New Synthesis of α-Amino Acid N-Carboxy Anhydrides through Baeyer–Villiger Oxidation of α-Keto β-Lactams†

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A conceptually new route for the generation of optically active α-aminoacid N-carboxy anhydrides (NCAs) and hence α-amino acid derivatives is described. The strategy developed is simple and consists of the oxidation of α-hydroxy β-lactams to the corresponding α-keto β-lactams followed by a Baeyer–Villiger rearrangement. By that means, a wide variety of functionalized α-aminoacid N-carboxy anhydrides can be obtained, i.e., α,β-diamino acid and α-amino β-hydroxy acid-derived NCAs. The starting α-hydroxy(alkoxy) β-lactams required for the study are easily prepared in large quantities either by the cycloaddition reaction of achiral alkoxyketenes with chiral aldehyde-derived imines or by the addition of Grignard reagents to a 3-(benzyloxy)-4-formylazetidin-2-one. The construction of a wide variety of NCA's from non-amino acid precursors becomes the most remarkable point of the reaction methodology developed.

α-Amino acid N-carboxy anhydrides,[1] NCAs, are of particular relevance as synthetic tools in the chemistry of α-amino acids because they offer both amino group protection and carboxylate activation simultaneously. As a result, since the first work of Leuchs[2] in the early 1900's, numerous procedures have been reported to sythesize NCAs, all of them involving reaction between an α-amino acid and dehydrating agents, particularly phosgene and its synthetic equivalents.[3] In this context, we reasoned (Figure 1) that the Baeyer–Villiger oxidation of enantiomerically pure azetidine-2,3-diones, which should be readily accessible from α-hydroxy β-lactams might serve as a key step in a concise and conceptually new route to NCAs and, therefore, to α-amino acid derivatives in an optically pure form.[4] Furthermore, in this strategy, the absolute configuration at the α-position of the resulting NCA might also be predicted on the basis of the method selected for the β-lactam formation.[5] Prior to the present work, which has been reported in a short preliminary form,[6a] no novel routes to NCAs had been described in the literature, although during the course of this investigation, Bateson and co-workers[7] reported that ozonolysis of ethylidene azetidinones can give NCAs instead of α-keto β-lactams.

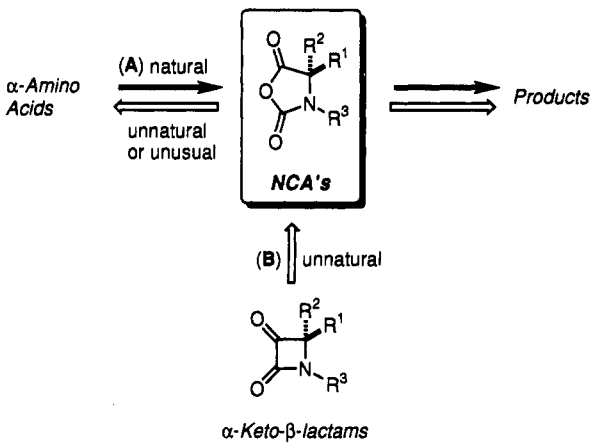

Figure 1. (A) Usual mode of NCA generation. (B) NCAs from non α-amino acid precursors.

The following study documents our efforts to develop the first route to optically active α-amino acid N-carboxy anhydrides from non α-amino acid precursors.

† Dedicated to Professor A. L. Palomo-Coll on the ocassion of his 70th birthday.

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(5) For recent reviews on asymmetric synthesis of β-lactams, see: (a) Copper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem.* **1987**, *59*, 485. (b) Thomas, R. C. In *Recent Progress in The Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; p 533. (c) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503. (d) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (e) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (f) Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A.-ur, Ed.; Elsevier: Amsterdam, 1989; Vol. 4, p 431. (g) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49. (h) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Vol. 5, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; p 85. (i) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*, Georg, G. I.; Ed.; VCH: New York, 1992; p 295. For a general recent review on β-lactams, see (j) Backes, J. in Houben-Weyl, *Methoden der Organischen Chemie*; Muller, E., Bayer, O., Eds.; Band E16B, Thieme: Stuttgart, 1991; p 31.

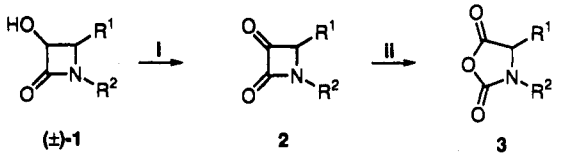
(6) (a) For a preliminary work, see: Cossío, F. P.; López, C.; Oiarbide, M.; Palomo, C.; Aparicio, D.; Rubiales, G. *Tetrahedron Lett.* **1988**, *29*, 3133. (b) By the time we carried out this work an elegant method for the synthesis of functionalized α-amino acids which exploits a C_2–C_3 bond cleavage has recently appeared in the literature see: Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307. For a C_2–C_3 scission of the β-lactam bond leading to β-halo isocyanates, see: (c) Kampe, K. D. *Tetrahedron Lett.* **1969**, 117. For a novel fragmentation of the β-lactam ring, see: (d) Alcaide, B.; Miranda, M.; Perez-Castells, J.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 297.

0022-3263/94/1959-3123$04.50/0

Results and Discussion

While literature pertaining to the chemistry of penicillanic and cephalosporanic ester-derived α-keto β-lactams is abundant,[8] very little is known about the synthesis[9] and applications[10] of monocyclic azetidine-2,3-diones and even less on their optically active derivatives.[11] We first prepared (Scheme 1) diaryl α-keto β-lactams in yields of 90–95% by oxidation of the corresponding racemic α-hydroxy β-lactams **1** ($R^1 = R^2 = Ar$) using Corey's reagent (Me_2SBr_2-NEt_3).[10c] However, our attempts to perform this oxidation on β-lactams **1a–c**, bearing aliphatic groups either at N_1 or C_4 positions, were not as straightforward as could be expected,[12] *vide infra*. The best results for these oxidations, both in terms of chemical yields and large-scale suitability, were obtained using Collins reagent (CrO_3–pyridine) under the conditions modified by Ratcliffe,[13] and dimethylsulfoxide in combination with phosphorus pentoxide (DMSO–P_2O_5).[14] The α-keto β-lactams **2a–c** thus prepared were then allowed to react with *m*-chloroperbenzoic acid (*m*-CPBA) which had been previously dried over $MgSO_4$ in methylene chloride as solvent. The reaction temperature was found to be critical for the success of the transformation, the optimum results being obtained when the rearrangement was performed at −40 °C.[15] Under these conditions the reaction proceeded cleanly to furnish the desired NCAs **3** in almost quantitative yields.

Scheme 1[a]



(±)-1 2 3

a R^1: $CH_2OSiPh_2{}^tBu$ R^2: 4-$MeOC_6H_4$
b R^1: CH_3 R^2: 4-$MeOC_6H_4$
c R^1: C_6H_5 R^2: CH_2Ph

[a] Reagents and conditions: (i) P_2O_5–DMSO; (ii) *m*-CPBA, CH_2Cl_2, −40 °C, 60 min.

Once we had established the best reaction conditions to carry out this new two-step synthesis of NCAs, the next question we explored was the application of this approach to the synthesis of enantiomerically pure compounds. Since the NCA method has been shown to be virtually racemization free,[16] the most critical aspects to be examined were the absence of epimerization during the oxidation of α-hydroxy β-lactams and the possible existence of a keto–enol tautomerism in the resulting α-keto β-lactams which, in accordance with literature precedent,[9b] could be observed in certain situations. For this purpose, the 3-hydroxy-4-(1-aminoalkyl) β-lactams **5** and **7** (Scheme 2) readily available from the acid chloride–imine method,[17] were selected for development.

As pointed out, oxidation of α-hydroxy β-lactams **5** and **7** (Scheme 2) was complicated by the formation of side products and, in general, the expected α-keto β-lactams **8** and **9** were obtained in very low yields, if at all. Guided by the results obtained with racemic compounds, Collin's reagent and DMSO–P_2O_5 were found to be the most effective oxidizing systems after other reagents were screened.[12] Nonetheless, oxidation of *N*-benzyl α-hydroxy β-lactams **7** using CrO_3–pyridine produced very low yields of the expected α-keto β-lactams. In contrast, the DMSO–P_2O_5 system gave these compounds in 80–90% yields after chromatographic purification on silica gel as pale yellow solids in the case of *N*-aryl compounds and as white solids for the *N*-benzyl derivatives.[18] The absence of epimerization or keto–enol tautomerism during the oxidation was established primarily by NMR spectroscopy and HPLC analysis, but further evidence was provided by sodium borohydride reduction of the carbonyl group in each compound **8** and **9** to the starting α-hydroxy β-lactams **5** and **7**, respectively. In all cases this reduction proceeded with complete stereoselectivity corresponding to attack at the less-hindered face of the keto group. In general, the ^{1}H-NMR spectra of adducts **5–9** showed two sets of signals when recorded at room temperature. When the solution was heated to 90 °C they coalesced to a single set of resonances, whereas cooling the sample restored the spectrum to its original condition.[17]

When each compound **8** was treated with *m*-CPBA in methylene chloride as solvent the Baeyer–Villiger rear-

(7) (a) Bateson, J. H.; Kauara, A. C., Southgate, R. *Tetrahedron Lett.* **1991**, *32*, 2065. (b) Bateson, J. H.; Fell, S. C. M.; Kauara, A. C., Southgate, R. *J. Chem. Soc.: Perkin Trans. 1* **1992**, 1577.

(8) For representative examples, see: (a) Sheehan, J. C.; Lu, Y. S. *J. Org. Chem.* **1973**, *38*, 3227. (b) Chandrasekaran, S.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 3972. (c) Applegate, H. E.; Cimarusti, C. M.; Slusarchyk, W. A. *Tetrahedron Lett.* **1979**, 1637. (d) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446. (e) Adams, S.; Arnold, W.; Schönholzer, P. *Tetrahedron* **1983**, *39*, 2485. (f) Brenner, D. G. *J. Org. Chem.* **1985**, *50*, 18. (g) Häbich, D.; Metzer, K. *Heterocycles* **1986**, *24*, 289. (h) Chen, Y. L.; Chang, C.-W.; Hedberg, K. *Tetrahedron Lett.* **1986**, *27*, 3449. (i) Chen, Y. L.; Chang, C.-W.; Hedberg, K.; Guarino, K.; Welch, W. M.; Kiessling, L.; Retsema, J. A.; Haskell, S. L.; Anderson, M.; Manousos, M.; Barrett, J. F. *J. Antibiot.* **1987**, *40*, 803. (j) Ursini, A.; Pellicciari, R.; Tamburini, B.; Carlesso, R.; Gaviraghi, G. *Synthesis* **1992**, 363. (k) Buynak, J. D.; Borate, H. B.; Lamb, G. W.; Khasnis, D. D.; Husting, Ch.; Isom, H.; Sriwardane, U. *J. Org. Chem.* **1993**, *58*, 1325.

(9) (a) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481. (b) Chiba, K.; Mori, M.; Ban, Y. *Tetrahedron* **1985**, *41*, 387. (c) van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758.

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(11) Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V.; Low, C. M. R.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2375.

(12) The oxidizing reagents that were screened were *N*-chlorosuccinimide–dimethyl sulfide–triethylamine, PDC, PCC, Jones reagent, trifluoroacetic anhydride–dimethyl sulfoxide–triethylamine, tetra-*n*-propylammonium perruthenate, and ruthenium tetraoxide–sodium periodate. All of these reagents met with failure on our substrates. For references concerning these reagents, see: Haines, A. H. In *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1988.

(13) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363. (b) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(14) (a) Onodera, K.; Hirano, S.; Kashimura, N. *J. Am. Chem. Soc.* **1965**, *87*, 4651. (b) Jordaan, J. H.; Smedley, S. *Carbohydr. Res.* **1971**, *16*, 117. (c) Taber, D. F.; Amedio, J. C., Jr.; Jung, K.-Y. *J. Org. Chem.* **1987**, *52*, 5621. The Goldman reagent, DMSO–acetic anhydride, was also tested for these oxidations, but proved satisfactory only on a 3–5-mmol scale. On a large preparative scale the α-keto β-lactams were often contaminated with variable amounts of acetate esters, see: (d) Albright, J. D.; Goldman, I. *J. Am. Chem. soc.* **1965**, *87*, 4214. *Ibid. J. Am. Chem. Soc.* **1967**, *89*, 2416. For the use of this reagent in the preparation of 6-oxopenicillinates, see: (e) Roets, E.; Vlietnck, A.; Vanderhaeghe, H. *J. Chem. Soc.; Perkin Trans. 1* **1976**, 704.

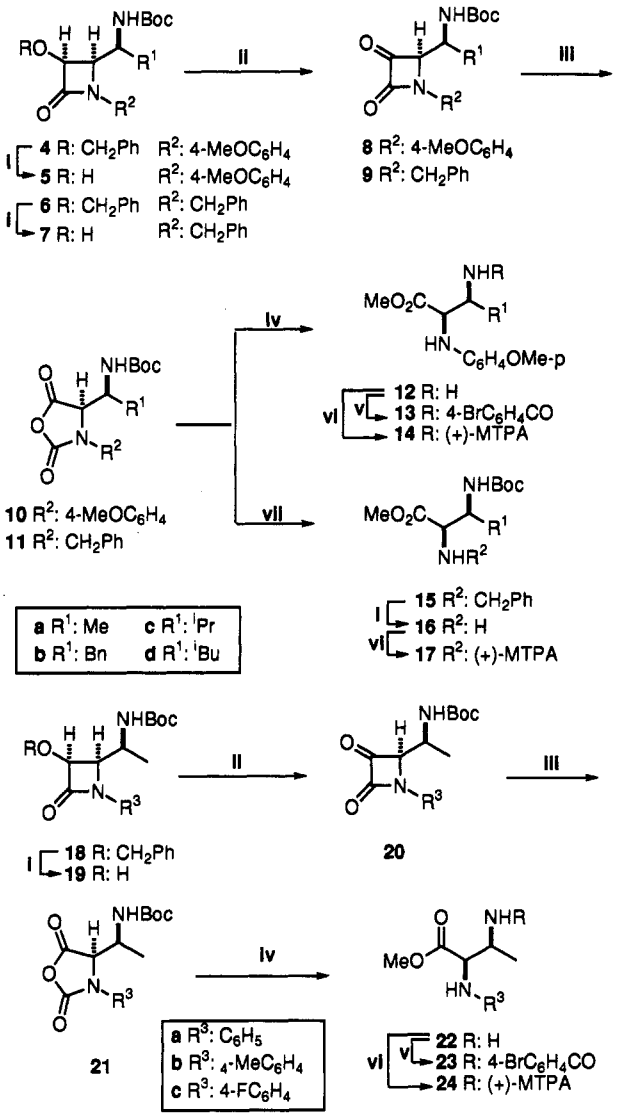
(15) When the rearrangement was performed either at room temperature or at 0 °C, complete destruction of the starting compounds was observed. Similar results were found when the Baeyer–Villiger oxidation was carried out at −20 °C for compounds **2a** and **2b**.

(16) (a) Deukevalter, R. G.; Schwam, H.; Strachan, R. G.; Beesley, T. E.; Veber, D. F.; Schoenewaldt, E. F.; Barkemeyer, H.; Palaveda, J. J. Jr.; Jacob, T. A.; Hirschmann, R. *J. Am. Chem. Soc.* **1966**, *88*, 3163. (b) Manning, J. M.; Moore, S. *J. Biol. Chem.* **1968**, *243*, 5591.

(17) Palomo, C.; Cossío, F. P.; Cuevas, C.; Lecea, B.; Mielgo, M.; Román, P.; Luque, A.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.

(18) This characteristic was also observed in the series of racemic compounds being the frequency of the first absorption band (FFAB) between 320 and 350 nm, see: Manhas, M. S.; Bari, S. S.; Bhawal, R. H.; Bose, A. K. *Tetrahedron Lett.* **1984**, *25*, 4733.

Scheme 2[a]



[a] Reagents and conditions: (i) HCO_2NH_4, Pd/C, MeOH, reflux; (ii) DMSO, P_2O_5, 16 h, rt; (iii) *m*-CPBA, CH_2Cl_2, −40 °C, 60 min; (iv) MeOH, $ClSiMe_3$, rt, 24 h; (v) 4-BrC_6H_4COCl, CH_2Cl_2, NEt_3, rt; (vi) (+)-MTPA-Cl, NEt_3, CH_2Cl_2, rt; (vii) MeOH, reflux.

rangement proceeded cleanly at −40 °C to afford the corresponding NCA **10**. Similarly each α-keto β-lactam **9** led to the formation of the corresponding NCA **11** in excellent chemical yield. Nonetheless, at times some of these NCAs showed traces of *m*-CPBA as the only byproduct, but none of them showed loss of optical purity as judged by the amino acids formed, *vide infra*. Initial attempts to purify them by crystallization or column chromatography on silica gel were unfruitful and led to partial or complete decomposition of the products. In general, practically pure NCAs can be obtained by trituration of the crude compounds with diethyl ether or mixtures of diethyl ether and hexane; however, this procedure results in a somewhat lower yield of the desired NCA.

The optical purities of the resulting NCAs were determined by their transformation into the corresponding α-amino esters. This was easily accomplished by methanolysis of **10a–d** in the presence of trimethylchlorosilane. Under these conditions, esterification and concomitant deprotection of the *N*-Boc group took place leading to the expected α,β-diamino esters **12** in yields in the range 65–75%. These compounds were isolated as the *p*-bromobenzoyl derivatives **13** and in all cases, only one diastereomer was observed by both 300-MHz NMR and HPLC analysis of the crude reaction products. Further evidence of their optical purities was provided by chemoselective acylation of the primary amino group using (+)-MTPA acid chloride and triethylamine.[19] All of the resulting amide derivatives **14** showed a single set of signals in the ^1H and ^{19}F NMR spectra, thus proving that there had been no loss of optical purity during Baeyer–Villiger rearrangement and α-amino ester formation. To ensure the validity of this purity assay the corresponding α-amino ester (±)-**12a** was prepared from racemic **4a** and acylated with (+)-MTPA acid chloride. In this case two sets of signals were obtained in ^1H and ^{19}F NMR spectra.

In order to differentiate the two amino functionalities in the resulting amino acids, the cleavage of the NCAs was tested in the absence of trimethychlorosilane to preserve the *N*-Boc protecting group intact. However, when the NCA **11a** was treated with methanol at room temperature the esterification proceeded very slowly. The use of tertiary organic bases such as triethylamine, pyridine, or 4-(dimethylamino)pyridine to activate the substrate was avoided for two reasons. First, in order to prevent possible polymerization processes[20] and, second, to facilitate product isolation. Nonetheless, when the reaction was carried out in refluxing methanol for 1–2 h each compound **11** was cleanly transformed into the corresponding amino esters **15** in excellent yields and without loss of optical integrity, as indicated by the ^1H and ^{19}F NMR spectra of Mosher amides **17**.

It should be noted that the *N*-*p*-methoxyphenyl group in the above α-amino esters could also be removed by the established protocol.[21] Nevertheless, the possibility of generating a wide variety of N-substituted α-amino acids, particularly *N*-aryl derivatives, added significance to the proposed methodology since, to date, very few general approaches to these compounds in their optically pure forms have been reported in the literature.[22] As illustrated in Scheme 2, the *N*-aryl α-keto β-lactams **20a**, **20b**, and **20c**, obtained from the corresponding hydroxy derivatives **19** in 80, 75, and 75% yields, respectively, upon Baeyer–Villiger oxidation and subsequent ring opening of the resulting NCAs **21** led to the expected *N*-aryl α-amino esters **22a**, **22b**, and **22c**, in 75, 70, and 75% yields, respectively. These compounds were characterized as the *p*-bromobenzoyl derivatives **23** and in each case the optical purity was determined, once again, by conversion into the respective Mosher amides **24**. The corresponding Mosher

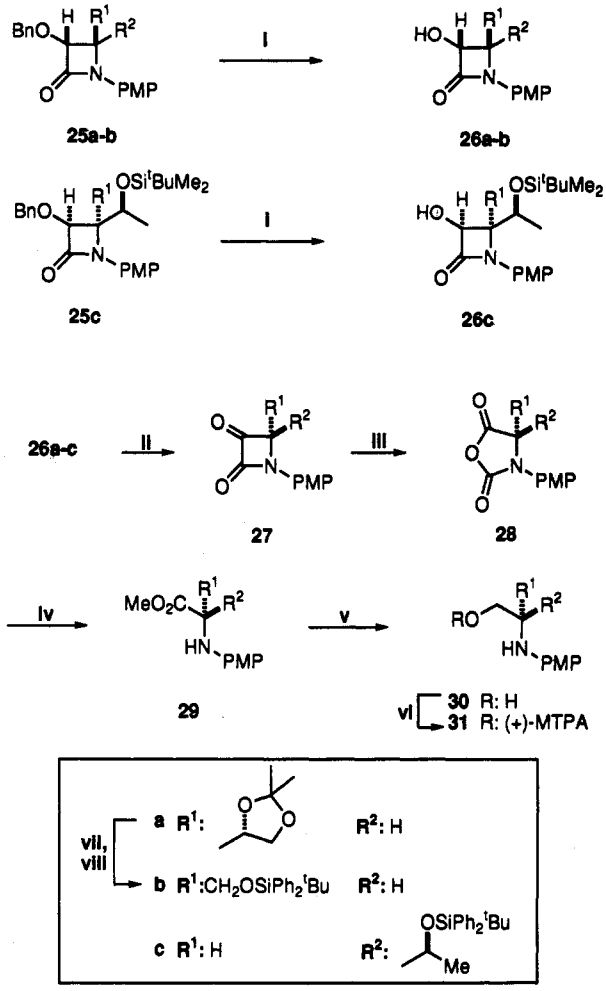
(19) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(20) The fact that these NCAs could also be polymerized by established techniques, see ref 3a, constitutes an additional interest to this α-keto β-lactam-derived NCA method in the field of polymer chemistry. For a recent paper on this matter see: Dorman, L. C.; Shiang, W. R.; Meyers, P. A. *Synth. Commun.* **1992**, *22*, 3257.

(21) (a) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765. (b) Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med. Chem.* **1987**, *30*, 1837. (c) Tomioka, K.; Inove, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681.

(22) For references leading to racemic compounds see: (a) Alcaide, B.; Plumet, J.; Sierra, M. A. *J. Org. Chem.* **1990**, *55*, 3143. (b) Doise, M.; Blondeau, D.; Sliwa, H. *Heterocycles* **1992**, *34*, 2079. For the synthesis of optically active compounds, through nucleophilic substitution of α-hydroxy esters, see: (c) Effenberger, F.; Burkard, U.; Willfahrt, *J. Liebigs Ann. Chem.* **1986**, 314. (d) Hoffman, R. V.; Kim, H.-O. *Tetrahedron* **1992**, *48*, 3007. Through N-arylation methodology, see: (e) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1989**, *30*, 937. Through enzymatic processes, see: (f) Groeger, U.; Drauz, K.; Klenk, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 195.

Scheme 3[a]

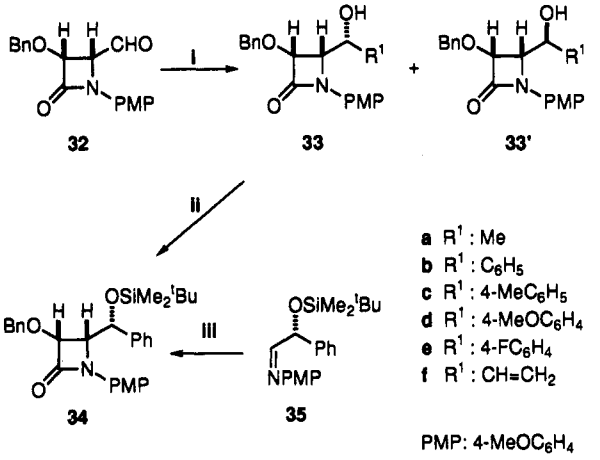


[a] Reagents and conditions: (i) HCO_2NH_4, Pd–C, MeOH, reflux; (ii) DMSO, P_2O_5, 16 h, rt; (iii) *m*-CPBA, CH_2Cl_2, −40 °C; (iv) MeOH, reflux; (v) $LiBH_4$, THF, (vi) (+)-MTPA-Cl, DMAP, CH_2Cl_2, rt; (vii) *p*-toluenesulfonic acid, THF–MeOH, reflux, 20 h, then $NaIO_4$, acetone–H_2O, rt, 6 h; (viii) $NaBH_4$, MeOH, 0 °C, and then $^tBuPh_2SiCl$, DBU, CH_2Cl_2, rt.

amide of racemic **24c** was also prepared to confirm the validity of this diastereomeric test.

A further example which defines the scope of this methodology is illustrated in Scheme 3 by the preparation of α-amino β-hydroxy acid *N*-carboxy anhydrides. As shown in Scheme 3, the known β-lactam (*R,S,S*)-**25a** was first transformed into **25b** under established conditions.[23] Hydrogenolysis of either **25a** or **25b** using ammonium formate and palladium on carbon[24] produced the corresponding hydroxy derivatives **26a** and **26b** in 93 and 80% yields, respectively. Both compounds were then subjected to oxidation with Collins reagent under the conditions modified by Ratcliffe to produce the expected α-keto β-lactams **27a** and **27b** in 45 and 67% yields. Better yields were obtained when the oxidation was performed using DMSO–P_2O_5 reagent to give the desired compounds **27a** and **27b** in 80 and 90% yields, respectively. Treatment

Scheme 4[a]



[a] Reagents and conditions: (i) R^1MgX, THF, −40 °C → rt or R^1MgX–Et_3Al; (ii) $ClSiMe_2{}^tBu$ (3 equiv), DMF, ImH (6 equiv), rt, 24 h; (iii) $BnOCH_2COCl$, NEt_3, CH_2Cl_2, −78 °C → rt, 20–24 h.

of these α-keto β-lactams with *m*-CPBA at −40 °C followed by addition of methanol to the resulting crude NCAs **28a** and **28b** produced the corresponding (*S*)-α-amino esters **29a** and **29b** in 70 and 93% isolated yields, respectively. In a similar way, the β-lactam (*S,R,S*)-**26c**, obtained as previously reported from this laboratory[25] was oxidized to **27c** in 96% yield using DMSO–P_2O_5. Further exposure of **27c** to *m*-CPBA provided the corresponding NCA **28c** which was directly subjected to ring opening with methanol at reflux to produce the expected *N*-*p*-methoxyphenyl-D-threonine methyl ester **29c** in 80% yield. The optical purities of the resulting α-amino esters were checked as shown in Scheme 3. After reduction of the methoxycarbonyl group in each compound **29** using lithium borohydride,[26] the resulting amino alcohols **30** were subjected to the Mosher test showing no detectable loss of optical purity during the amino alcohol formation and derivatization sequences.

At this stage we reasoned that it would be possible to obtain this class of α-amino acid *N*-carboxy anhydrides from a single β-lactam, such as **32** (Scheme 4), if successful stereochemical control in the addition of organometallic reagents to the formyl group could be effected. In particular, straightforward access to 4-[1-(alkoxy)arylmethyl] β-lactams would provide a general route to an activated form of the β-hydroxyarylalanine fragment commonly found in complex α-amino acids.[27] On the basis of the literature precedent concerning 1,3-asymmetric induction,[28] our initial trials to prove this strategy were performed using various Grignard reagents under standard conditions.[29] While methylmagnesium bromide reacts at −40 °C with **32** with relatively poor stereoselectivity (**33a**:**33'a**, 67:33), the addition of phenylmagnesium bromide produced **33b** together with **33'b** in a ratio of 91:9 as determined by ^1H NMR spectroscopy. Some representa-

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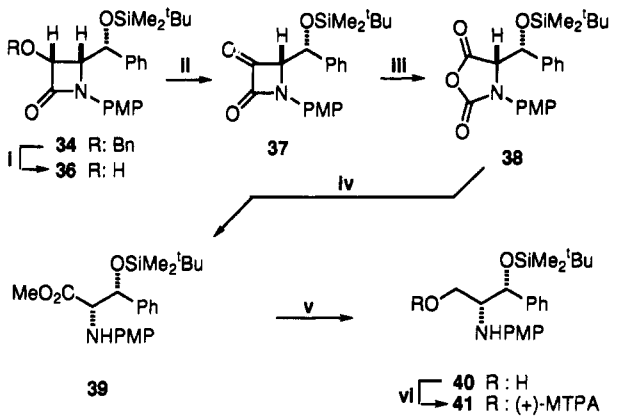
Table 1. Addition of Grignard Reagents and Aluminum Ate Complexes to the 4-Formyl β-Lactam 32

entry	R^1	yield, %[b]	33:33′ product distribution[c]	mp, °C[d]	^{1}H-NMR ($CDCl_3$) δ_{H_3} 33	33′
a	CH_3	91	67:33	120–121 (cyclohexane)	4.79	4.81
b	C_6H_5	90 (72)	91:9 (>95%)	108–109	4.81	4.87
c	4-$CH_3C_6H_4$	93 (68)	90:10 (>95%)	93–94 (ethanol)	4.78	4.86
d	4-$CH_3OC_6H_4$	89 (70)	90:10 (>95%)	118–119	4.77	4.88
e	4-FC_6H_4	76 (66)	90.5:9.5 (>95%)	125–127	4.83	4.89
f	$CH{=}CH_2$	65	87.5:12.5	102–105	4.80	4.86

[a] Reactions conducted on 10-mmol scale; molar ratio Grignard reagent:substrate 1.3:1. [b] Yield refers to the crude reaction mixture. The number in parentheses represents the yield of isolated compound **33**. [c] Determined by 300-MHz ^{1}H-NMR spectroscopy. The number in parentheses represents the stereoselectivity observed using the corresponding aluminum ate complex. In these cases we also observed the formation of small amounts of ethyl derivatives which were not characterized. [d] Crystallized from hexane/methylene chloride if not otherwise stated.

tive aryl Grignard reagents were successfully employed in such a reaction (Table 1). In every case, 4-[1-(hydroxy)-arylmethyl] β-lactams **33** were prepared in good yields with excellent stereoselectivity (**33**:**33′** > 90:10) and the major isomers could be separated in an enantiomerically pure form by a single crystallization from ethanol or column chromatography. We also found that vinylmagnesium bromide reacts analogously with the aldehyde **32** as aryl Grignards do although the degree of diastereoselectivity was somewhat lower (**33f**:**33′f**, 85:15). After consideration of a number of possibilities to increase the above observed stereoselectivity,[30] particularly in the case of the addition of aryl Grignard reagents, we focused on aluminum ate complexes as a potential option.[31] Indeed, the reaction of **32** with phenylmagnesium bromide in the presence of triethylaluminum produced the carbinol **33b** without detectable amounts of the product **33′b** as judged by ^{1}H NMR analysis of the crude reaction mixture. Some examples are summarized in Table 1. From this data it is evident that this addition reaction enjoys wide scope while displaying virtually complete diastereofacial selectivity.[32] The absolute configuration at the newly created stereocenter of the major diastereomer **33b** was firmly established by its conversion into **34**, using TBDMS-Cl and imidazole in DMF as solvent.[33] The resulting β-lactam **34** was identical to that obtained by the cycloaddition reaction of (benzyloxy)ketene to the imine **35** derived from (R)-[(*tert*-butyldimethylsilyl)oxy]-2-phenylacetaldehyde following the procedure of Terashima.[34] On the other hand, the β-lactam **33a** was identified as the enantiomer of the desilylated product derived from **25c**. The stereochemistry of the other adducts was established by analogy.

Scheme 5[a]



[a] Reagents and conditions: (i) HCO_2NH_4, Pd–C, MeOH, reflux 60 min; (ii) CrO_3, pyridine, CH_2Cl_2, rt; (iii) *m*-CPBA, CH_2Cl_2, −40 °C; (iv) MeOH, reflux, 90 min; (v) $LiBH_4$, THF, rt, 24 h; (vi) (+)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, rt, 18 h.

As illustrated in Scheme 5, the synthesis of β-hydroxyarylalanine-derived NCAs is exemplified by the formation of **38** as a representative compound. Thus, the β-lactam **34** upon hydrogenolytic cleavage of the benzyloxy group and further oxidation of the resulting α-hydroxy β-lactam **36** by means of CrO_3–pyridine gave **37** as a pale yellow solid in 86% yield. Subsequent Baeyer–Villiger rearrangement led to the NCA **38** which was directly transformed into the protected (2*S*,3*R*)-β-hydroxyphenylalanine **39** in 80% overall yield. Finally, conversion of the methoxycarbonyl group into the hydroxymethyl functionality furnished the amino alcohol **40** which was acylated with Mosher acid chloride in the presence of triethylamine. The resulting Mosher ester **41** proved that all the reaction sequence performed proceeded without detectable racemization. These results demonstrate that a number of enantiomerically pure α-amino-β-hydroxy acid *N*α-carboxy anhydrides can be obtained via this approach using a chiral 4-formyl β-lactam as common starting material.

Finally, the utility of the fully synthetic new NCAs prepared was tested for a stepwise peptide synthesis. As illustrated in Scheme 6, a few representative α-keto

(30) (a) The use of methylene chloride as solvent or a lower reaction temperature (−90 °C) did not improve the stereochemical course of the addition of phenylmagnesium bromide to the aldehyde **32**. For factors that could influence the stereoselectivity of the addition of organometallics to aldehydes, see: Reetz, M.; Stanchev, S.; Haning, H. *Tetrahedron* **1992**, *48*, 6813. (b) In a first experiment use of $TiCl_4$ to improve the stereoselectivity was unfruitful causing complete degradation of the starting material, see: Reetz, M.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (c) Lithium dimethylcuprate and lithium diphenylcuprate addition to the 3-benzyloxy β-lactam **32** also gave similar stereochemical results to those obtained from Grignard reagents. For asymmetric induction in the reaction of organocuprates with β-alkoxy aldehydes see: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(31) The choice of the ate complexes was based on the 1,3-asymmetric induction in β-alkoxy imines via metal tuning discovered by Yamamoto, see: Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc.; Chem. Commun.* **1985**, 814.

(32) Although the stereoselectivity observed in these addition reactions can be accounted for by invoking a chelated transition state between the benzyloxy group and the aldehyde carbonyl, we defer further analysis and speculation pending the outcome of the experiments in progress.

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Scheme 6

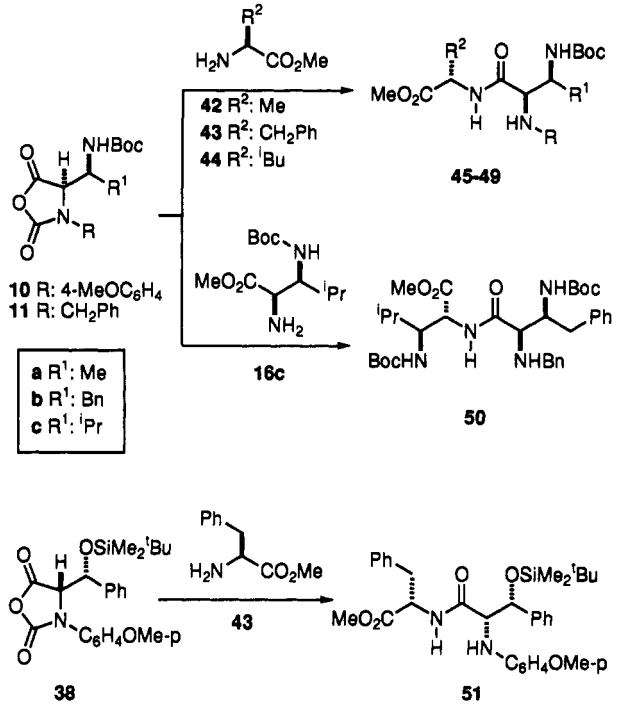

Table 2. Peptide Coupling Reactions[a] (Scheme 6)

NCA	R	R¹	R²	product	yield, %[b]	mp, °C[c]
10a	4-MeOC$_6$H$_4$	Me	Me	**45**	75	157–158
10a	4-MeOC$_6$H$_4$	Me	CH$_2$Ph	**46**	81	164–165
10c	4-MeOC$_6$H$_4$	ⁱPr	CH$_2$Ph	**47**	80	155–156
11a	CH$_2$Ph	Me	CH$_2$Ph	**48**	70	115–117
11b	CH$_2$Ph	CH$_2$Ph	ⁱBu	**49**	73	129–130
11b	CH$_2$Ph	ⁱPr	–	**50**	70	60–62
38	–	–	–	**51**	77	97–98

[a] Reactions conducted on 2-mmol scale in methylene chloride at room temperature using crude NCAs. [b] Isolated yield after purification by column chromatography. [c] Crystallization solvent: AcOEt–hexane.

β-lactam-derived NCAs were selected and treated with various α-amino esters. The reactions were conducted at room temperature in methylene chloride as solvent and in each case the corresponding dipeptide was isolated in good yield (Table 2). In particular, formation of the triamino dipeptide **50** from NCA **11b** and **16c**, the latter being obtained from the NCA **11c**, defines the scope of substrates suitable for use in the present α-hydroxy β-lactam-derived NCA methodology. In addition, HPLC analysis of the dipeptide products from each experiment did not reveal either diastereomeric cross-contaminants or detectable epimerization.

In conclusion, the examples described serve to illustrate that the approach developed is clearly distinguished from the conventional Leuchs procedure, provides structurally elaborated NCA's from non α-amino acid precursors, is very simple in execution, and is easily extendible to further applications.[35]

Experimental Section

General Experimental. Commercially available compounds were used without further purification unless otherwise noted. Starting β-lactams were prepared by previously reported procedures (see text). Hexane was purified by distillation. Tetrahydrofuran and diethyl ether were distilled over sodium with benzophenone as indicator. Methylene chloride was shaken with concentrated H_2SO_4, dried over K_2CO_3, and distilled. Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. Infrared spectra were obtained on a Shimadzu IR-435 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP2000 spectrometer operated at 70 eV. Capillary GLC analyses were performed on a Shimadzu GC-14A gas chromatograph equipped with a 15 m × 0.25 mm fused-silica Supelco SPB-5 column. HPLC analyses and purifications were performed on a Shimadzu LC-8A system equipped with Merck Lichosorb Si 60 (7 μm) columns. Specific rotations were determined on a Perkin-Elmer 243B polarimeter, thermostated at 25 °C by means of a Selecta-Frigiterm 6000382 apparatus. NMR spectra were recorded on a Varian VXR300 spectrometer at either 90 °C or ambient temperature and on a Varian VXR 200. ^{1}H and ^{19}F nuclei were observed at 300 MHz and 282.2 MHz, respectively. ^{1}H-NMR chemical shifts are reported in δ vs Me_4Si. ^{19}F-NMR chemical shifts are reported in δ vs $CFCl_3$ at 0.00 ppm.

General Procedure for the Preparation of α-Hydroxy β-Lactams. To a stirred solution of the corresponding 3-benzyloxy β-lactam (20 mmol) in dry acetone or methanol (300 mL) was added 10% palladium on carbon (7 g) and ammonium formate (11.3 g, 180 mmol). The resulting mixture was refluxed for 1–2 h until the starting material could no longer be detected by TLC analysis and then cooled to room temperature. The reaction mixture was filtered through a pad of silica gel and washed with acetone (133 mL). The filtrate was evaporated under reduced pressure to give a residue which was dissolved in methylene chloride (266 mL) and washed with water (2 × 266 mL), 0.1 N HCl (2 × 266 mL), and aqueous $NaHCO_3$ (saturated solution, 260 mL) and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding α-hydroxy β-lactam which was purified by crystallization or by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2 as eluent).

(3*S*,4*R*)-1-Benzyl-4-[(*S*)-1-[(*tert*-butyloxycarbonyl)amino]ethyl]-3-hydroxyazetidin-2-one (7a). The title compound was prepared from **6a**: yield 80%; mp 227–9 °C (hexane); $[\alpha]^{25}_D$ = −15.5° (*c* = 0.8, CH_2Cl_2); IR (KBr) ν 3442 (NH, OH), 1750, 1680 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90 °C) δ 7.43–7.20 (m, 5H, arom), 6.41 (d, 1H, *J* = 8.5 Hz, NH), 5.92 (d, 1H, *J* = 7.3 Hz, OH), 4.72 (dd, 1H, *J* = 5.0 Hz, *J'* = 7.3 Hz, C$_3$H), 4.53 (d, 1H, *J* = 15 Hz, NC*H*$_2$Ph), 4.09 (d, 1H, *J* = 15 Hz, NC*H*$_2$Ph), 3.78 (m, 1H, C*H*NHBoc), 3.46 (dd, 1H, *J* = 5.0 Hz, *J'* = 9.3 Hz, C$_4$H), 1.37 (s, 9H, C(CH$_3$)$_3$), 1.03 (d, 3H, *J* = 6.6 Hz, CH$_3$). Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.82; H, 7.67; N, 8.78.

(3*S*,4*R*)-1-Benzyl-4-[(*S*)-1-[(*tert*-butyloxycarbonyl)amino]phenethyl]-3-hydroxyazetidin-2-one (7b). The title compound was prepared from **6b**: yield 85%; mp 248–249 °C (THF–MeOH); $[\alpha]^{25}_D$ = −26.0° (*c* = 0.5, DMSO); IR (KBr) ν 3560 (NH, OH); 1750, 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90 °C) δ 7.32–7.13 (m, 10H, arom.), 6.43 (s$_b$, 1H, NH); 6.12 (d, 1H, *J* = 6.8 Hz, OH), 4.82 (dd, 1H, *J* = 5.0 Hz, *J'* = 6.8 Hz, C$_3$H), 4.56 (d, 1H, *J* = 15.3 Hz, NC*H*$_2$Ph), 4.05 (d, 1H, *J* = 15.3 Hz, NC*H*$_2$Ph), 3.95 (dddd, 1H, *J* = 3.0 Hz, *J'* = 9.4 Hz, *J''* = 9.5 Hz, *J'''* = 10.5 Hz, C*H*NHBoc), 3.59 (dd, 1H, *J* = 5.0 Hz, *J'* = 9.4 Hz, C$_4$H), 2.88 (dd, 1H, *J* = 3.0 Hz, *J'* = 13.6 Hz, HC*H*Ph), 2.56 (dd, 1H, *J* = 10.5 Hz, *J'* = 13.6 Hz, HC*H*Ph), 1.25 (s, 9H, C(CH$_3$)$_3$). Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.50; H, 7.35; N, 7.04. Found: C, 69.83; H, 7.54; N, 7.32.

General Procedure for the Oxidation of α-Hydroxy β-Lactams to α-Keto β-Lactams. Method A. To a stirred solution of pyridine (16.2 mL, 200 mmol) in dry methylene chloride (250 mL) was added chromium trioxide (10 g, 100 mmol) at 0 °C and then allowed to warm to 20 °C over 15 min. The corresponding α-hydroxy β-lactam (10 mmol) was added in one portion to the well-stirred mixture and a black tar-like solid was formed. The reaction mixture was stirred at room temperature for 30–60 min and then filtered through a pad of silica gel (70–230 mesh) and washed with methylene chloride (200 mL). The resulting solution was washed with 0.1 N HCl (5 × 250 mL) and aqueous $NaHCO_3$ (250 mL, saturated solution) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding α-keto β-lactam which was purified by

(35) For additional applications of this methodology, see: Palomo, C.; Aizpurua, J. M.; Cabré, F.; García, J. M.; Odriozola, J. M. *Tetrahedron Lett.*, in press. (b) Palomo, C.; Aizpurua, J. M.; Cabré, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.*, in press.

column chromatography (silica gel, 70–230 mesh, CH_2Cl_2 as eluent). **Method B.** To a stirred solution of dimethyl sulfoxide (30 mL) at room temperature was added phosphorus pentoxide (2 g, 7 mmol calculated on P_4O_{10}) in one portion. The reaction temperature rose to 35–40 °C and the resulting mixture was stirred for 2–5 min at the same temperature. The corresponding α-hydroxy β-lactam (10 mmol) was added in one portion to the above well-stirred mixture and after stirring 24 h (for *N*-benzyl derivatives) or 10–15 h (for *N*-aryl compounds) the mixture was gradually poured into a cold aqueous $NaHCO_3$ (150 mL, saturated solution) and extracted with methylene chloride. The organic solution was washed with aqueous NaCl (3 × 150 mL, saturated solution) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding α-keto β-lactam of sufficient purity for use in the next step.

(4*R*)-1-Benzyl-4-[(*S*)-1-[(*tert*-butyloxycarbonyl)amino]-ethyl]azetidine-2,3-dione (9a). The title compound was obtained from **7a** following the general procedure described in method B: column chromatography on silica gel (eluant: hexane/EtOAc, 1:1) afforded **9a** as a white solid: yield 83%; HPLC (EtOAc as eluant, 10 mL/min, retention time 12.93 min); mp 116–8 °C (hexane/EtOAc); $[\alpha]^{25}_D = -65.3°$ ($c = 0.58$, CH_2Cl_2); IR (KBr) ν 3350 (NH), 1820, 1760, 1695 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90 °C) δ 7.34–7.22 (m, 5H, arom), 6.78 (s_b, 1H, NH), 4.95 (d, 1H, J = 15.4 Hz, NCH_2Ph), 4.55 (d, 1H, J = 15.4 Hz, NCH_2Ph), 4.16 (d, 1H, J = 5.9 Hz, C$_4$H), 3.82 (m, 1H, C*H*NHBoc), 1.37 (s, 9H, C(CH$_3$)$_3$), 1.05 (d, 3H, J = 7 Hz, CH$_3$). Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.96; N, 8.80. Found: C, 64.42; H, 6.85; N, 8.96.

(4R)-1-Benzyl-4-[(*S*)-1-[(*tert*-butyloxycarbonyl)amino]-phenethyl]azetidine-2,3-dione (9b). The title compound was obtained from **7b** following the general procedure described in method B: column chromatography on silica gel (eluant: hexane/EtOAc, 1:1) afforded **9b** as a white solid: yield 78%; HPLC (EtOAc as eluant, 10 mL/min, retention time, 12.79 min); mp 150–2 °C (hexane/EtOAc); $[\alpha]^{25}_D = -40.0°$ ($c = 0.51$, DMSO); IR (KBr) ν 3340 (NH), 1825, 1760, 1705 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90 °C) δ 7.38–7.05 (m, 10H, arom), 6.68 (s_b, 1H, NH), 5.01 (d, 1H, J = 15.3 Hz, NCH_2Ph), 4.59 (d, 1H, J = 15.3 Hz, NCH_2Ph), 4.26 (d, 1H, J = 5.3 Hz, C$_4$H), 4.01 (m, 1H, C*H*NHBoc), 2.65 (m, 2H, CH_2Ph), 1.26 (s, 9H, C(CH$_3$)$_3$). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.45; H, 6.72; N, 7.22.

(4*S*)-4-[1(*R*)-[(*tert*-Butyldimethylsilyl)oxy]benzyl]-1-(4-methoxyphenyl)azetidine-2,3-dione (37). Following the general procedure described in method A, starting from (3*R*,4*S*)-4-[1(*R*)-[(*tert*-butyldimethylsilyl)oxy]benzyl]-3-hydroxy-1-(4-methoxyphenyl)acetidin-2-one (**36**) (4.13 g, 10 mmol), the title β-lactam was obtained as a yellow solid: yield 3.54 g (86%); mp 102–4 °C (Et_2O); $[\alpha]^{25}_D = 84.9°$ ($c = 0.92$, CH_2Cl_2); IR (KBr) ν 1812, 1750 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.25–7.15 (m, 5H, arom), 7.08 (d, 2H, J = 9 Hz, arom), 6.70 (d, 2H, J = 9 Hz, arom), 5.19 (d, 1H, J = 3.3 Hz, CH), 4.84 (d, 1H, J = 3.3 Hz, C$_4$H), 3.76 (s, 3H, OCH$_3$), 0.85 (s, 9H, SiC(CH$_3$)$_3$), −0.02 (s, 3H, SiCH$_3$), −0.19 (s, 3H, SiCH$_3$); ^{13}C-NMR ($CDCl_3$) δ 192.4, 160.9, 157.5, 139.7, 130.2, 128.4, 128.2, 126.0, 120.0, 114.1, 77.2, 72.3, 55.4, 25.6, 18.0, −4.6, −5.7. Anal. Calcd for $C_{23}H_{29}NO_4Si$: C, 67.12; H, 7.10; N, 3.40. Found: C, 67.90; H, 7.34; N, 3.58.

General Procedure for The Synthesis of α-Amino Acid *N*-Carboxy Anhydrides (NCAs). To a stirred solution of *m*-CPBA (50%) (2.24 g, 6.5 mmol) in methylene chloride (25 mL) was added $MgSO_4$ and the mixture was stirred for 30 min and then the $MgSO_4$ filtered off. A solution of the corresponding α-keto β-lactam (5 mmol) in dry methylene chloride (10 mL) was added dropwise to the above precooled (−40 °C) solution of *m*-CPBA and the resulting mixture stirred at the same temperature until complete disappearance of the starting product was observed by TLC analysis, usually between 15 min and 30 min. During this time a white precipitate appeared and the mixture was successively washed with aqueous $NaHCO_3$ (50 mL, saturated solution), 40% $NaHSO_3$ (50 mL), and aqueous $NaHCO_3$ (50 mL, saturated solution). The organic solvent was dried ($MgSO_4$) and concentrated in vacuo to give the corresponding NCAs which, in the case of racemic compounds, were crystallized from hexane–chloroform or diethyl ether. For optically active compounds, the crude NCAs were used as such in the next steps.

General Procedure for the Synthesis of α-Amino Esters. Method A. To a solution of the corresponding NCA (5 mmol) in methanol (30 mL) was added trimethylchlorosilane (1.92 mL, 15 mmol). After the reaction was stirred at room temperature for 16–20 h, the solvent was evaporated under reduced pressure to give a residue which was dissolved in CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (20 mL, saturated solution), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding α-amino ester. **Method B.** A solution of the corresponding NCA (5 mmol) in dry methanol (30 mL) was stirred under reflux for 1–2 h. After completion the solvent was evaporated under reduced pressure, the residue was dissolved in methylene chloride (20 mL), and the same workup as above was followed, to give the corresponding α-amino ester in fairly pure form.

Methyl 2(*R*)-(Benzylamino)-3-[(*S*)-1-(*tert*-butyloxycarbonyl)amino]-4-phenylbutanoate (15b). The azetidine-2,3-dione **9b** was subjected to Baeyer–Villiger oxidation under the conditions described in the general procedure. The resulting NCA **11b** was refluxed in methanol for 2 h to give the title compound **15b** which was isolated by flash column chromatography on silica gel (eluant: hexane/EtOAc, 4:1) as a colorless oil: yield 72%; $[\alpha]^{25}_D = -41.4°$ (c = 1.5, CH_2Cl_2); IR (film) ν 3320 (NH), 1732, 1705 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90 °C) δ 7.41–7.18 (m, 10H, arom); 6.30 (s_b, 1H, N*H*Boc), 4.35 (m, 1H, C$_3$H), 3.87 (d, 1H, J = 12.5 Hz, NCH_2Ph), 3.75 (s, 3H, OCH$_3$), 3.60 (d, 1H, J = 12.5 Hz, NCH_2Ph), 3.21 (s, 1H, C$_2$H), 2.97–2.92 (m, 2H, HC*H*Ph), 2.12–2.05 (s_b, 1H, N*H*CH$_2$), 1.41 (s, 9H, C(CH$_3$)$_3$). Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.58; N, 7.03. Found: C, 69.52; H, 7.84; N, 7.14.

Methyl 2(*R*)-Amino-3-[(*S*)-1-(*tert*-butyloxycarbonyl)-amino]-4-phenylbutanoate (16b). The title compound was prepared from **15b** and isolated by column chromatography on silica gel (eluant: hexane/EtOAc, 1:1) as a colorless oil: yield 0.86 g (93%); $[\alpha]^{25}_D = -27.4°$ ($c = 1.2$, CH_2Cl_2); IR (film) ν 3450 (NH), 1750, 1690 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.33–7.20 (m, 5H, arom), 5.10 (d, 1H, J = 7.3 Hz, N*H*Boc), 4.32 (m, 1H, C$_3$H), 3.69 (s, 3H, OCH$_3$), 3.47 (m, 1H, C$_2$H), 2.91–2.83 (m, 2H, HC*H*Ph), 2.52–1.93 (s_b, 2H, NH$_2$), 1.82–1.68 (s_b, 2H, NH$_2$), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C-NMR($CDCl_3$) δ 174.9, 155.8, 138.3, 129.7, 129.2, 127.1, 79.9, 55.1, 54.7, 52.9, 39.1, 28.8. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.12; H, 7.72; N, 9.15.

General Procedure for the Synthesis of Carbinols 33. To a stirred suspension of 3-(benzyloxy)-4-formyl-1-(*p*-methoxyphenyl)azetidin-2-one (**32**) (3.11 g, 10 mmol) in dry THF (50 mL) was added an ethereal solution (13 mL) of freshly prepared Grignard reagent (13 mmol) dropwise at −40 °C under nitrogen, and the resulting solution was stirred at room temperature for 90 min. The progress of the reaction was monitored by TLC analysis and on completion the reaction mixture was quenched with NH_4Cl (35 mL, saturated solution) and extracted with CH_2Cl_2 (50 mL). The organic layer was separated and dried with $MgSO_4$. Evaporation of the solvent gave a crude residue which was analyzed by ^{1}H-NMR to determine the diastereomeric ratio of adducts. The residue was chromatographed on silica gel (70–230 mesh, CH_2Cl_2–hexane 1:1 as eluent) and the product was crystallized to give the corresponding pure carbinol **33**.

(3*R*,4*S*)-3-(Benzyloxy)-4-[(*R*)-1-hydroxybenzyl]-1-(4-methoxyphenyl)acetidin-2-one (33b). Following the general procedure, a mixture of β-lactams was obtained: yield 90%; mp 108–9 °C (hexane/CH_2Cl_2); $[\alpha]^{25}_D = +32.2°$ ($c = 1.11$, CH_2Cl_2); IR (KBr) ν 3488 (OH), 1738 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.35–7.24 (m, 10H, arom), 6.89 (d, 2H, J = 9 Hz, arom), 6.58 (d, 2H, J = 9 Hz, arom), 5.02 (t, 1H, J = 3.0 Hz, CHOH), 4.93 (d, 1H, J = 11.7 Hz, HCH), 4.81 (d, 1H, J = 5.1 Hz, C$_3$H), 4.68 (d, 1H, J = 11.7 Hz, HCH), 4.48 (dd, 1H, J = 5.1 Hz, J = 3.0 Hz, C$_4$H), 3.70 (s, 3H, OCH$_3$), 3.06 (d, 1H, J = 3.0 Hz, OH); ^{13}C-NMR ($CDCl_3$) δ 164.5, 155.7, 139.8, 135.9, 130.2, 128.2, 128.1, 128.0, 127.9, 127.2, 125.7, 119.4, 113.2, 80.1, 73.5, 71.4, 62.8, 55.4. Anal. Calcd for $C_{24}H_{23}NO_4$: C 74.01; H, 5.95; N, 3.60. Found: C, 74.63; H, 6.08; N, 3.49.

(3*R*,4*S*)-3-(Benzyloxy)-4-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]benzyl]-1-(4-methoxyphenyl)azetidin-2-one (34). To a stirred solution of (3*R*,4*S*)-3-(benzyloxy)-4-[1(*R*)-hydroxybenzyl]-1-(4-methoxyphenyl)azetidin-2-one (**33b**) (7.8 g, 20 mmol)

in dry DMF (40 mL) were added *tert*-butyldimethylchlorosilane (9.04 g, 60 mmol) and imidazole (8.17 g, 120 mmol). The resulting solution was stirred magnetically and heated at 35 °C for 24 h. Then methylene chloride (400 mL) was added and the resulting mixture was washed with 0.1 N HCl (2 × 400 mL) and brine (3 × 400 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the β-lactam **34** as a white solid: yield 9.67 g (96%); mp 93–4 °C (EtOH); $[\alpha]^{25}_D$ = −4.5° (*c* = 1.1, CH_2Cl_2); IR (KBr) ν 1753 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.55 (d, 2H, *J* = 9 Hz, arom), 7.45–7.35 (m, 10H, arom), 6.87 (d, 2H, *J* = 9 Hz, arom), 5.11 (d, 1H, *J* = 7.8 Hz, CH), 4.60 (d, 1H, *J* = 12 Hz, HCH), 4.56 (d, 1H, *J* = 5.4 Hz, C_3H), 4.53 (dd, 1H, *J* = 5.4 Hz, *J* = 7.8 Hz, C_4H), 4.44 (d, 1H, *J* = 12 Hz, HCH), 3.82 (s, 3H, OCH_3), 0.64 (s, 9H, $SiC(CH_3)_3$), −0.26 (s, 3H, $SiCH_3$), −0.35 (s, 3H, $SiCH_3$); ^{13}C-NMR ($CDCl_3$) δ 166.1, 156.3, 141.4, 136.9, 131.6, 128.3, 128.1, 128.0, 127.8, 120.1, 113.8, 80.0, 75.7, 73.3, 63.3, 55.5, 25.6, 17.9, −4.9, −5.1. Anal. Calcd for $C_{30}H_{37}NO_4Si$: C, 71.54; H, 7.40; N, 2.78. Found: C, 71.98; H, 7.49; N, 2.73.

Methyl (2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[(4-methoxyphenyl)amino]-3-phenylpropanoate (39). The azetidine-2,3-dione **37** (2.06 g, 5 mmol) was subjected to Baeyer–Villiger oxidation under the conditions described in the general procedure. The resulting NCA **38** (^{1}H-NMR ($CDCl_3$) δ 7.24–6.91 (m, 5H, arom), 6.88 (d, 2H, *J* = 9 Hz, arom), 6.56 (d, 2H, *J* = 9 Hz, arom), 5.27 (d, 1H, *J* = 3.3 Hz, CH), 4.90 (d, 1H, *J* = 3.3 Hz, CH), 3.71 (s, 3H, OCH_3), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), −0.19 (s, 3H, $SiCH_3$)) was refluxed in methanol for 90 min to give the title compound **39**, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2 as eluent) to afford the title compound as a colorless oil: yield 1.66 g (80%); $[\alpha]^{25}_D$ = −53.2° (*c* = 0.84, CH_2Cl_2); IR (KBr) ν 3385 (NH), 1724 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.39–7.22 (m, 5H, arom), 6.67 (d, 2H, *J* = 8.7 Hz, arom), 6.42 (d, 2H, *J* = 8.7 Hz, arom), 5.20 (d, 1H, *J* = 3 Hz, CH), 4.04 (d, 1H, *J* = 3 Hz, CH), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.89 (s, 1H, NH), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $SiCH_3$), −0.15 (s, 3H, $SiCH_3$); ^{13}C-NMR ($CDCl_3$) δ 172.7, 152.6, 141.2, 128.0, 127.7, 126.5, 115.3, 114.7, 75.5, 65.4, 55.7, 52.0, 25.7, 18.1, −4.7, −5.4.

General Procedure for the Synthesis of Amino Alcohols. To a stirred 0–5 °C solution of the corresponding α-amino ester (2 mmol) in dry THF (10 mL) was added a suspension $LiBH_4$ (4 mmol). The reaction mixture was stirred at room temperature for 20 h, poured into 0.1 N HCl (20 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (saturated solution, 20 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding amino alcohol which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2 as eluant).

(2*R*,3*R*)-3-[(tert-Butyldimethylsilyl)oxy]-2-[(4-methoxyphenyl)amino]-3-phenylpropan-1-ol (40). The general procedure was followed, starting from (2*S*,3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-[(4-methoxyphenyl)amino]-3-phenylpropanoate (**39**) (0.83 g, 2 mmol), the title compound was obtained as a colorless oil: yield 0.59 g (76%); $[\alpha]^{25}_D$ = −5.6° (*c* = 1.24, CH_2Cl_2); IR (KBr) ν 3374 (NH, OH), 1511 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90 °C) δ 7.36–7.18 (m, 5H, arom), 6.64 (d, 2H, *J* = 9 Hz, arom), 6.51 (d, 2H, *J* = 9 Hz, arom), 4.99 (d, 1H, *J* = 3.6 Hz, CH), 3.87 (sb, 2H, NH and OH), 3.62 (s, 3H, OCH_3), 3.47 (dd, 1H, *J* = 6 Hz, *J* = 9.6 Hz, HCH), 3.37 (ddd, 1H, *J* = 3.6 Hz, *J* = 5.1 Hz, *J* = 6 Hz, CH), 3.31 (dd, 1H, *J* = 5.1 Hz, *J* = 9.6 Hz, CH), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), −0.13 (s, 3H, $SiCH_3$); ^{13}C-NMR (DMSO-d_6, 90 °C) δ 151.0, 142.7, 142.2, 127.3, 126.6, 114.6, 113.8, 73.3, 62.1, 60.4, 55.4, 25.5, 17.6, −5.1, −5.3.

General Procedure for the Coupling of NCAs with α-Amino Esters. The corresponding crude NCA (2 mmol) was dissolved in dry methylene chloride (6 mL), and a solution of the corresponding α-amino ester (2.2 mmol) in dry methylene chloride (8 mL) was added dropwise at 0–5 °C. The resulting solution was stirred at room temperature for 24 h, washed with 0.1 N HCl (2 × 20 mL) and aqueous $NaHCO_3$ (20 mL, saturated solution), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding dipeptide.

Coupling of the NCA 11b with 16c To Give 50. The yield was 70% after flash column chromatography (eluant: hexane/EtOAc, 1:1): mp 60–2 °C (EtOAc/hexane); $[\alpha]^{25}_D$ = −30.2° (*c* = 0.65, CH_2Cl_2); IR (KBr) ν 3465 (NH), 1740, 1710, 1705, 1680 (C=O), 1490 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 100 °C) δ 8.15–8.11 (s_b, 1H, NH), 7.37–7.12 (m, 10H, arom), 6.72–6.53 (s_b, 1H, N*H*Boc), 6.32–6.18 (s_b, 1H, N*H*Boc), 4.76 (m, 1H, C*H*COOMe), 3.93–3.64 (m, 4H, C*H*NHBoc, C*H*NHBoc, NCH_2Ph), 3.72 (s, 3H, OCH_3), 3.17 (m, 1H, C*H*NHCH$_2$Ph), 2.84 (m, 1H, HC*H*Ph), 2.69 (m, 1H, HC*H*Ph), 1.72 (m, 1H, C*H*$(CH_3)_2$), 1.39 (s, 9H, $C(CH_3)_3$), 1.03 (d, 3H, *J* = 5.6 Hz, $CH(CH_3)_2$), 0.94 (d, 3H, *J* = 5.6 Hz, $CH(CH_3)_2$); ^{13}C-NMR ($CDCl_3$) δ 173.0, 172.1, 156.3, 156.0, 139.1, 138.0, 129.8, 129.1, 128.0, 127.1, 80.2, 65.1, 59.2, 53.9, 53.1, 38.5, 30.1, 28.8, 20.5, 19.8. Anal. Calcd for $C_{34}H_{50}N_4O_7$: C, 65.15; H, 8.04; N, 8.34. Found: C, 65.31; H, 8.14; N, 8.47.

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Supplementary Material Available: Listing of experimental details and spectral data for compounds **3b,c, 5a–d, 6a–d, 7c,d, 8a–d, 9c,d, 13b,d, 14a–d, 15c,d, 16a,c,d, 17a–d, 18a–c, 19a–c, 20a–c, 23a–c, 24a–c, 27a–c, 29a–c, 30a–c, 31a–c, 33a,c–f, 36, 41, 45, 46, 47, 48, 49,** and **51** (31 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.