Novel Enantioselective Approach to γ-Lactams from Chiral Enol Ethers: Synthesis of (−)-Statine

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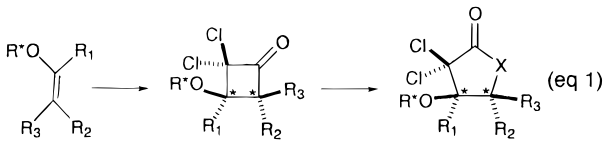
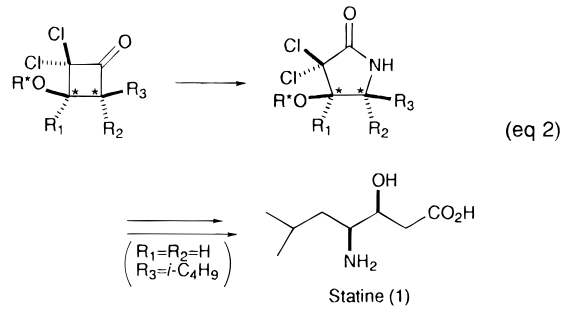
In previous publications we have shown that chiral *O*-alkyl enol ethers undergo clean, diastereofacially selective 2 + 2 cycloaddition with dichloroketene to provide α,α-dichlorocyclobutanones.[1] These 4-membered carbocycles, in transformations driven by inherent ring stain and favorable electronic effects, can then be converted rapidly and efficiently with diazomethane and *m*-chloroperbenzoic acid to α,α-dichlorocyclopentanones and α,α-dichloro-γ-butyrolactones, respectively (eq 1, X = CH_2,O).[2] These in turn have proven to be valuable substrates for the preparation of several natural products in native form.[1b−e]



(eq 1)

It was felt that these same α,α-dichlorocyclobutanones might also allow access to γ-lactams (X = NH) and hence offer a novel entry to not only enantiopure γ-amino acid, but also pyrrolidine, pyrrolizidine, and indolizidine natural products.[3,4] The first example of the use of dichloroketene−chiral olefin diastereofacial differentiation for the enantioselective construction of a γ-lactam and its conversion to the novel amino acid statine are now reported (eq 2).

With the ultimate goal of a broad approach in mind, 1-(2,4,6-triisopropylphenyl)ethanol (**2**), a chiral benzylic alcohol auxiliary recently developed and used effectively in our laboratory for the synthesis of several natural β-hydroxy-γ-butyrolactones,[1e] was selected as the control



(eq 2)

element. This choice was based on the expectation that reduction of the intermediate α,α-dichloropyrrolidinones would occur *without* concomitant auxiliary elimination, in parallel with the behavior of most of the α,α-dichloro-γ-butyrolactones that have been studied to date.[1e] This would then give access, through benzylic cleavage, not only to β-hydroxy-γ-lactams, but potentially to a variety of others as well.[3]

Conversion of (*R*)-1-(2,4,6-triisopropylphenyl)ethanol (**2**)[5] to ynol ether **3a** using our published procedure[6] was initially compromised by the reluctance of the acetylide to undergo alkylation with isobutyl iodide at low temperature, which was essential to prevent decomposition of this sensitive intermediate. Fortunately, however, the corresponding triflate[7] was sufficiently reactive at low temperature and produced the crystalline ynol ether **3a** in 61% yield after dry silica gel chromatography[8] (Scheme 1). Semihydrogenation of the triple bond in ynol ether **3a** in pyridine with palladium on barium sulfate[6b] then smoothly afforded the chiral *Z*-enol ether **3b** in 93% yield. It is noteworthy that in this conversion the formation of over-reduced and/or hydrogenolyzed material was not encountered.

The reaction of dichloroketene[9] with **3b** was found to proceed best at 0 °C and resulted in clean, diastereoselective cycloaddition to afford the dichlorocyclobutanone

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(1) (a) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525−5528. (b) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752−4753. (c) B. M. de Azevedo, M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567−4569. (d) Murta, M. M.; B. M. de Azevedo, M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7537−7541. (e) B. M. de Azevedo; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940−4942.

(2) Significantly, it has been found that the cycloadducts (or a subsequent intermediate prior to removal of the chiral auxiliary) as a rule can be efficiently upgraded to diastereomeric purity by simple recrystallization.

(3) For recent syntheses of chiral pyrrolidinones, see: (a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36−42. (b) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248−6249. (c) Wei, Z.-Y.; Knaus, E. E. *Tetrahedron Lett.* **1993**, *34*, 4439−4442. (d) Wee, A. G. H.; Liu, B. *Tetrahedron Lett.* **1996**, *37*, 145−148 and references cited therein.

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(5) 1-(2,4,6-Triisopropylphenyl)ethanol was conveniently and efficiently resolved (ca. 39% *R*, 40% *S*, 100-g scale) in analogy with a published procedure (Reyes, A.; Juraristi, E. *Synth. Commun.* **1995**, *25*, 1053−1058). *R*: $[\alpha]^{22}_D$ +46.2 (*c* 1, chloroform); mp 84−85 °C. (The values cited in ref 1e are in error.)

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(7) Salomon, M. F.; Salomon, R. G.; Gleim, R. D. *J. Org. Chem.* **1976**, *41*, 3983−3987.

(8) Yields are for purified, chromatographically homogeneous substances. Physical data for key compounds. Ynol ether **3a**: mp 34−36 °C; $[\alpha]^{20}_D$ +163 (*c* 1.0, chloroform); IR 2266, 1608, 1579, 1231 cm^{-1}; ^1H NMR (200 MHz) δ 0.72 (d, *J* = 6.5 Hz, 3 H), 0.73 (d, *J* = 6.9 Hz, 3 H), 1.16−1.30 (m, 18 H), 1.44−1.63 (m, 1 H), 1.68 (d, *J* = 6.9 Hz, 3 H), 1.88 (d, *J* = 5.8 Hz, 2 H), 2.84 (hept, *J* = 6.9 Hz, 1 H), 3.20−3.47 (m, 2 H), 5.61 (q, *J* = 6.9 Hz, 1 H), 6.99 (s, 2 H); mass spectrum (CI) *m/z* 329 (M^+ + 1), 231 (100). Anal. Calcd for $C_{23}H_{36}O$: C, 84.09; H, 11.04. Found: C, 83.94; H, 11.05. Enol ether **3b**: $[\alpha]^{21}_D$ −10 (*c* 1.0, chloroform); IR 3032, 1662, 1609, 1573, 1085 cm^{-1}; ^1H NMR (200 MHz) δ 0.888 (d, *J* = 6.5 Hz, 3 H), 0.892 (d, *J* = 6.8 Hz, 3 H), 1.20−1.27 (m, 18 H), 1.58 (d, *J* = 6.5 Hz, 3 H), 1.48−1.71 (m, 1 H), 1.99 (m, 2 H), 2.85 (hept, *J* = 6.9 Hz, 1 H), 2.72−2.96 (m, 2 H), 4.28 (q, *J* = 7.0 Hz, 1 H), 5.30 (dt, *J* = 6.7, 6.7 Hz, 1 H), 5.97 (dt, *J* = 6.5, 1.5 Hz, 1 H), 7.00 (s, 2 H); HRMS *m/e* calcd for $C_{23}H_{38}O$ (M^+) 330.2923, found 330.2937. Lactam **5b**: mp 144−146 °C; $[\alpha]^{20}_D$ +82 (*c* 1.0, chloroform); IR 3208, 3090, 1709, 1608, 1579, 1113, 1074 cm^{-1}; ^1H NMR (200 MHz) δ 0.82 (d, *J* = 6.2 Hz, 3 H), 0.93 (d, *J* = 6.2 Hz, 3 H),1.15−1.28 (m, 18 H), 1.38−1.54 (m, 3 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 2.46 (d, *J* = 6.5 Hz, 1 H), 2.47 (d, *J* = 6.8 Hz, 1 H), 2.83 (hept, *J* = 6.9 Hz,1 H), 3.13 (hept, *J* = 6.5 Hz,1 H), 3.58−3.63 (m, 1 H), 3.85 (hept, *J* = 6.5 Hz,1 H), 4.10 (q, *J* = 7.0 Hz, 1 H), 5.03 (q, *J* = 6.7 Hz, 1 H), 6.05 (s, 1 H), 6.93 (s, 1 H), 7.02 (s, 1 H); mass spectrum (EI) *m/z* 387 (M^+), 372, 215, 140, 43 (100). Anal. Calcd for $C_{25}H_{41}NO_2$: C, 77.47; H, 10.66; N, 3.61. Found: C, 77.80; H, 10.67; N, 3.48.

(9) For a recent review on ketene cycloaddition chemistry, see: Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159−646.

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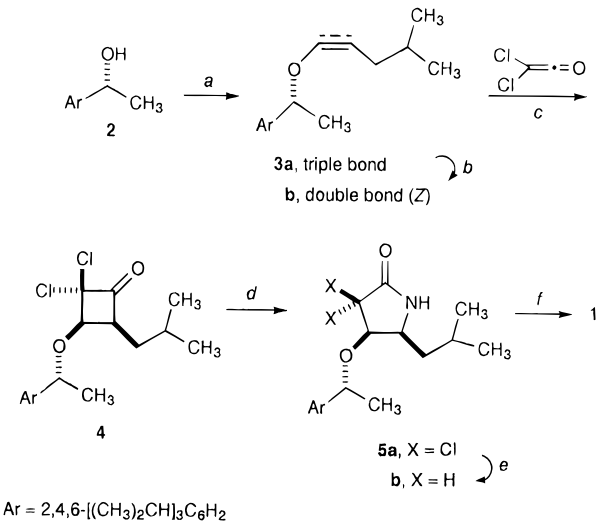
Scheme 1[a]



[a] Key: (a) (1) KH, THF, 20 °C; $Cl_2C{=}CHCl$, −50 → 15 °C, 81%; (2) C_4H_9Li, THF, −85 → −40 °C; isobutyl triflate, THF, −28 °C, 75%; (b) 10% Pd/$BaSO_4$, H_2, C_5H_5N, 93%; (c) Cl_3CCOCl, Zn−Cu, $(C_2H_5)_2O$, 0 °C; (d) $NH_2OSO_2C_6H_2(CH_3)_3$, CH_2Cl_2, 20 °C; Al_2O_3; (e) Zn−Cu, CH_3OH-NH_4Cl, 20 °C, 40% (three steps); (f) CF_3CO_2H, 20 °C; concd HCl, 80 °C; Dowex H^+, 60%.

4. Proton NMR of the crude reaction product indicated that a most pleasing 94:6 ratio of diastereomeric cycloadducts had been reached in this reaction. Molecular mechanics calculations clearly showed that cycloaddition should in fact take place selectively on the C_α-*si* face to generate **4** as the major product. The correctness of this prediction was eventually borne out.

In that all attempts to purify **4** led to unacceptable loss of material, the diastereomeric upgrading was temporarily postponed and the key conversion to the γ-lactam was examined. Remarkably, Beckmann ring expansion of cyclobutanone **4** with Tamura's reagent (*O*-(mesitylenesulfonyl)hydroxylamine)[10] proceeded without apparent side reactions, in spite of the dense substitution and sensitive nature of the molecule, to give regioselectively crude α,α-dichloro-γ-lactam **5a** as an oil. On brief exposure at ambient temperature to excess zinc−copper couple in methanol saturated with ammonium chloride,[11] this material, as had been predicted, suffered reduction without concomitant elimination of the inductor to provide γ-lactam **5b**.[12] On simple recrystallization from methanol−water, this substance efficiently yielded highly crystalline, diastereomerically pure lactam **5b** (40% from **3b**, 74%/step).

As an initial application of this approach, lactam **5b** was converted to the hydroxy amino acid statine, a key component of several acid protease inhibitors and thus of considerable medicinal interest.[13] Many of the reported syntheses of this unusual amino acid, however, fail to yield stereochemically pure material. After some experimentation, it was found that one-pot inductor cleavage−ring opening could be effected by simply stirring lactam **5b** with trifluoroacetic acid[1e] at 20 °C for a short period followed by addition of concentrated hydrochloric acid and heating.[3b] Ion-exchange column chromatography of the resulting salt then afforded (3*S*,4*S*)-statine, identified through comparison with the naturally derived material.

In summary, it has been demonstrated that cycloaddition of chiral enol ethers with dichloroketene coupled with the Beckmann ring expansion can provide an effective, stereocontrolled approach to chiral pyrrolidinones. While in the present instance this method has been used to prepare a natural β-hydroxy-γ-amino acid, we expect it will also find application in pyrrolidine, pyrrolizidine, and indolizidine natural product synthesis. This possibility is currently under study.

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Supporting Information Available: Experimental procedures and characterization data (6 pages).

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(11) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114−117.

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