Titanium(III)-Mediated Synthesis of a 1,2,3-Tricarbonyl Moiety from an α-Oximido-β-keto Ester: Application to the Synthesis of the Carbacephem Nucleus

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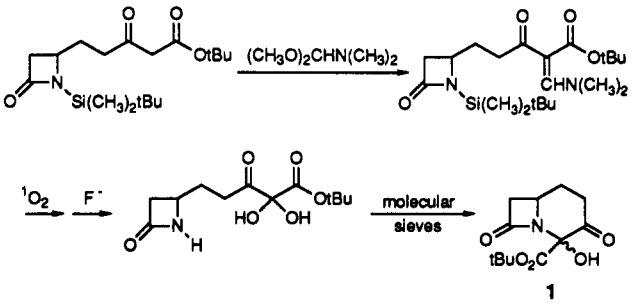
A general procedure for the conversion of α-oximido-β-keto esters into vicinal tricarbonyl moieties by $TiCl_3$ in aqueous, buffered (pH 5) conditions with acetone cosolvent was demonstrated. As applied to *N*-hydroxy β-lactam **17**, which contained an α-oximido-β-keto ester side chain, these combined reductive and hydrolytic conditions effected *simultaneous* tricarbonyl formation and β-lactam N–O bond reduction. Vicinal tricarbonyl-containing N-unsubstituted β-lactam **18** was a direct precursor to semifunctionalized carbacephem **1**.

The demonstrated synthetic utility of the 1,2,3-tricarbonyl functionality by Wasserman is mainly responsible for the current interest in this important moiety. Several classes of biologically active alkaloids have been synthesized by routes employing it as part of key intermediates.[1] Furthermore, the functionality has been found in nature—the immunomodulating agent FK-506[2] and related antibiotics[3] contain a latent vicinal tricarbonyl group.

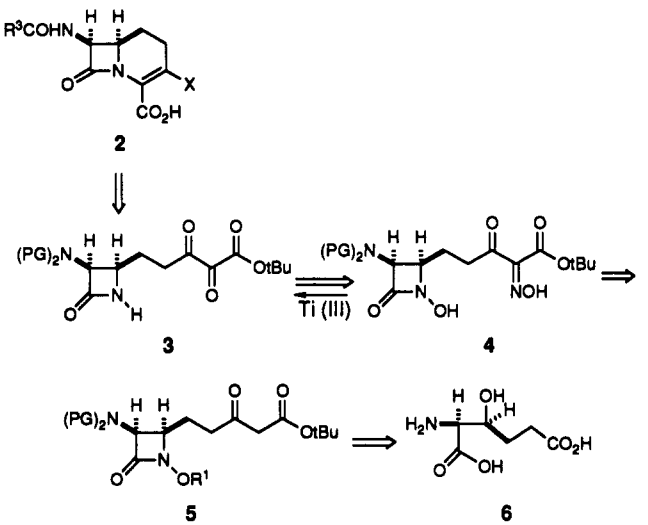
Several syntheses of the vicinal tricarbonyl moiety have been published,[4] many of which use a β-keto ester as the starting material.[5–9] These methods include conversion of the β-keto ester into an α-enamino- or α-(phenyliodoniumyl)-β-keto ester followed by oxidative cleavage by singlet oxygen[5] or ozonolysis,[6] respectively. Formation of an α-imino-β-keto ester with subsequent hydrolysis[1e,j,7] or synthesis of a β-keto-α-nosyl ester followed by reaction with base led to the vicinal tricarbonyl moiety.[8]

Our interest in this versatile functional group originated from Wasserman's synthesis of semifunctionalized carbacephem skeleton **1** (Scheme I).[9] One of the goals of our laboratory has been the development of stereoselective routes to carbacephem β-lactam antibiotics **2**[10] (Scheme II). Present syntheses are nonstereoselective[11] or multistep.[10a,b] One route envisaged began with L-*erythro*-β-hydroxy-α-aminoadipic acid **6** (Scheme II). Thus, an appropriate means of converting the accessible intermediate

Scheme I



Scheme II



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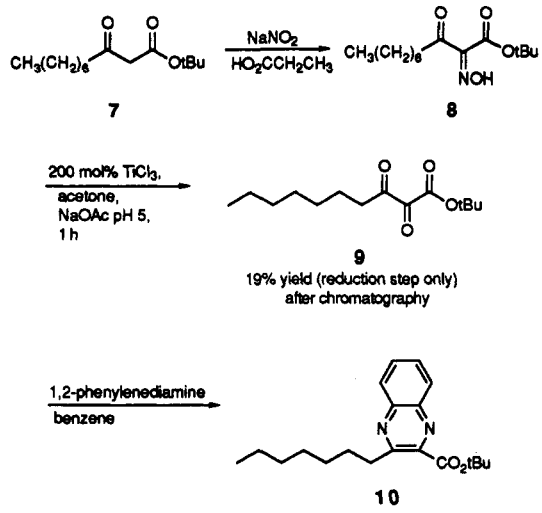
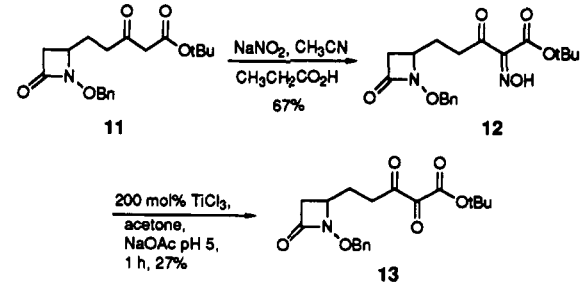
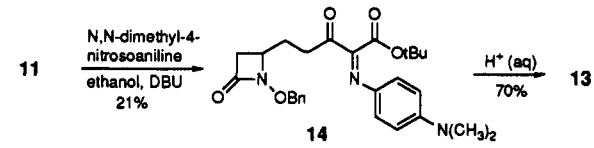
Scheme III



Scheme IV



Scheme V



5 into tricarbonyl-containing β-lactam 3 was sought. Although more than one of the procedures above could effect this transformation, a potentially more efficient route involved α-oximido-β-keto ester 4. By the action of titanium(III), *simultaneous* reduction of both the azetidinone and oxime N–O bonds was postulated.

Facile reduction of *N*-hydroxy β-lactams by $TiCl_3$ had been demonstrated in our laboratory over a decade ago.[12] We also found that α-oximido-β-keto esters were reduced to the unstable α-amino-β-keto esters—not the vicinal tricarbonyl compound—in the presence of $TiCl_3$ buffered at pH ≥ 7.[13] In contrast, Timms and Wildsmith[14] reported the deoximination of simple aromatic or alkyl oximes by $TiCl_3$ under acidic conditions to yield the parent aldehyde or ketone. The reduction could be accomplished in aqueous dioxane, acetic acid, DMF, or acetone after 1 h in up to 96% yield. The method was also applicable to the synthesis of β-diketones (although the reaction was not as clean), but no attempt to produce a vicinal tricarbonyl moiety was mentioned. We decided to use the conditions of Timms and Wildsmith as a starting point to develop a means for the single-step, $TiCl_3$-mediated transformation of 4 into 3 (Scheme II). This publication reports not only our progress toward this goal based on simpler models of 4 but also a *novel* synthesis of the vicinal tricarbonyl system.

Results and Discussion

In order to develop appropriate reduction conditions for vicinal tricarbonyl formation, it became apparent that a simpler model without any other potentially interfering functionality was required. Thus, α-oximido-β-keto ester 8 (Scheme III) was synthesized from the corresponding β-keto ester 7 without complication. It was successfully converted into tricarbonyl 9 with 200 mol % $TiCl_3$ (as a 1.1 M solution in 20% aqueous HCl) in a biphasic mixture of acetone and sodium acetate buffer at pH 5. In order to prevent any sudden drop in pH during addition of the acidic Ti(III) reagent, it was added slowly to the reaction vessel via syringe with the needle below the surface of the substrate solution during vigorous stirring so that the thin stream of reagent could be quickly buffered. After 1 h of reaction, an extractive workup procedure yielded a mixture of compounds that included starting material and the desired product in monohydrated form. Tricarbonyl 9 could be purified to near homogeneity by column chromatography in an overall 19% yield from 8 (35% yield based on recovered 8).

Variations of mode of addition of $TiCl_3$, solvent (DMF, THF), or pH (4.0 or 6.0) led to more complex product mixtures. In this model system, the inherent instability of the vicinal tricarbonyl moiety of 9 may have led to some loss during chromatographic purification. However, for our desired application discussed in Scheme VII below, the tricarbonyl would be trapped by an intramolecular reaction such that chromatography would be avoided. With model tricarbonyl 9, further characterization was done on the corresponding quinoxaline derivative 10, which was made in the manner of Hoffman[8] with 1,2-phenylenediamine in 73% yield.

Although the reaction with our first model system was not fully optimized, we attempted the combined reduction and hydrolysis with a slightly more complicated α-oximido-β-keto ester. This model, 12 (readily available from β-keto ester 11,[15] Scheme IV), contained a β-lactam in which the benzyl-protected N–O azetidinone bond was not expected to be susceptible to Ti(III) reduction. As predicted, exposure of 12 to the reducing conditions developed with the first model (8) did produce tricarbonyl 13, in 27% yield after chromatographic purification. As with tricarbonyl 9, the yield of compound 13 could have been adversely affected by side product formation and the purification process. The fact that the yield was actually *higher* than that for the simpler model 8 suggested that facile and chemoselective reduction and hydrolysis of the α-oximido-β-keto ester was not encumbered by the surrounding functionalization.

The identity of 13 was confirmed by comparison of NMR spectra with that from authentic compound obtained from β-keto ester 11 by the α-imino-β-keto ester hydrolysis route mentioned earlier (Scheme V).[1e,j,7] In our hands, this route liberated tricarbonyl 13 in 15% overall yield, which was comparable to the 18% yield from 11 obtained by the Ti(III)-mediated reduction pathway developed here (Scheme IV). Unlike the imine hydrolysis step which employed dilute aqueous HCl, the Ti(III) method developed here utilized carefully controlled, weakly acidic (pH 5) buffered conditions.

As a last preliminary study before attempting the synthesis of the carbacephem skeleton, we confirmed that our

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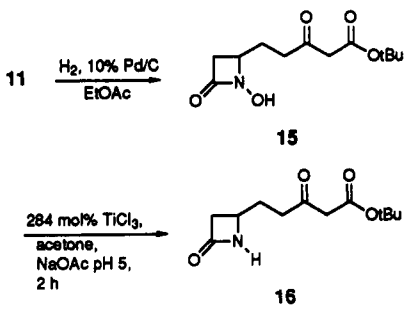
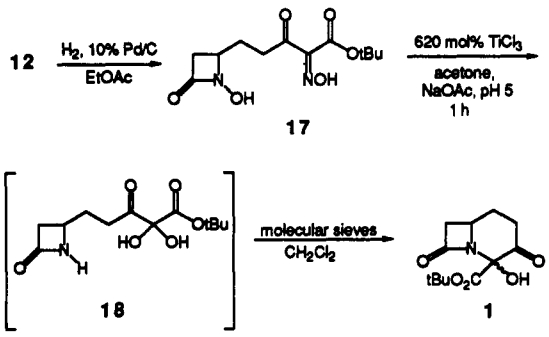
Scheme VI

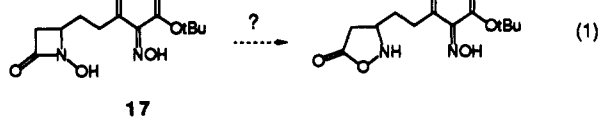


Scheme VII



reducing conditions would also cleave the azetidinone N–O bond. Our present conditions were slightly varied from those originally employed for reduction of *N*-hydroxy-β-lactams[12] in that acetone was employed as cosolvent instead of THF or CH_3OH. β-Lactam **16** (Scheme VI) was produced from **15** in 58% yield.

On the basis of the positive results on these simplified substrates, compound **17** was subjected to similar reducing conditions (Scheme VII). This model substrate was the first one in which *both* azetidinone N–O bond cleavage and α-oximido-β-keto ester reduction were expected in one reaction step. An additional factor had to be considered with **17**—the consequences of acidic pH on the *N*-hydroxyazetidinone with regard to rearrangement to the corresponding 1,2-oxazolidin-5-one[16] were unknown (eq 1).



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Thus, similar reduction conditions as developed on the other model substrates were used with one minor variation. The pH 5 buffer was added to the acetone solution of freshly prepared **17** via cannula; during the addition of the last three quarters of the total buffer, the $TiCl_3$ (620 mol %) was added as described above. Thus, the buffer was in contact with the substrate only momentarily before the Ti(III) reagent was added. In this manner, the reaction pH did not plunge precipitously below pH 5, and the N–O bond cleavage was expected to be faster than acid-catalyzed rearrangement.

Since the expected product **18** was not thought to be stable,[9] the crude reaction product was subjected to Wasserman's cyclization conditions immediately after aqueous workup without any purification. (In fact, tricarbonyl **18** partially cyclized upon standing at room temperature over 48 h as determined by TLC.) After stirring for 48 h with molecular sieves and after chromatography, bicyclic β-lactam **1** was obtained in 31% yield from **17** as a mixture of diastereomers. Further purification by recrystallization gave crystalline product in 20% yield. Only one of the two possible diastereomers was expected to be crystalline;[17] less than 1% yield of the other diastereomer, an oil, was obtained. X-ray analysis of the crystalline diastereomer confirmed that the relative stereochemistry of the C_4 hydroxy and the C_6 hydrogen was cis.

The investigations recorded here present a new and generally useful method for the synthesis of vicinal tricarbonyl compounds by Ti(III)-mediated conversion of the α-oximido-β-keto precursors, which are readily available from the corresponding β-keto ester. The procedure is mild and can be accomplished under slightly acidic, buffered conditions. Not only was evidence obtained to suggest that the method is tolerant to surrounding functionalization, but *N*-hydroxy β-lactams can be reduced under these conditions as well. Thus, this method showed particular potential in the application shown in Scheme VII. Under the buffered Ti(III) conditions, compound **17** underwent multiple transformations—oxime reduction, imine hydrolysis, and *N*-hydroxy β-lactam N–O bond cleavage. These studies on model substrate **17** have layed the foundation for carbacephem synthesis by Ti(III) reduction.

Experimental Section

General Comments. The general methods, instruments and conditions used have been described previously.[18]

Solvents and reagents were purified by standard methods[19] before use as necessary. The $TiCl_3$ was obtained from Fluka in 20% HCl(aq). This solution was determined to be 1.1 M in Ti(III) by titration with $Ce(SO_4)_2$.[20] Removal of solvent was accomplished under reduced pressure. Procedures requiring moisture-free conditions were accomplished with anhydrous, purified reagents in oven- and/or flame-dried glassware and syringes under argon atmosphere. Those methods involving oxygen-sensitive reagents ($TiCl_3$ reductions) were done under argon atmosphere as well. The term "workup" indicates the reaction mixture was taken up into organic solvent, usually ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated.

***tert*-Butyl 3-Oxodecanoate (7).** The magnesium salt of mono-*tert*-butyl malonate was made by dissolving this monoester (2.451 g, 15.30 mmol, 110 mol %) in 30 mL of anhydrous THF, cooling to −78 °C in a dry ice/acetone bath, and adding dibutylmagnesium (0.5 M in heptane, 15.3 mL, 7.64 mmol, 55 mol %) dropwise. The reaction was stirred for 15 min at −78 °C, then in an ice bath for 15 min, and subsequently at room temperature for 1 h. The solvent was removed, and the acylimidazole of octanoic acid was added via cannula. The acylimidazole was made by addition 1,1′-carbonyl diimidazole (2.473 g, 15.30 mmol, 110 mol %) to an ice bath-cooled solution of octanoic acid (2.20 mL, 13.9 mmol, 100 mol %) in 30 mL of anhydrous THF and stirring for 1 h. The Masamune–Brooks reaction[21] was stirred for 19 h at room temperature, after which time the solvent was removed and the residue redissolved in a practical amount of ether. Workup, including washes with H_2O, 10% citric acid, brine, saturated $NaHCO_3$, and brine again, gave 2.904 g of a cloudy oil, **7** (86% yield). The product was estimated to be 90% pure by ^1H NMR and was used in the next reaction in crude form: R_f = 0.5 (80:20 hexanes/ethyl acetate); ^1H NMR δ 3.34 (s, 2 H, H-2), 2.52 (t, J = 7.4 Hz, 2 H, H-4), 1.6 (m, 2 H, alkyl CH_2), 1.47 (s, 9 H, *tert*-butyl H; also a small s at δ 1.49 which could be due to

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the enol form), 1.27 (m, 10 of the expected 8 H, alkyl H), 0.88 (t with virtual coupling, J = 6.9 Hz, 3 H, H-10 CH_3); ^{13}C NMR δ 202.62, 166.32, 81.61, 50.60, 42.80, 31.57, 29.03, 28.89, 27.97, 23.58, 22.44, 13.74; IR (neat) 3000–2850, 1745, 1720 cm^{-1}; HRMS (EIMS) calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1884.

***tert*-Butyl 2-Oximido-3-oxodecanoate (8).** *tert*-Butyl 3-oxodecanoate (7, 400 mg, 1.65 mmol) was dissolved in 470 mg of propionic acid (6.3 mmol, 384 mol %) and 1 mL of CH_3CN and was cooled in a bath at −20 to −25 °C. $NaNO_2$ (171 mg, 2.48 mmol, 150 mol %) as a solution in 300 μL of H_2O was added over 15 min, and the reaction was allowed to warm to room temperature and stirred overnight. After this time, the reaction had turned from colorless and heterogeneous to yellow and homogeneous. After diluting at least 10-fold with ethyl acetate, workup gave 358 mg of a yellow oil (80% crude yield). After column chromatography (80:20 hexanes/ethyl acetate), 276 mg of α-oximido-β-keto ester 8 as a yellow oil was obtained (62% yield after chromatography): R_f = 0.38 (80:20 hexanes/ethyl acetate); ^1H NMR δ 10.0 (bs, heteroatom H), 2.76 (t, J = 7.36 Hz, 2 H, H-4), 1.57 and 1.56 (m, s, total 11 H, alkyl CH_2, *tert*-butyl H), 1.28 (m, 8 H, alkyl CH_2), 0.87 (t with virtual coupling, J = 6.9 Hz, 3 H, H-10 CH_3); ^{13}C NMR δ 196.89, 161.44, 150.94, 84.85, 37.6, 31.6, 29.02, 28.96, 27.98, 23.61, 22.51, 13.96; IR (neat) 3500–3100, 3050–2800, 1750–1690 cm^{-1};[22] HRMS (EIMS) calcd for M − 56 fragment $C_{10}H_{17}NO_4$ 215.1158, found 215.1155; CIMS gave M + 1 at 272 and M + 1 − 56 at 216.

***tert*-Butyl 2,3-Dioxodecanoate (9).** All solutions were deoxygenated, and all manipulations were done under argon. The substrate *tert*-butyl 2-oximido-3-oxodecanoate (8, 800 mg, 2.95 mmol) was dissolved in 11 mL of distilled acetone, and 14.4 mL of sodium acetate buffer (4.1 M, 59 mmol of NaOAc, 2000 mol %, pH 5.0–5.2) was added to make a biphasic mixture. An aqueous solution of $TiCl_3$ (5.36 mL, 5.90 mmol, 200 mol %) was then added slowly via syringe with the needle under the surface of the solution during vigorous stirring. The reaction was followed by TLC and was quenched after 1 h of stirring by pouring into a 1:1 mixture of ethyl acetate/tartrate buffer (sodium L-tartrate, 0.78 M, pH 5.0). Enough buffer was added to dissolve any titanium(IV) oxides. The aqueous phase was extracted with fresh solvent and worked up. The residue was chromatographed on a silica gel column first with a 90:10 mixture of hexanes/ethyl acetate as eluent and then with an 80:20 mixture of hexanes/ethyl acetate. About 280 mg (35%) of starting material was recovered. An impure sample (320 mg) containing the expected product was recovered and was washed as a solution in ethyl acetate with saturated $NaHCO_3$ and brine. After drying over $MgSO_4$ and filtering, the solvent was evaporated. The residue was again chromatographed by column (90:10 hexanes/ethyl acetate) to yield a 76-mg fraction of a yellow oil which was tricarbonyl product 9 and a second fraction (137 mg) which was rechromatographed to yield 74 mg of tricarbonyl product 9. Total yield of compound 9 after chromatography was 19%. NMR and mass spectroscopy were consistent with the tricarbonyl existing in its hydrated form:[4b] R_f = 0.22 (80:20 hexanes/ethyl acetate); ^1H NMR δ 5.05 (s, heteroatom H), 2.57 (t, J = 7.4 Hz, 2 H, H-4 CH_2), 1.65 (m, 2 H, alkyl CH_2), 1.49 (s, 9 H, *tert*-butyl CH_3), 1.28 (m, 10 of the expected 8 H, alkyl CH_2), 0.88 (t with virtual coupling, J = 6.9 Hz, 3 H, H-10 CH_3), (note extra singlet at δ 1.57, ~1 H, was consistent with the *tert*-butyl signal of the unhydrated form of 9; also, a barely detectable triplet at δ 2.8 is in the region expected for the unhydrated form of product 9);[4b] ^{13}C NMR δ 203.67, 168.23, 92.46, 84.87, 35.66, 31.57, 28.98, 28.94, 27.88, 27.63, 23.31, 22.53, 13.98 (note one unexpected additional ^{13}C resonance perhaps due to some unhydrated form of the product); IR (neat) 3600–3200, 3000–2750, 1730 cm^{-1}; CIMS on crude product gave M + 1 at 275 (monohydrate form of 9), 257 (*unhydrated* tricarbonyl product), M + 1 − 56 at 201.

Derivatization of *tert*-Butyl 2,3-Dioxodecanoate (9) with 1,2-Phenylenediamine 10.[8] *tert*-Butyl 2,3-dioxodecanoate (9, 74.0 mg, 0.270 mmol) was dissolved in 2 mL of anhydrous benzene and 1,2-phenylenediamine (58.4 mg, 0.549 mmol, 200 mol %; recrystallized in H_2O (50 g/175 mL) in the presence of 1.5 g of sodium hydrosulfite and Norite alkaline charcoal; expected mp = 99–101 °C,[23] observed mp = 98–99 °C) was added as a solid, at which time the solution turned from yellow to colorless. A catalytic amount of *p*-toluenesulfonic acid (13.4 mg, 0.070 mmol, 26 mol %) was added. A white precipitate was soon visible. The light yellow reaction mixture was stirred for 1.5 h under argon at room temperature. Quenching was accomplished by diluting about 10-fold with 1:1 ethyl acetate/saturated $NaHCO_3$. Workup, including washes with saturated $NaHCO_3$, brine, 5% acetic acid, and brine again, gave 72 mg of a brown oil. This material was chromatographed by column chromatography (90:10 hexanes/ethyl acetate) to yield 65 mg of a clear colorless oil, 10 (73% yield): R_f = 0.42 (80:20 hexanes/ethyl acetate); ^1H NMR δ 8.16–8.03 (m, 2 H, aromatic H), 7.75 (m, 2 H, aromatic H), 3.16 (m, 2 H, alkyl CH_2 bonded to quinuclidine ring), 1.85 (m, 2 H, alkyl CH_2), 1.70 (s, 9 H, *tert*-butyl H), 1.5–1.2 (m, 9 of the expected 8 H, alkyl CH_2), 0.9 (t with virtual coupling, J = 6.9 Hz, 3 H, alkyl side chain CH_3); ^{13}C NMR 165.50, 155.10, 146.83, 142.23, 139.81, 130.89, 129.54, 129.45, 128.52, 83.72, 36.08, 31.69, 29.68, 29.46, 29.10, 28.09, 22.56, 14.00; IR (neat) 3050–2850, 1735, 1550 cm^{-1}; HRMS (EIMS) calcd for $C_{20}H_{22}N_2O_2$ 328.21508, found 328.2143.

***tert*-Butyl 5-(1-(Benzyloxy)-2-oxo-4-azetidinyl)-2-oximido-3-oxopentanoate (12).** A solution of *tert*-butyl 5-(1-(benzyloxy)-2-oxo-4-azetidinyl)-3-oxopentanoate (11,[15,24] 1.10 g, 3.166 mmol) in CH_3CN (2.4 mL) and propionic acid (1.29 g, 17.4 mmol, 550 mol %) was cooled in a dry ice/acetone bath at −20 °C (external temperature). While the solution was stirred at this temperature, a solution of $NaNO_2$ (328 mg, 4.75 mmol, 150 mol %) in 570 μL of H_2O was added in small portions over 5 min. Additional propionic acid and H_2O were added if the reaction became too viscous for adequate stirring. The reaction was allowed to warm to room temperature and was stirred for 3 h. Workup including diluting the reaction 10-fold with 1:1 ether/H_2O gave a residue which was recrystallized from ethyl acetate/hexanes to give white crystalline product 12 (805 mg) 68% yield: R_f = 0.23 (1:1 hexanes/ethyl acetate); mp = 122–124 °C; ^1H NMR δ 10.83 (bs, heteroatom H), 7.36 (m, 5 H, aromatic H), 4.93 and 4.89 (AB quartets, J = 11.4 Hz, total 2 H, benzyl H), 3.60 (m, 1 H, H-4 azetidinyl), 2.74 and 2.67 (m and dd, J = 4.8, 13.8 Hz, total 3 H, H-4 pentanoate and H-3 cis to H-4 on azetidinyl ring, respectively), 2.24 (dd, J = 1.8, 13.8 Hz, 1 H, H-3 trans to H-4 on azetidinyl ring), 2.0–1.7 (m, 2 H, H-5 pentanoate), 1.56 (s, 9 H, *tert*-butyl H); ^{13}C NMR δ 194.43, 164.57, 160.68, 150.84, 134.68, 129.42, 129.18, 128.73, 84.58, 78.30, 57.12, 37.34, 32.98, 28.13, 25.90; IR (KBr pellet) 3400–3100, 1750, 1690 cm^{-1}; HRMS (EIMS) calcd for M − 56 at $C_{15}H_{16}N_2O_6$ 320.1008, found 320.1001.

***tert*-Butyl 5-(1-(Benzyloxy)-2-oxo-4-azetidinyl)-2,3-dioxopentanoate (13) Obtained by Ti(III) Reduction.** *tert*-Butyl 5-(1-(benzyloxy)-2-oxo-4-azetidinyl)-2-oximido-3-oxopentanoate (12, 50 mg, 0.133 mmol) was dissolved in 650 μL of distilled acetone and 650 μL of sodium acetate buffer (4.1 M, pH 5.2, 2.66 mmol, 2000 mol %). After deoxygenating by bubbling with argon, $TiCl_3$ (242 μL, 0.266 mmol, 200 mol %) was added slowly via syringe with the needle under the surface of the reaction solution. The reaction was stirred under argon for 1 h, during which time the color changed from green to purple to brown. The reduction was quenched by pouring into a 1:1 mixture of ethyl acetate/tartrate buffer (sodium L-tartrate, 0.78 M, pH 5.0). Enough tartrate buffer was added to dissolve any titanium(IV) oxides. Workup gave 47 mg of a yellow oil which was chromatographed by column (elution with 1:1 hexanes/ethyl acetate). Expected tricarbonyl-containing β-lactam 13 was obtained in 27% yield (13.6 mg of a nearly colorless oil). By comparison of TLC, ^1H NMR, and ^{13}C NMR data with those obtained by hydrolysis of corresponding imine 14, the tricarbonyl obtained by Ti(III) reduction was about 80–90% pure with minor aromatic- and alkyl-containing impurities.

***tert*-Butyl 5-(1-(Benzyloxy)-2-oxo-4-azetidinyl)-2-[*N*-(*p*-(dimethylamino)phenyl)imino]-3-oxopentanoate (14).**[1e,j,7] A solution of *tert*-butyl 5-(1-(benzyloxy)-2-oxo-4-azetidinyl)-3-

(22) Iido, H.; Hayashida, K.; Yamada, M.; Takahashi, K.; Yamada, K. *Synth. Commun.* **1973**, *3*, 225. This reference reported 1720 and 1665 cm^{-1} for the ester and oxime, respectively, for the α-oxime of ethyl acetoacetate.

(23) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; pp 834–835.

(24) Gasparski, C. M. Ph.D. Dissertation, University of Notre Dame, Sept 1991.

oxopentanoate (11, 68.9 mg, 0.199 mmol) was dissolved in 3 mL of distilled absolute ethanol. While under argon, *N,N*-dimethyl-4-nitrosoaniline (32.8 mg, 0.218 mmol, 110 mol %) was added as a solid followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.0 μL, 0.02 mmol, 10 mol %). The green solution was heated to gentle reflux under argon for 40 min. The reaction was cooled to 4 °C and the solution decanted from the crystalline solid. The solid was recrystallized twice from ethanol to yield 21 mg of yellow-orange crystals: R_f = 0.41 (1:1 hexanes/ethyl acetate); mp = 133–136 °C dec; ^{1}H NMR δ 7.4–7.3 (m and overlapping d at δ 7.27, J = 9.0 Hz, 7 H, phenyl H and 2 H of the *p*-(dimethylamino)phenyl moiety), 6.66 (d, J = 9.0 Hz, 2 H, 2 H of the *p*-(dimethylamino)phenyl moiety), 4.99 and 4.95 (AB quartet, J = 10.8 Hz, 2 H, benzyl H), 3.65 (m, 1 H, H-4 azetidinyl), 3.04 and 2.98 (s, m, total 8 H, dimethylamino H, H-4 pentanoate), 2.75 (dd, J = 5.4, 13.8 Hz, 1 H, H-3 *cis*-azetidinyl), 2.36 (dd, J = 2.4, 13.8 Hz, 1 H, H-3 *trans*-azetidinyl), 2.05–1.77 (m, 2 H, H-5 pentanoate), 1.53 (s, 9 H, *tert*-butyl); ^{13}C NMR δ 198.19, 165.27, 164.01, 150.91, 150.05, 135.04, 134.71, 129.21, 128.86, 128.51, 125.85, 111.60, 83.88, 78.11, 57.13, 40.14, 37.65, 32.41, 27.89, 26.48; IR (KBr pellet) 1755, 1720, 1680, 1620 cm^{-1}; MS (FAB) parent ion at 479.6.

***tert*-Butyl 5-(1-(Benzyloxy)-2-oxo-4-azetidinyl)-2,3-dioxopentanoate (13) Obtained by Hydrolysis of Compound 14.**[1e,j,7] *tert*-Butyl 5-(1-(benzyloxy)-2-oxo-4-azetidinyl)-2-[*N*-(*p*-(dimethylamino)phenyl)imino]-3-oxopentanoate (14, 155 mg, 0.323 mmol) was dissolved in a mixture of 20 mL of ethyl acetate and 10 mL of H_2O. Aqueous HCl (6 N) was added dropwise with vigorous stirring until a distinct color change from the original yellow-orange organic solution occurred and until starting material was consumed as determined by TLC. After the reaction, the aqueous layer was orange and the organic layer was colorless. Workup gave 145 mg of a brown oil. Desired tricarbonyl 13 was obtained in monohydrated form by column chromatography (1:1 hexanes/ethyl acetate) as 86 mg of a clear, colorless oil (70% yield): R_f = 0.18 (1:1 hexanes/ethyl acetate); ^{1}H NMR δ 7.39 (m, 5 H, aromatic H), 5.15 (bs, heteroatom H), 4.97 and 4.92 (AB quartet, J = 11.1 Hz, total 2 H, benzylic H), 3.54 (m, 1 H, H-4 azetidinyl), 2.72 (dd, J = 5.1, 13.8 Hz, 1 H, H-3 *cis*-azetidinyl), 2.60 (m, 2 H, H-4 pentanoate), 2.28 (dd, J = 2.4, 13.8 Hz, 1 H, H-3 *trans*-azetidinyl), 2.1–2.7 (m, 2 H, H-5 pentanoate), 1.46 (s, 9 H *tert*-butyl H); ^{13}C NMR δ 202.69, 167.71, 163.78, 134.94, 129.25, 128.96, 128.56, 92.62, 84.93, 78.12, 56.70, 37.49, 31.50, 27.55, 25.97; IR (neat) 3600–3100, 1760–1730 cm^{-1}; CIMS gave M + 1 at 362 (unhydrated form) and M + 1 − 56 at 306.

***tert*-Butyl 5-(2-Oxo-4-azetidinyl)-3-oxopentanoate (16).** *tert*-Butyl 5-(1-(benzyloxy)-2-oxo-4-azetidinyl)-3-oxopentanoate (11, 80 mg, 0.230 mmol) was hydrogenated in ethyl acetate (~10 mL) in the presence of 10% Pd/C (10% w/w, 8.0 mg) for 2 h. The reaction was filtered through Celite and the solvent removed to yield 15 as an oil which was immediately used in the next step. The oil was dissolved in 1 mL of anhydrous THF and deoxygenated by bubbling with argon, and the reaction was performed under an argon atmosphere. Sodium acetate buffer (4.1 M, pH 5.0, 1.6 mL, 6.5 mmol acetate, 2840 mol %), deoxygenated in the same manner, was added via syringe and was followed immediately by $TiCl_3$ (594 μL, 0.653 mmol, 284 mol %, 1.1 M) which was added slowly via syringe with the needle tip below the surface of the reaction solution. The dark purple reaction was stirred for 2 h and was then quenched by diluting into about 25 mL of 1:1 ethyl acetate/sodium L-tartrate buffer (0.78 M, pH 5.0). Workup, including washes with additional tartrate buffer, brine, saturated Na_2CO_3(aq), and brine, sequentially gave 32.4 mg of a yellow oil which was determined to be reduced β-lactam 16 (58% crude yield) by comparison of ^{1}H NMR and CIMS data with those from authentic material.[15a]

Synthesis of Bicyclic β-Lactam 1. *tert*-Butyl 5-(1-(benzyloxy)-2-oxo-4-azetidinyl)-2-oximido-3-oxopentanoate (12, 65 mg, 0.173 mmol) was hydrogenated in the presence of 10% Pd/C (~10% w/w, 7 mg) in about 10 mL of ethyl acetate. The starting material was consumed within 45 min. The reaction was filtered through Celite, and the solvent was removed. The resulting *tert*-butyl 5-(1-hydroxy-2-oxo-4-azetidinyl)-2-oximido-3-oxopentanoate (17) was reduced immediately without further purification.

The hydrogenated product, 17, was taken up in acetone (2.7 mL) and was thoroughly purged with argon. Previously deoxygenated sodium acetate buffer (4.1 M, pH 5.0, 2.7 mL, 11 mmol acetate, 6200 mol %) was added via cannula. The $TiCl_3$ (1 mL, 1.1 mmol, 620 mol %) was then added slowly via a syringe keeping the needle tip well below the buffer layer of the biphasic system, so that the reaction mixture never came in contact with a large amount of unbuffered droplets of reagent. After about one-third of the total volume of $TiCl_3$ had been added, the color of the reagent persisted, and the reaction mixture remained dark purple-blue toward the end of the addition. After being stirred for 1 h, the reaction was quenched by pouring into a 1:1 mixture of ethyl acetate/tartrate buffer (sodium L-tartrate, 0.78 M, pH 5.0). Enough buffer was added to dissolve any titanium(IV) oxide. Workup gave an oil which was stirred in 2 mL of anhydrous CH_2Cl_2 in the presence of about 100 mg of activated crushed molecular sieves (3 Å). After 48 h, the solution was filtered and solvent was removed. The yellow oil was subjected to preparative layer chromatography (1:1 hexanes/ethyl acetate, two developments) to afford a white solid (13.7 mg, 31%), the ^{1}H NMR of which indicated the presence of both diastereomers. Recrystallization from ethyl acetate/hexanes gave 8.9 mg of one diastereomer as a white, crystalline solid. Note that 2-D CSCMR techniques aided in NMR peak assignment: mp = 137–139 °C; R_f = 0.64 (ethyl acetate); ^{1}H NMR δ 4.78 (bs, heteroatom H), 3.96 (m, 1 H, H-6), 3.21 (dd, J = 5.0, 15.0 Hz, 1 H, H-7 cis), 2.80–2.77 (m, 2 H; H-2, H-7 trans), 2.67–2.55 (m, 1 H, H-2), 2.48–2.33 (m, 1 H, H-1), 2.21–2.00 (m, 1 H, H-1); 1.51 (s, 9 H, *tert*-butyl H); ^{13}C NMR δ 200.12, 165.20, 164.55, 85.89, 80.18, 46.90, 43.27, 35.84, 28.98, 27.61; IR (KBr pellet) 3500–3200, 3000–2880, 1780–1710 cm^{-1}; CIMS gave M + 1 at 256 and M + 1 − 56 at 200; HRMS (EIMS) for M − 56 calcd for $C_8H_9N_1O_5$ 199.0481, found 199.0485.

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Registry No. *cis*-1, 93552-85-3; *trans*-1, 93552-84-2; 7, 66697-00-5; 8, 141198-13-2; 9, 141198-14-3; 10, 141198-15-4; 11, 141198-16-5; 12, 141198-17-6; 13, 141220-89-5; 14, 141220-90-8; 15, 141198-18-7; 16, 141198-19-8; 17, 141198-20-1; 1,2-phenylenediamine, 95-54-5; *tert*-butyl malonate magnesium salt, 104197-11-7; 1-octanoylimidazole, 17450-31-6; titanium trichloride, 7705-07-9.

Supplementary Material Available: X-ray crystallographic data for compound 1 and ^{13}C and ^{1}H NMR spectra for 1, 7–10, and 12–14 (30 pages). Ordering information is given on any current masthead page.