New Approach to the Coupling of γ-Amino β-Hydroxy Acids and β,γ-Dihydroxy Acids with α-Amino Acid Esters

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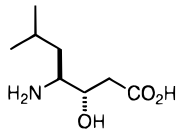
α,α-Dichloro β-lactones, readily obtained by a highly diastereoselective cycloaddition of dichloroketene to *N*-Boc-α-amino aldehydes and α-(silyloxy) aldehydes, coupled efficiently with α-amino acid esters leading, after dehalogenation with H_2 over 10% Pd on charcoal, to peptide mimics under mild reaction conditions.

The development of new approaches to the stereocontrolled synthesis of γ-amino β-hydroxy acids and their coupling with α-amino acid esters has been a subject of interest within the context of biologically active peptide mimics.[1] Two well-known representatives are statine (**1**), a key component of the naturally occurring peptide pepstatin (**2**),[2] and the (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (**3**) (AHPPA),[3] which has been employed for the design of HIV protease inhibitors.[4] However, most of the investigations on this topic have



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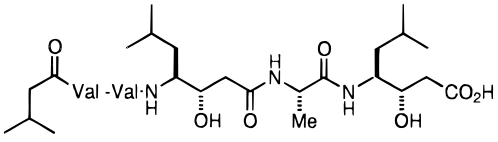

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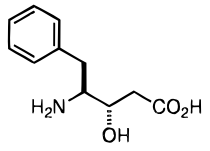

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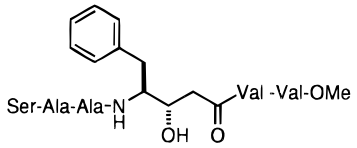

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dealt with the synthesis of the γ-amino β-hydroxy acid itself rather than with the contruction of activated species ready for subsequent peptide coupling steps.[5] For example, the most efficient approaches to date involve, on the one hand, the conversion of N,N-dibenzylated α-amino acids into β-keto esters followed by stereoselective reduction to the corresponding β-hydroxy esters[6] and, on the other hand, the aldol reaction of achiral acetate enolates with *N*,*N*-dibenzyl α-amino aldehydes.[7] The resulting β-hydroxy esters after deprotection and carboxyl group activation can be incorporated into peptides by standard procedures. Our recent studies on β-lactam coupling reactions[8] suggest that peptide derivatives containing γ-amino or γ-hydroxy acids could be directly obtained by ring opening of β-lactones by α-amino acid esters. Nevertheless, a literature precedent concerning the β-lactone cleavage by nitrogen nucleophiles revealed the *O*-acyl fission as the major competitive reaction,[9] and only a very limited number of procedures addressing the desired *O*-acyl fission have been reported to date.[10] The only work related to the idea of coupling β-lactones with α-amino acid esters was that of Seebach and co-workers,[11] who realized the coupling of (±)-β-butyrolactone with (*S*)-valine methyl ester. Although their work led to the expectation that other families of α-unsubstituted β-lactones could also be able to undergo *O*-acyl cleavage by α-amino acid esters, we found that the use of α-dichloro β-lactones allows efficient peptide coupling reactions under conditions in which the corresponding α-unsubstituted lactones are completely inert to ring opening.

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(1) Williams, R. M. In *Biologically Active Peptides: Design, Synthesis and Utilization*; Williams, W. V., Weiner, D. B., Eds.; Technomic: Lancaster, 1993; Vol. 1, p 187.

(2) Umezawa, H.; Aoyagi, T.; Moroshima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.

(3) Omura, S.; Imamura, N.; Kawakita, N.; Mori, Y.; Yamazaki, Y.; Masuma, R.; Takahashi, Y.; Tanaka, H.; Huang, L.; Woodruff, H. *J. Antibiot.* **1986**, *39*, 1079.

(4) Moore, M. L.; Bryan, W. M.; Fakhoury, S. A.; Magaard, V. W.; Huffan, W. F.; Dayton, B. D.; Meek, T. K.; Hyland, L. J.; Dreyer, G. B.; Metcalf, B. W.; Strickler, J. G.; Gorniak, J. G.; Debouck, C. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 420.

(5) For reviews documenting this aspect, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (c) Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1992**, *33*, 1051. (d) Dondoni, A. In *Antibiotics and Antiviral Compounds*; Khron, K., Kirst, H. A., Maas, H., Eds.; VCH: Weinheim, 1993; p 57. For a recent asymmetric synthesis see: (e) Enders, D.; Reinhold, V. *Liebigs Ann. Chem.* **1996**, 11 and references cited therein.

(6) Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1474.

(7) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) Gennari, C.; Pain, G.; Moresca, D. J. *J. Org.Chem.* **1995**, *60*, 6248.

(8) (a) Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1957. (b) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *J. Chem. Soc., Chem. Commun.* **1996**, 663.

(9) For reviews on β-lactones, see: (a) Pommier, A.; Pons, J. M. *Synthesis* **1993**, 441; *Synthesis* **1995**, 729. (b) Laduwahetty, T. *Contemp. Org. Synth.* **1995**, *2*, 133. (c) Lowe, C.; Vederas, C. *Org. Prep. Proc.* **1995**, *27*, 305.

(10) (a) Rosenberg, S. H.; Boyd, S. A.; Mantei, R. A. *Tetrahedron Lett.* **1991**, *32*, 6507. (b) Ratemi, E. S.; Vederas, J. C. *Tetrahedron Lett.* **1994**, *35*, 7605. For regioselective ring opening with cysteine derivatives, see: (c) Shao, H.; Wang, S. H. H.; Lee, C.-W.; Osapay, G.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 2956.

(11) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1236. (b) Breitschuh, R.; Seebach, D. *Synthesis* **1992**, 83.

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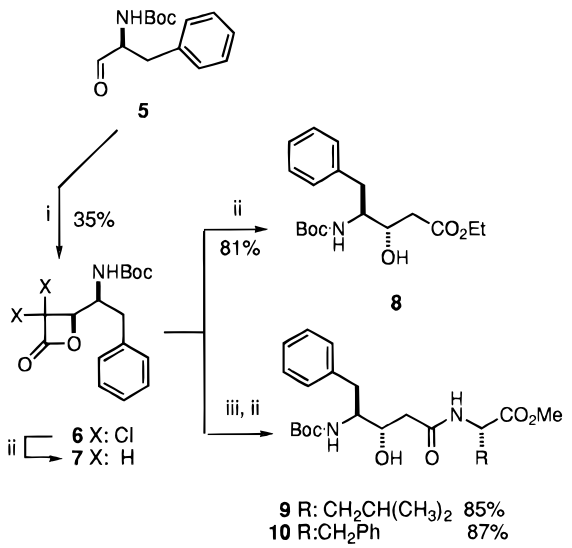
Scheme 1[a]



[a] Reagents and conditions: (i) $Cl_2CHCOCl$, NEt_3, $LiClO_4$, CH_2Cl_2, −78 °C, 4 h; (ii) H_2 (1 atm), Pd/C, NEt_3, EtOH or EtOAc, 15 h; (iii) (*S*)-$H_2NCH(R)CO_2Me$, CH_2Cl_2, rt, 24 h.

To illustrate the above issue we selected first the α-dichloro β-lactone **6**, which on the basis of our hypothesis should be considered as a simultaneously protected and activated form of the AHPPA (**3**). The approach employs the aldehyde **5**, which possesses the required structural subunit of the γ-amino acid and at the same time provides the β-lactone **6** with high diastereoselectivity in a single synthetic step (Scheme 1).[12] Thus, the [2 + 2] cycloaddition reaction of dichloroketene, generated from dichloroacetyl chloride and triethylamine,[13] with **5** afforded an oil, which on purification by silica gel flash chromatography led to the β-lactone **6** in 35% yield.[14] The ^{1}H NMR spectrum of the crude product indicated the exclusive formation of one diastereomer and the relative configuration of the two stereocenters was determined from the known ethyl ester **8**. Namely, in an attempt to obtain the α-unsubstituted β-lactone **7** by means of hydrogenolysis of **6** in EtOH containing triethylamine, we found that the open product **8** was formed in 81% yield without traces of the expected β-lactone **7**. The ethyl ester thus obtained was identical to that previously described by Noyori and co-workers[15] and firmly established the stereochemical assignment made for the adduct.[16] On the other hand, this result suggested that carrying out this reaction under nonsolvolytic conditions, but in the presence of other nucleophiles, it would also be possible to obtain the corresponding acylated products. The question was, therefore, to establish first whether the ester **8** was formed after both chlorine atoms were removed from the β-lactone **6**, and if so, whether the resulting β-lactone could indeed be coupled with α-amino acid esters. To this end, we have prepared the α-unsubstituted β-lactone **7** by performing the dehalogenation of **6** in ethyl acetate, containing triethylamine as above, and both **6** and **7** were then subjected to treatment with 1.5 equiv of (*S*)-leucine methyl ester in methylene chloride at room temperature. While the latter β-lactone did not react to give the desired dipeptide, the former one cleanly produced the expected coupling product, which was isolated as **9** in 85% yield. Likewise, **6** coupled efficently with (*S*)-phenylalanine methyl ester to give the expected dipetide, which after dehalogenation afforded **10** in 87% yield. To ensure that no epimerization occurred during the coupling step, products **11** and **12** (Figure 1) were prepared in the same way as above and submitted to HPLC analysis. As Figure 1 shows, this β-lactone coupling method allows an efficient practical synthesis of short γ-amino β-hydroxy acid peptides with high enantiomeric purity. However, some limitation arose when the coupling reaction was applied to dipeptides, Scheme 2, where yields generally fell to 30−40%. For instance, treatment of dipeptide (*S*)-Val-ValOMe with **6**, under the above reaction conditions, furnished the expected coupling product **13**, but only in 40% yield. The same result was attained when the reaction was carried out in DMF as the solvent. Therefore, the alternative conventional coupling methodology was adopted. Namely, we first prepared the product **14** by reaction of **6** with (*S*)-valine benzyl ester and further exposure of the resulting coupling product to H_2 and 10% Pd/C. Subsequent DCC coupling of **14** with (*S*)-valine methyl ester allowed formation of **13** in 80% yield identical to that obtained by the earlier route.

On the basis of the above results and taking advantage of the ready availability of dichloro β-lactones from α-oxy aldehydes,[12] their coupling with α-amino acid esters could also be anticipated. At this point, however, it should be mentionated that, prior to our work, the asymmetric synthesis of β-lactones from either α-amino aldehydes, vide supra, or α-oxy aldehydes in only one step had remained unexplored.[17] In this context, and contemporary to our work, Romo and co-workers[18] have also addressed this issue, and high levels of diasteroselectivity have been found in the cycloaddition reaction of (trimethylsilyl)ketene with chiral α- and β-(benzyloxy) aldehydes. In our case, as Scheme 3 illustrates, the cycloaddition reaction of **15a** with dichloroketene, generated from trichloroacetyl chloride and Zn/Cu,[19] afforded

(12) Palomo, C.; Miranda, J. I.; Cuevas, C.; Odriozola, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1735.

(13) Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615. For a general review on ketene chemistry, see: Tidwell, T. T. *Ketenes*; John Wiley: New York, 1995.

(14) The chemical yield of this reaction was found to be variable between 30 and 45% over several preparations. Only when the reaction was carried out in the presence of $LiClO_4$ have we obtained a uniform 35% yield. The exact role of this Lewis acid is not clear at present and other Lewis acids tested, i.e., $ZnCl_2$, $BF_3{\cdot}Et_2O$... have been completely unsuccessful. For the effect of lithium perchlorate on the Mukaiyama aldol reaction, see: Reetz, M. F.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119.

(15) Nishi, T. Kitamura, M. Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327.

(16) We have also prepared the racemic form of the β-lactone **6** and dehalogenated to (±)-**7**. HPLC analysis of the reaction crude of (±)-**7** and (−)-**7** revealed that no appreciable epimerization had occurred during cycloaddition reaction and dehalogenation step. Further information is available in the Supporting Information.

(17) A recent paper by another group from this laboratory, which appeared after our preliminary work was published, documents the synthesis of β-lactones from α-oxy aldehydes via Danheiser reaction. For pertinent information on this subject see: (a) Arrastia, I.; Lecea, B.; Cossio, F. P. *Tetrahedron Lett.* **1996**, *37*, 245. (b) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176. (c) Danheiser, R. L.; Nowick, J. S.; Lee, J. H.; Miller, R. F.; Huboux, A. H.; Mathre, D. J.; Shinkai, I. *Org Synth.* **1995**, *73*, 61. For related Danheiser β-lactone synthesis, see: (d) Wedler, C.; Kunath, A.; Schick, H. *J. Org. Chem* **1995**, *60*, 758. (e) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1996**, 881 and references therein.

(18) (a) Zemribo, R.; Romo, D. *Tetrahedron Lett.* **1995**, *36*, 4159. (b) Zemribo, R.; Champ, M. S.; Romo, D. *Synlett* **1996**, 278. Also, see: (c) Pommier, A.; Pons, J.-M. *Synthesis* **1994**, 1294. For other synthesis of β-lactones involving (trialkylsilyl)ketenes, see: (d) Concepcion, A. B.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 4011. (e) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *J. Chem. Soc., Chem Commun.* **1996**, 1053.

(19) Brady, W. T.; Liddell, H. G.; Waughan, W. L. *J. Org. Chem.* **1966**, *31*, 626.

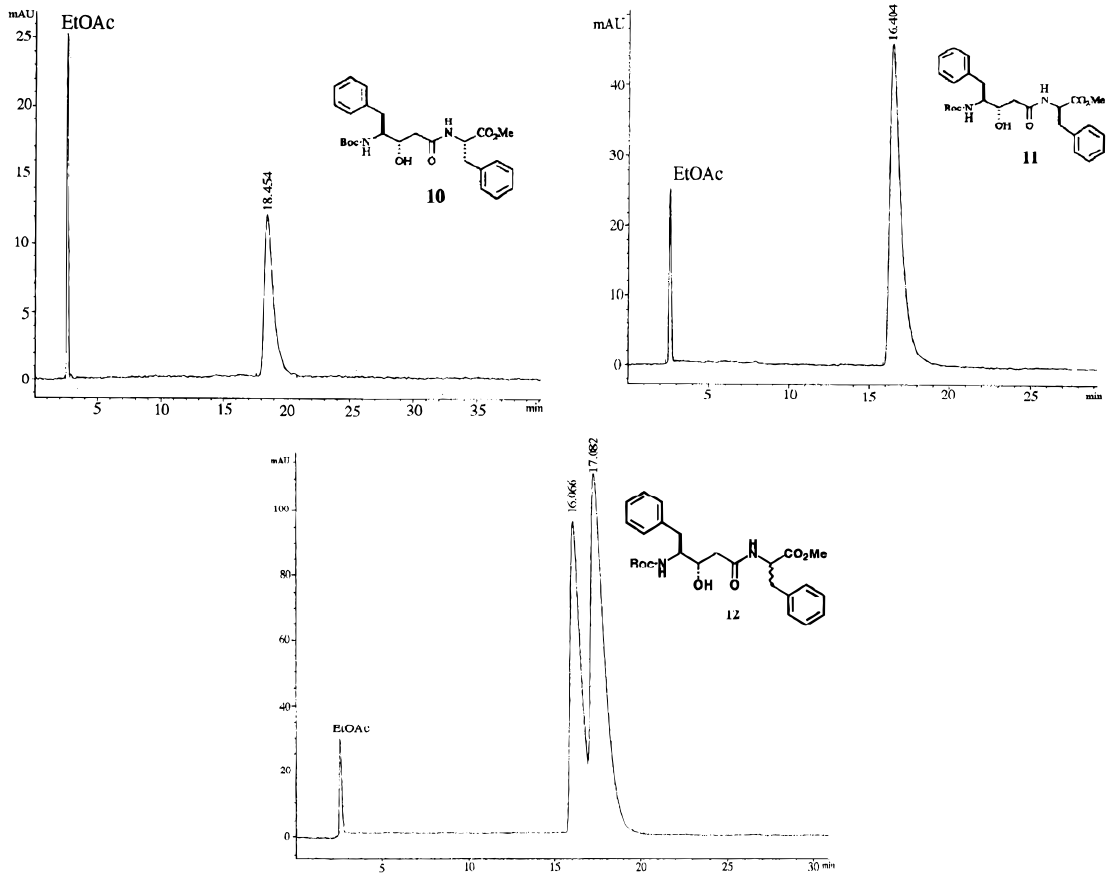
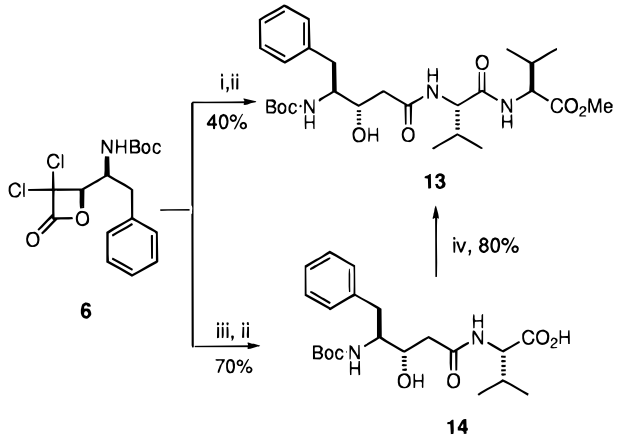


Figure 1. HPLC Chromatograms of (a) product **10**, elution time 18.45 min; (b) product **11**, elution time 16.40 min; (c) product **12** obtained by coupling of **6** with (±)-phenylalanine methyl ester, elution time 16.06 and 17.29 min. Conditions: LiChrosorb Si 60 7 μm, flow 1 mL/min; det 254 nm; mobile phase, EtOAc−hexane 30/70.

Scheme 2[a]



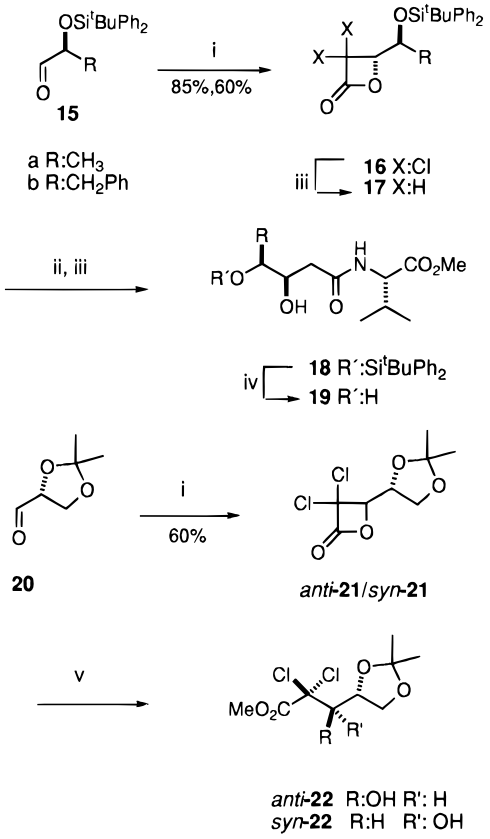
[a] Reagents and conditions: (i) (*S*)-Val-ValOMe, CH_2Cl_2, rt, 15 h; (ii) H_2 (1 atm), Pd/C, NEt_3, EtOAc, 15 h; (iii) (*S*)-ValOBn, CH_2Cl_2, rt, 24 h; (iv) (*S*)-ValOMe, DCC, *N*-hydroxybenzotriazole, THF, 0 °C, 1 h.

after aqueous workup an oil that on purification by silica gel flash chromatography led to the β-lactone **16a** in 85% yield. In a similar way, **15b** on treatment with dichloroketene afforded the β-lactone **16b** in 60% yield after purification by column chromatography. In both cases, examination of the crude product by ^{1}H-NMR indicated that only one diastereomer had been formed. With **20**, however, the cycloaddition was found to be less stereoselective, giving in 60% yield a mixture of the β-lactones *anti*-**21**/*syn*-**21** in a ratio of 70:30, respectively, as determined by ^{1}H-NMR (300 MHz) by integration of the corresponding C_4-H protons appearing at δ 4.70 ppm for the *anti*-isomer and at 4.75 ppm for the *syn*-isomer. In an effort to improve this result, dichloroketene was generated from dichloroacetyl chloride and triethylamine and treated with **20** at −78 °C for 3 h and then at room temperature overnight. In this experiment, an analogous ratio (80:20) of the *anti*/*syn* β-lactones **21** was also produced albeit in somewhat better yield (70%). Both isomers were not separated; instead, the crude mixture was transformed into the corresponding opened products *anti*-**22**/*syn*-**22**, of which the major isomer, *anti*-**22** was isolated by crystallization from hexane in 50% yield. The stereochemistry of this compound was assigned on the basis of previously reported data.[20] In view of this

(20) Rague, B.; Chapleur, Y.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2063.

(21) Although the precise origin of asymmetric induction requires further study, analysis of Cram's rule formulation via the Felkin−Anh model may account for the results obtained with α-(silyloxy) aldehydes, while in the case of α-amino aldehydes the observed stereoselectivity can be attributed to the prior formation of a five-membered chelate and/or and assisted hydrogen-bonding model between the 2-amino group and the carbonyl oxygen function, as postulated for [4 + 2] cycloadditions involving α-amino aldehydes. For more detailed information on this latter subject, see: (a) Jurczak, J.; Golebiowski, A. In *Antibiotics an Antiviral Compounds*; Krohn, K., Kirst, H. A., Maag, H., Eds.; VCH: Weinheim, 1993; p 343. (b) Golebiowski, A; Jurczak, J. *Synlett* **1993**, 241. (c) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H.-J., Braun, M., Krohn, K., Reissig, H. V., Eds.; VCH: Weinheim, 1991; p 3. In addition, a chelation-controlled model has also been proposed by Romo to account for the stereochemical outcome of the reaction of the (trimethylsilyl)-ketene with α- and β-(benzyloxy) aldehydes under the influence of Lewis acids; see ref 18a,b.

Scheme 3[a]



[a] Reagents and conditions: (i) Cl_3CCOCl, Zn−Cu, Et_2O, rt, 4 h; (ii) (*S*)-ValOMe, CH_2Cl_2, 24 h; (iii) H_2 (1 atm), Pd/C, Et_3N, AcOEt, 15 h; (iv) *n*-Bu_4NF, THF; (v) MeOH, NaOMe (cat), rt, overnight.

result,[21] we elected to use β-lactones **16a** and **16b** for coupling reactions. For example, **16a**, upon exposure to (*S*)-valine methyl ester in methylene chloride at room temperature overnight, furnished the expected coupling product, which on dehalogenation led to **18a** in 90% yield. Likewise, the β-lactone **16b**, coupled with (*S*)-valine methyl ester to give, after dehalogenation of the resulting intermediate, **18b** in 92% yield. Both compounds were then isolated as **19a** and **19b** in 75% and 60% yields, respectively, after purification by column chromatography. To corroborate the influence of electron-withdrawing groups at the α-position of the β-lactone ring, compound **17b** was prepared from **16b** and subjected to treatment with (*S*)-valine methyl ester. Once again, no reaction was observed under those conditions that caused the β-lactone **16b** to react and the starting β-lactone **17b** was recovered unchanged. Finally, the β-lactone **17b** was submitted to a single-crystal X-ray analysis to further confirm the stereochemistry assigned for the adducts and derived coupling products.[22] From these results it is interesting to note that peptide mimics in which the γ-amino moiety has been replaced by the hydroxy functionality can also be made accessible without the need to initially prepare the corresponding α-substituted β,γ-dihydroxy carboxylic acid in its free form. Therefore, we have demonstrated that α,α-dichloro β-lactones, which can be obtained in a single synthetic step and with virtually complete diastereoselectivity, are able to undergo *O*-acyl fission by α-amino acid esters providing a new dipeptide coupling methodology. On the basis of the results presented here, the approach developed complements the existing available protocols to synthesize γ-amino β-hydroxy acid and β,γ-dihydroxy acid derived peptides and will find further applications in oxetanone chemistry.

Experimetal Section

Melting points were determined with a capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300 MHz) spectra and ^{13}C spectra (75 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CDCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards, respectively. Mass spectra were obtained on a mass spectrometer (70 eV) using GC-MS coupling (column: fused silica gel, 15 m, 0.25 mm, 0.25 mn phase SPB-5). Optical rotations were measured at 25 ± 0.2 °C in methylene chloride unless otherwise stated. HPLC analyses were performed on analytical columns (25 cm, phase Lichrosorb-Si60) and (25 cm, phase Chiralcel OD) with flow rates using 1 mL/min and 0.5 mL/min, respectively, using a DAD detector. Flash chromatography was executed with Merck Kiesegel 60 (230−400 Mesh) using mixtures of ethyl acetate and hexane as eluants. Ether was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potasium carbonate, and distilled. Commercially available compounds were used without further purification.

Preparation of the α-Dichloro β-Lactone 6. A solution of dichloroacetyl chloride (1.55 mL, 16 mmol) in dry methylene chloride (30 mL) was added dropwise to a stirred solution containing (2*S*)-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanal (0.99 g, 4 mmol), triethylamine (18 mmol), and $LiClO_4$ (0.42 gr, 4 mmol) in dry methylene chloride under nitrogen atmosphere at −78 °C. The resulting mixture was stirred for 4 h at the same temperature and then was allowed to warm to room temperature. The mixture was washed with water (25 mL), 0.1 N HCl (25 mL), and a saturated solution of $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give a crude that was purified by column chromatography using EtOAc /Hex (1:10) as eluent. Yield: 0.50 g (35%). Mp: 124−125 °C (Et_2O). $[\alpha]^{25}_D = +32.3$ (c = 1, CH_2Cl_2). IR (KBr) ν: 3362 cm^{-1} (NH); 1858 cm^{-1} (C=O), 1684 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.18−7.01 (m, 5H); 4.72 (d, 1H, J = 5.9 Hz); 4.43 (d, 1H, J = 9.1 Hz); 4.05 (m, 1H); 2.81 (m, 2H); 1.19 (s, 9H). ^{13}C-NMR (solid, δ ppm): 160.0, 156.1, 137.2, 129.2, 87.2, 80.9, 55.5, 35.6, 28.9. Anal. Calcd for $C_{16}H_{19}Cl_2NO_4$ (360.23): C, 53.34; H, 5.31; N, 3.88. Found: C, 53.10; H, 5.58; N, 4.01.

General Procedure for the Preparation of α-Dichloro β-Lactones 16. To a suspension of Zn/Cu and the corresponding α-(silyloxy) aldehyde (4 mmol) in dry diethyl ether (30 mL) at room temperature was added dropwise a solution of trichloroacetyl chloride (5 mmol) in dry diethyl ether (5 mL). The resulting solution was stirred for 4 h at the same temperature, and then hexane (50 mL) was added and the mixture washed with a saturated solution of $NaHCO_3$ (30 mL). The solid obtained was filtered off through a pad of Celite, and the organic layer was washed with 0.1 N HCl (25 mL) and a saturated solution of $NaHCO_3$ (30 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated

(22) Crystal data for compound **17b**: $C_{27}H_{30}O_3Si$, M_r = 430.61, tetragonal, space group $P4_22_12$, a = 14.061(2) Å, c = 24.703(3) Å, V = 4884(1) Å^3, Z = 8, D_c = 1.171 g cm^{-3}, T = −100 °C, Mo Kα radiation, λ = 0.710 69 Å, μ = 0.121 mm^{-1}. The structure was solved by direct methods and refined on F by full-matrix least-squares methods to give R = 0.0461, wR = 0.0377, S = 1.322 using 280 refined parameters and 2974 observed reflections with $I > 2\sigma(I)$ from the 4961 collected with 5° < 2θ < 55°. The enantiomorph was fixed by the known configuration at C(5) and supported by refinement of the absolute structure parameter [x = 0.1(2)], although in this case this parameter has a large standard deviation. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

under reduced pressure to give a crude that was used without further purification.

(4*S*)-3,3-Dichloro-4-[(1*S*)-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]oxetan-2-one (16a). The general procedure was followed starting from 2(*S*)-[(*tert*-butyldiphenylsilyl)oxy]propanal. Yield: 0.33 g (85%), oil. $[\alpha]^{25}_D = -20.7$ ($c = 1$, CH_2Cl_2). IR (film) ν: 1860 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, δ ppm): 7.34−7.20 (m, 10H); 4.65 (d, 1H, $J = 7.7$ Hz); 4.10 (qd, 1H, $J = 7.7$, 6.4 Hz); 1.20 (d, 3H, $J = 6.4$ Hz); 1.06 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm): 160.9, 135.9, 135.8, 133.6, 132.4, 130.1, 129.9, 127.8, 127.6, 89.3, 68.1, 26.8, 19.2, 19.1.

(4*S*)-3,3-Dichloro-4-[(1*S*)-[(*tert*-butyldiphenylsilyl)oxy]-2-phenylethyl]oxetan-2-one (16b). The general procedure was followed starting from 2(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-3-phenylpropanal. Yield: 1.14 g (60%), oil. $[\alpha]^{25}_D = -12.6$ ($c = 1$, CH_2Cl_2); IR (film) ν: 1860 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, δ ppm): 7.74−7.69 (m, 4H); 7.49−7.37 (m, 7H); 7.20−7.15 (m, 3H); 6.84−6.79 (m, 1H); 4.56 (d, 1H, $J = 3.9$ Hz); 4.36 (ddd, 1H, $J = 9.7$, 5.1, 3.9 Hz); 3.13 (dd, $J = 13.8$, 9.7 Hz); 2.85 (dd, $J = 13.8$, 5.1 Hz); 1.08 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm): 161.0, 136.2, 136.0, 135.9, 135.5, 130.3, 130.1, 129.2, 128.7, 127.9, 127.8, 127.7, 127.6, 127.0, 87.5, 72.9, 39.5, 26.8, 19.3.

General Procedure for the Preparation of α-Unsubstituted *β*-Lactones. To a solution of the corresponding 3,3-dichloro-*β*-lactone (1 mmol) and triethylamine (2.5 mmol) in dry EtOAc (10 mL) was added 10% palladium on charcoal (50 mg), and the mixture was kept under hydrogen (1 atm) at room temperature for 24 h. Then the suspension was filtered through a pad of Celite, and the filtrate was washed with 0.1 N HCl (10 mL) and then with a saturated solution of $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated at reduced pressure to give the corresponding *β*-lactone, which was purified by column chromatography and further crystallization.

(4*S*)-4-[(1*S*)-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl]oxetan-2-one (7). The general procedure was followed starting from **6**. Yield: 0.28 g (97%). Mp: 114−116 °C (Et_2O). $[\alpha]^{25}_D = -9.4$ ($c = 0.56$, CH_2Cl_2). IR (KBr) ν: 3335 cm^{-1} (NH), 1819, 1773 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.39−7.25 (m, 5H); 4.72 (d, 1H, $J = 9.3$ Hz); 4.53 (m, 1H); 4.24 (m, 1H); 3.40 (dd, $J = 16.7$, 5.7 Hz); 3.30 (dd, $J = 16.7$, 4.4 Hz); 3.00 (dd, $J = 13.5$, 7.1 Hz); 2.88 (dd, $J = 13.5$, 8.7 Hz); 1.44 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm): 167.7, 156.0, 136.5, 129.5, 129.2, 128.7, 126.9, 80.3, 70.4, 52.3, 39.7, 38.5, 28.1. Anal. Calcd for $C_{16}H_{21}NO_4$ (291.34): C, 65.96; H, 7.26; N, 4.80. Found: C, 65.90; H, 7.30; N, 4.89.

(4*R*)-4-[(1*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-2-phenylethyl]oxetan-2-one (17b). The general procedure was followed starting from **14b**. Yield: 0.40 g (95%). Mp: 126−128 °C (Et_2O). $[\alpha]^{25}_D = +1.2$ ($c = 1$, CH_2Cl_2). IR (KBr) ν: 1819 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.80−7.75 (m, 4H); 7.52−7.41 (m, 6H); 7.21−7.16 (m, 3H); 6.80−6.75 (m, 3H); 4.35−4.30 (m, 2H); 3.60 (d, 1H, $J = 15.9$, 4.2 Hz); 3.52 (d, 1H, $J = 15.9$, 5.8 Hz); 2.79 (d, 1H, $J = 13.6$, 4.4 Hz); 2.48 (d, 1H, $J = 13.6$, 9.4 Hz); 1.13 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm): 167.9, 136.2, 135.9, 133.8, 132.1, 130.1, 130.0, 129.0, 128.6, 127.8, 126.8, 72.1, 71.2, 40.4, 37.5, 26.8, 19.5. Anal. Calcd for $C_{27}H_{30}O_3Si$ (430.595): C, 75.30; H, 7.02. Found: C, 75.28; H, 7.02.

General Procedures for the Coupling of *β*-Lactones with α-Amino Acid Esters. To a solution of the corresponding α,α-dichloro *β*-lactone (0.5 mmol) in dry methylene chloride was added the α-amino acid ester (0.75 mmol), and the resulting mixture was stirred for 24 h at room temperature. The mixture was then washed with 1 N HCl and a saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated at reduced pressure to give the corresponding coupling product, which was dissolved in dry EtOAc (10 mL). Triethylamine (2.5 mmol) and 10% palladium on charcoal (50 mg) were added, and the mixture was kept under hydrogen (1 atm) at room temperature for 24 h. The suspension was then filtered through a pad of Celite, and the filtrate was washed with 0.1 N HCl (10 mL) and a saturated solution of $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated at reduced pressure to give the corresponding peptide, which was purified by column chromatography. **9**. Yield: 85%. Mp = 120−122 °C (Et_2O−hexane). $[\alpha]^{25}_D = -29.3$ ($c = 1$, CH_2Cl_2). IR (film) ν: 3550, 3533 cm^{-1} (N-H), 1753 cm^{-1} (C=O), 1693 cm^{-1} (C=O), 1659 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.35−7.22 (m, 5H); 6.37 (m, 1H), 5.02 (d, 1H, $J = 9.71$ Hz); 4.60 (m, 1H); 4.00 (d, 1H, $J = 7.5$ Hz); 3.79 (m, 1H); 3.76 (s, 3H); 2.92 (d, 2H, $J = 7.6$ Hz); 2.54 (dd, 1H, $J = 15.3$, 9.8 Hz); 2.28 (dd, 1H, $J = 15.3$, 3.1 Hz); 1.70 (m, 3H); 1.44 (s, 9H); 0.97 (d, 6H, $J = 5.1$ Hz). ^{13}C-NMR ($CDCl_3$, δ ppm): 173.2, 172.4, 156.3, 138.2, 129.3, 128.3, 126.2, 79.4, 68.1, 55.2, 52.2, 50.8, 45.7, 40.9, 40.1, 38.8, 28.5, 24.7, 22.7, 21.7. Anal. Calcd for $C_{23}H_{36}N_2O_6$ (436.53): C, 63.27; H, 8.31; N, 6.41. Found: C, 63.39; H, 8.36; N, 6.42. **10**. Yield: 87%. Mp: 96−98 °C (Et_2O). $[\alpha]^{25}_D = +3.3$ ($c = 1$, CH_2Cl_2). ^1H-NMR ($CDCl_3$, δ ppm): 7.31−7.08 (m, 5H); 6.69 (d, 1H, $J = 7.69$ Hz); 5.02 (d, 1H, $J = 9.7$ Hz); 4.77 (dd, 1H, $J = 13.36$, 7.1 Hz); 3.90 (m, 1H); 3.75 (m, 1H); 3.67 (s, 3H); 3.12 (dd, 1H, $J = 13.9$, 5.7 Hz); 3.01 (dd, 1H, $J = 13.9$, 6.9 Hz); 2.87 (d, 2H, $J = 7.6$ Hz); 2.38 (dd, 1H, $J = 15.0$, 9.0 Hz); 2.19 (dd, 1H, $J = 15.0$, 4.0 Hz); 1.38 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm): 172.2, 171.8, 156.2, 138.1, 135.7, 129.3, 129.1, 128.5, 128.3, 127.0, 126.3, 79.4, 68.1, 55.3, 53.3, 52.3, 40.0, 38.4, 37.5, 28.3. Anal. Calcd for $C_{26}H_{34}N_2O_6$ (470.54): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.11; H, 7.32; N, 6.04. **13**. Yield: 40%. Mp: 170−172 °C (Et_2O). $[\alpha]^{25}_D = -26.5$ ($c = 1$, CH_2Cl_2). ^1H-NMR ($CDCl_3$, δ ppm): 7.39−7.24 (m, 5H); 6.73 (m, 2H), 5.08 (d, 1H, $J = 9.6$ Hz); 4.54 (dd, 1H, $J = 8.7$, 5.0 Hz); 4.31 (m, 1H); 3.98 (m, 1H); 3.77 (s, 3H); 2.95 (2H, $J = 7.6$ Hz); 2.55 (dd, $J = 14.9$, 9.5 Hz); 2.32 (1H, $J = 14.9$, 3.1 Hz); 2.15 (m, 2H); 1.44 (s, 9H); 0.99−0.89 (m, 12H). ^{13}C-NMR ($CDCl_3$, δ ppm): 172.6, 172.1, 170.9, 156.2, 139.1, 129.3, 126.3, 79.5, 68.1, 58.7, 57.2, 55.4, 52.2, 40.1, 38.4, 31.0, 30.9, 28.3, 19.1, 18.9, 18.1, 17.7. Anal. Calcd for $C_{27}H_{43}N_3O_7$ (521.63): C, 62.16; H, 8.30; N, 8.05. Found: C, 61.85; H, 8.71; N, 7.77. **18a**. Yield: 90%, oil. $[\alpha]^{25}_D = +1.4$ ($c = 1.20$, CH_2Cl_2). IR (film) ν: 3304 cm^{-1} (NH), 2949 cm^{-1} (OH), 2849 cm^{-1} (OH), 1735 cm^{-1} (C=O), 1652 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.69−7.64 (m, 4H); 7.44−7.33 (m, 6H); 6.62 (d, 1H, $J = 8.7$ Hz); 4.53 (dd, 1H, $J = 8.7$, 4.5 Hz); 3.93 (m, 1H); 3.81 (dd, 1H, $J = 6.2$, 4.1 Hz); 3.74 (s, 3H); 3.2 (sb, 1H); 2.34 (d, 2H, $J = 6.2$ Hz); 2.16 (m, 1H); 1.06 (s, 9H); 1.04 (d, 3H, $J = 6.2$ Hz); 0.92 (d, 3H, $J = 6.2$ Hz); 0.90 (d, 3H, $J = 6.8$ Hz). ^{13}C-NMR ($CDCl_3$, δ ppm): 172.4, 171.6, 135.6, 133.8, 133.2, 129.7, 129.6, 127.7, 127.4, 72.5, 72.0, 56.9, 51.9, 38.4, 30.8, 26.9, 19.1, 18.8, 17.7. **18b**. Yield: 90%, oil. $[\alpha]^{25}_D = +1.6$ ($c = 0.98$, CH_2Cl_2); IR (film) ν: 3318 cm^{-1} (NH), 2947 cm^{-1} (OH), 2849 cm^{-1} (OH), 1744 cm^{-1} (C=O), 1645 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.76−7.66 (m, 2H); 7.62−7.57 (m, 2H); 7.48−7.32 (m, 6H); 7.25−7.09 (m, 3H); 6.86 (m, 2H); 6.44 (d, 1H, $J = 8.6$ Hz); 4.49 (dd, 1H, $J = 8.7$, 4.9 Hz); 4.05 (m, 1H); 3.88 (m, 1H); 3.70 (s, 3H); 2.7 (m, 2H); 2.3 (m, 2H); 2.1 (m, 1H); 1.04 (s, 9H); 0.91 (d, 3H, $J = 6.8$ Hz); 0.87 (d, 3H, $J = 6.8$ Hz). ^{13}C-NMR ($CDCl_3$, δ ppm): 172.3, 172.2, 137.5, 135.8, 133.4, 133.3, 129.7, 129.6, 129.2, 128.1, 127.6, 127.5, 126.1, 77.3, 70.5, 56.9, 51.9, 39.2, 37.6, 30.9, 26.9, 19.2, 18.7, 17.6. **19b**. Yield: 90%. Mp: 68−70 °C. $[\alpha]^{25}_D = +5.9$ ($c = 1$, CH_2Cl_2). IR (film) ν: 3285 cm^{-1} (NH), 2949 cm^{-1} (OH), 2918 cm^{-1} (OH), 1735 cm^{-1} (C=O), 1648 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, δ ppm): 7.31−7.20 (m, 5H); 6.62 (sb, 1H); 4.51 (dd, 1H, $J = 8.7$, 5.0 Hz); 4.20 (m, 1H); 3.9 (m, 1H); 3.80 (m, 1H); 3.70 (s, 3H); 2.93 (dd, 1H, $J = 13.8$, 3.6 Hz); 2.68 (dd, 1H, $J = 13.8$, 9.0 Hz); 2.53 (d, 2H, $J = 3.9$ Hz); 2.14 (m, 1H); 0.92 (d, 3H, $J = 6.8$ Hz); 0.88 (d, 3H, $J = 6.9$ Hz). ^{13}C-NMR ($CDCl_3$, δ ppm): 172.8, 172.7, 138.1, 129.4, 128.5, 126.5, 74.7, 71.3, 57.2, 52.2, 39.1, 37.8, 30.8, 18.9, 17.7. Anal. Calcd for $C_{17}H_{25}NO_5$ (323.38): C, 63.13; H, 7.79; N, 4.33. Found: C, 63.26; H, 7.71; N, 4.28.

Preparation of Methyl Ester 22. To a suspension of Zn/Cu and isopropylidene-D-glyceraldehyde (4 mmol, 0.52 g) in dry diethyl ether (30 mL) at room temperature was added dropwise a solution of trichloroacetyl chloride (5 mmol, 0.55 mL) in dry diethyl ether (5 mL). The resulting solution was stirred for 4 h at the same temperature, and then hexane (50 mL) was added and the mixture washed with a saturated solution of $NaHCO_3$ (30 mL). The solid obtained was filtered off through a pad of Celite, and the organic layer was washed

with 0.1 N HCl (25 mL) and a saturated solution of $NaHCO_3$ (30 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated at reduced pressure to give a crude. This crude was dissolved in dry methanol (20 mL), sodium methoxide (0.4 mmol) was added, and the resulting mixtutre was stirred overnight at room temperature. The solvent was then evaporated, and the resulting crude was dissolved in dichloromethane (30 mL) and successively washed with saturated solutions of NH_4Cl (20 mL) and $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated at reduced pressure to give a crude that was crystallized in hexane. *anti*-**22**. Mp: 100−102 °C. $[\alpha]^{25}_D = +3.2$ ($c = 1$, ethanol). *syn*-**22**. Oil. $[\alpha]^{25}_D = -10.4$ ($c = 1$, ethanol) (lit.[20] *anti*-**22**. Mp: 100 °C. $[\alpha]^{25}_D = +3.6$ ($c = 1$, ethanol)). *syn*-**22**. Oil. $[\alpha]^{25}_D = -10.6$ ($c = 1$, ethanol).

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Supporting Information Available: Copies of spectra (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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