 33.8, 42.4, 59.9, 61.9, 67.7, 75.2, 76.2, 109.1, 127.8, 128.2, 128.5, 137.2, 153.4, 172.0; GC-MS *m*/*z* (%) 349 (3), 263 (22), 176 (15), 128 (9), 101 (8), 91 (100); $[\alpha]_D^{20}$ −14.7 (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.32; H, 6.65; N, 7.71.

(4″*S*)-(*Z*)-3-[3′-(2″,2″-Dimethyl[1″,3″]dioxolan-4″-yl)propenoyl]oxazolidin-2-one (6). To a solution of (*Z*)-methyl-4,5-isopropylidendioxy-2-pentenoate (0.40 g, 2.20 mmol), easily prepared according to literature as described in the General Remarks section, in MeOH (12 mL), a 6 N solution of LiOH in water (8 mL) was added with stirring at 0 °C. After 3 h, methanol was evaporated at reduced pressure, and a solution of 1 N HCl was added until the pH was adjusted to 2−3. The mixture was extracted three times with EtOAc, and the organic layers were collected and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, giving (4′S)-(*Z*)-3-(2′,2′-dimethyl[1′,3′]dioxolan-4′-yl)-2-propenoic acid (**9**) as an oily residue (0.36 g, 98%). Spectroscopic characterization was identical with the literature.[23] IR (neat) ν 3400−3000, 1726, 1180, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.46 (s, 3 H), 3.61 (dd, J = 6.4, 8.1 Hz, 1H), 4.35 (dd, J = 7.0, 8.1 Hz, 1H), 5.47−5.56 (m, 1H), 5.88 (dd, J = 2.0, 11.5 Hz), 6.54 (dd, J = 7.0, 11.5 Hz).

To a stirred solution of **1** (0.24 g, 2.70 mmol) in THF (15 mL) in a 50-mL, two-necked, round-bottom flask was added *i*-PrMgCl (2 N in THF, 1.5 mL, 3.0 mmol) dropwise at −10 °C under inert atmosphere, and the mixture was stirred for 1 h. In the meantime, a solution of acid **9** (0.36 g, 2.1 mmol) and 4-methyl morpholine (0.51 mL, 4.6 mmol) in dry THF (15 mL) was stirred at −5 °C under inert atmosphere in a second two-necked flask provided with a filter. After 10 min, a solution of isobuthyl chloroformate (0.32 mL, 2.5 mmol) in THF (5 mL) was added dropwise at −5 °C, and the mixture was stirred for 30 min. Then, the mixture was transferred under inert atmosphere through the filter to the flask containing the magnesium salt of **1**, and the reaction was stirred at −5 °C for 2 h. The reaction was quenched with water (10 mL), THF was evaporated at reduced pressure, and residue was extracted three times with EtOAc. The organic layers were collected and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by flash chromatography over silica gel (eluant EtOAc:cyclohexane 1:4) giving **6** (0.40 g, 80%). IR (Nujol) ν 2972, 1772, 1673, 1660, 1381, 1215, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.46 (s, 3 H), 3.65 (dd, J = 6.9, 8.4 Hz, 1 H), 4.06 (t, J = 8.1 Hz, 2 H), 4.39−4.48 (m, 3 H), 5.36 (q, J = 6.6 Hz, 1 H), 6.51 (dd, J = 6.3, 11.7 Hz, 1 H), 7.17 (d, J = 11.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.5, 42.4, 61.9, 65.3, 69.4, 110.3, 119.1, 151.1, 164.4, 196.7; GC-MS *m*/*z* (%) 241 (M^+, 6), 226 (17), 211 (9), 166 (100), 153 (67), 122 (36), 97 (40); $[\alpha]_D^{20}$ +97.2 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.81; H, 6.29; N, 5.80.

(3*R*,4′*S*)-3-Benzyloxyamino-3-(2′,2′-dimethyl[1′,3′]-dioxolan-4′-yl)propionic Acid Methyl Ester (12). A stirred mixture of **7** (100 mg, 0.27 mmol) and $MgBr_2 \cdot Et_2O$ complex (14 mg, 0.054 mmol) in toluene (2.5 mL) and methanol (0.5 mL) was heated at 80 °C for 2 h. After evaporation of solvents at reduced pressure, water (5 mL) was added, and the mixture was extracted three times with EtOAc. The organic layers were collected and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by flash chromatography over silica gel (eluant EtOAc:cyclohexan 1:5) giving **12** (76 mg, 97%) as an oil. Oxazolidin-2-one **1** remained in the water layers, but no recovery was attempted. IR (Nujol) ν 2995, 1745, 1681, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.42 (s, 3H), 2.41 (dd, J = 4.8, 15.8 Hz, 1H), 2.63 (dd, J = 8.4, 15.8 Hz, 1H), 3.39−3.47 (m, 1H), 3.68 (s, 3H), 3.80 (dd, J = 6.6, 8.2 Hz, 1H), 4.00 (dd, J = 6.4, 8.2 Hz, 1H), 4.24 (q, J = 6.5 Hz, 1H), 4.69 (s, 2H), 6.02−6.20 (br s, 1H), 7.26−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 172.2, 131.0, 128.6, 128.4, 127.9, 109.4, 76.8, 75.4, 66.4, 59.7, 51.9, 38.9, 26.7, 25.4; GC-MS *m*/*z* (%) 309 (M^+, 0.5), 294 (2), 251 (1), 220 (2), 208 (31) 186 (2), 160 (3), 148 (4), 101 (5), 91 (100); $[\alpha]_D^{20}$ +16.5 (*c* 0.5, MeOH). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.09; H, 7.50; N, 4.54.

(3*R*,4′*S*)-3-Amino-3-(2′,2′-dimethyl[1′,3′]dioxolan-4′-yl)-propionic Acid Methyl Ester (13). A mixture of **12** (80 mg, 0.26 mmol) and 10% Pd/C (50 mg) in MeOH (8 mL) was shaken at rt under nitrogen (4 kg/cm^2). After 36 h the suspension was filtered, the solid was washed with MeOH, and the filtrate was concentrated at reduced pressure. The residue was purified by flash chromatography over silica gel (eluant EtOAc: MeOH 95:5) giving oily **13** (34 mg, 65%). Spectroscopic characterization was identical with the literature.[15a] IR (neat) ν 3290, 1727, 1441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.40 (s, 3H), 2.41−2.55 (m, 2H), 2.82−3.18 (m, 3H), 3.70 (s, 3H), 3.63−4.20 (m, 3H); $[\alpha]_D^{20}$ +11.2 (*c* 0.4, $CHCl_3$).

(3*R*,4′*S*)-3-Amino-3-(2′,2′-dimethyl[1′,3′]dioxolan-4′-yl)-propionic Acid (14). To a stirred suspension of LiOH (10 mg, 0.41 mmol) in THF (6 mL) and water (1.5 mL) was added a solution of H_2O_2 (30 wt %, 0.093 mL, 0.82 mmol) at 0 °C. After 15 min, the suspended solid was completely dissolved, and a solution of **7** (50 mg, 0.14 mmol) in THF (2 mL) was added at 0 °C with stirring. After 2 h, THF was evaporated at reduced pressure, pH was adjusted at 3 with 1 N HCl, and the mixture was extracted three times with EtOAc. The collected organic layers were dried over Na_2SO_4. The evaporation of solvent at reduced pressure gave **14** (37 mg, 90%) as a waxy solid. Oxazolidin-2-one **1** remained in the water layers, and recovery was not attempted. IR (Nujol) ν 3400−2950 (br), 1740, 1689, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.40 (s, 3H), 2.47 (dd, J = 4.4, 16.3 Hz, 1H), 2.63 (dd, J = 8.0, 16.3 Hz, 1H), 3.36 (dt, J = 4.8, 7.0 Hz, 1H), 3.80 (dd, J = 6.2, 8.5 Hz, 1H), 4.02 (dd, J = 6.6, 8.5 Hz, 1H), 4.15−4.27 (m, 1H), 4.73 (s, 2H), 6.10−6.26 (br s, 1H), 7.23−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 171.1, 136.8, 130.8, 128.7, 128.4, 128.0, 109.5, 76.6, 74.7, 66.3, 60.4, 38.7, 26.6, 25.2; $[\alpha]_D^{20}$ +4.0 (*c* 0.7, MeOH). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 59.98; H, 7.15; N, 4.74.

(2′*R*,3′*R*,4″*S*)-3-{[3′-(2″,2″-Dimethyl[1″,3″]dioxolan-4″-yl)-2′-aziridinyl]carbonyl}oxazolidin-2-one (15). To a stirred solution of **7** (90 mg, 0.25 mmol) in CH_2Cl_2 (12 mL) was added $TiCl_4$ (27 μL, 0.25 mmol) under inert atmosphere at 0 °C, and after 5 min this brown mixture was transferred at room temperature via cannula within 5 min to a solution of TEA (0.070 mL, 0.50 mmol) in CH_2Cl_2 (8 mL). After 10 min the reaction was quenched with a saturated solution of Na_2CO_3 (5 mL), and the mixture was extracted three times with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. The purification of the residue by flash chromatography over silica gel (eluant EtOAc:cyclohexan 1:2) gave **15** (35 mg, 55%) as a waxy solid, accompanied by an unseparable mixture of byproducts. The purity was measured at 94% by GC-MS analysis, temperature from 50 °C, 2 min, to 250 °C, slope 10 °C/min. IR (Nujol) ν 3250, 1720, 1655, 1160, 1110, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.46 (s, 3 H), 1.80−2.00 (br s, 1 H), 2.36 (dd, J = 2.9, 7.0 Hz, 1 H), 3.62 (d, J = 2.9 Hz, 1 H), 3.82 (dd, J = 4.7, 7.0 Hz, 1 H), 4.00−4.22 (m, 3 H), 4.41−4.57 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.0, 154.0, 109.6, 81.6, 65.8, 64.5, 56.1, 44.6, 42.0, 26.7, 25.4; GC-MS *m*/*z* (%) 241 (25), 181 (15), 155 (18), 113 (20), 84 (100).

(6*R*, 4′*S*)-1-Benzyloxy-6-(2′,2′-dimethyl[1′,3′]dioxolan-4′-yl)-5,6-dihydropyrimidine-2,4-dione (16). To a stirred solution of **7** (60 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added $AlMe_2Cl$ (1 M in hexane, 0.33 mL, 0.33 mmol) at 0 °C under inert atmosphere. After 5 min the mixture was transferred via cannula to a solution of DIPEA (0.11 mL, 0.65 mmol) in CH_2Cl_2, (5 mL) and the resulting pale yellow mixture was quenched after 10 min. The solution was washed with saturated $NaHCO_3$, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were collected and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by flash chromatography over silica gel (eluant EtOAc:cyclohexane 1:3) giving **16** (51 mg, 85%) as an oil. IR (Nujol) ν 3436 (br), 3063, 3025, 2980, 2926, 1719, 1680, 1434, 1381, 1156, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.40 (s, 3H), 2.55 (br t, J = 5.0 Hz, 1H), 2.66 (dd, J = 2.7, 16.8 Hz, 1H), 2.82 (dd, J = 7.2, 16.8 Hz, 1H), 3.48 (ddd, J = 2.1, 2.7, 7.2 Hz, 1H), 3.81 (br q, J = 5.0 Hz, 2H), 3.99 (dd, J = 5.1, 7.2 Hz, 1H), 4.05 (t, J = 5.1 Hz, 2H), 4.10 (ddd, J = 2.1, 5.1, 7.2 Hz, 1H), 4.15 (t, J = 5.1 Hz, 1H), 4.96 (d, J = 11.0 Hz, 1H), 5.04 (d, J = 11.0 Hz, 1H), 7.38−7.46 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 182.7, 168.4, 135.2, 130.0, 129.4, 129.0, 110.5, 77.7, 77.6, 66.2, 61.6, 55.7, 43.6, 35.6, 26.1, 25.7; GC-MS *m*/*z* (%) 364 (M^+, 0.4), 359 (0.8), 306 (1), 264 (1), 241 (1), 200 (7), 157 (6), 129 (3), 101 (8), 91 (100); $[\alpha]_D^{20}$ −84.7 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.29; H, 6.64; N, 7.70.

(4*R*,5*S*)-4-Benzyloxyamino-5-hydroxymethyltetrahydrofuran-2-one (18). To a solution of **7** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (6 mL) was added dimethylaluminum chloride (1 M in hexane, 0.14 mL, 0.14 mmol) at rt. After 10 h, the reaction was quenched with water (5 mL), and the mixture was extracted three times with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was analyzed by ^1H NMR, revealing an ca. 8/2 mixture of **17** and **18**. The mixture was purified by flash chromatography over silica gel (eluant EtOAc: cyclohexane 1:4), affording oily **18** (29 mg, 90%) as the only product.

17: ^1H NMR ($CDCl_3$) δ 2.08 (br t, J = 6.8 Hz, 1H), 2.46 (dd, J = 4.9, 17.8 Hz, 1H), 2.69 (br d, J = 5.3 Hz, 1H), 2.80 (dd, J = 8.1, 17.8 Hz, 1H), 3.64 (t, J = 7.8 Hz, 3H), 3.78−3.86 (m, 3H), 4.06−4.18 (m, 1H), 4.47 (t, J = 7.8 Hz, 3H), 4.72 (s, 2H), 5.53 (d, J = 5.2 Hz, 1H), 7.30−7.41 (m, 5H); GC-MS *m*/*z* (%) 324 (M^+, 0.6), 308 (4), 279 (1), 265 (2), 222 (64), 174 (3) 148 (7), 91 (100).

18: IR (Nujol) ν 3420 (br), 3264, 3058, 3026, 2954, 2919, 2851, 1782, 1451, 1364, 1265, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (br s, 1H), 2.48 (dd, J = 8.1, 17.4 Hz, 1H), 2.63 (dd, J = 8.7, 17.4 Hz, 1H), 3.69 (dd, J = 4.2, 10.5 Hz, 1H), 3.78 (dd, J = 3.0, 10.5 Hz, 1H), 4.00−4.19 (m, 1H), 4.58−4.63 (m, 1H), 4.71 (s, 2H), 6.18 (br d, J = 8.5 Hz, 1H), 7.23−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 179.3, 137.4, 128.5, 128.4, 128.1, 128.0, 79.7, 74.0, 60.6, 57.8, 33.8; GC-MS *m*/*z* (%) 237 (M^+, 6), 219 (2), 206 (2), 130 (2), 112 (2), 105 (5), 91 (100); $[\alpha]_D^{20}$ +8.0 (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.79; H, 6.36; N, 5.88.

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