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Formation of γ-Lactones through CAN-Mediated Oxidative Cleavage of Hemiketals

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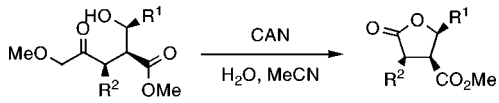
Received June 11, 2008

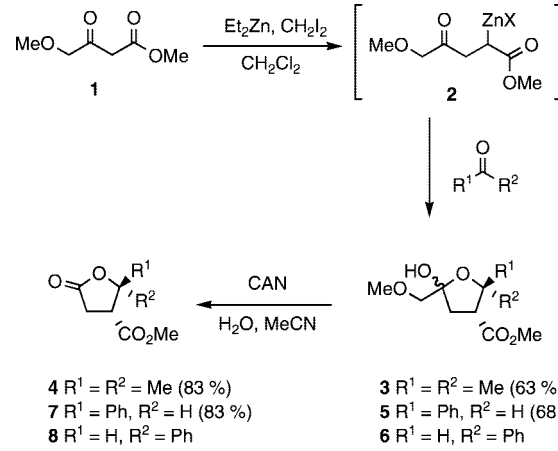


The generation of substituted γ-lactones can be accomplished through application of a tandem chain extension-aldol reaction, followed by CAN-mediated oxidative cleavage of the aldol product. The oxidative cleavage requires the intermediacy of a hemiketal and the presence of an α-heteroatom. Formation of the γ-lactone through the oxidative cleavage is used to assign stereochemistry of the aldol reaction and as the final step in a short synthesis of members of the phaseolinic acid family of natural products.

Our interest in a zinc carbenoid-mediated chain extension reaction[1] has led to the development of a number of tandem reaction variants. One of these variations is a tandem chain extension-aldol reaction[2] that produces an α-substituted-γ-keto ester (amide) from β-keto ester (amide) in one reaction flask. In many cases this tandem chain extension-aldol reaction exhibits good diastereoselection, with an average *syn*:*anti* selectivity of 10:1 when simple β-keto esters are used as starting materials. Studies by our group have established that the aldol reaction is kinetically controlled, which suggests that the diastereoselectivity of the zinc−enolate reaction might be understood on the basis of enolate geometry applied to a closed transition state.[3] The assessment of the diastereoselectivity of these aldol reactions is complicated by the appearance of closed hemiketal forms, which are prevalent in both the *syn* and *anti* aldol stereoisomers. The determination of absolute stereochemistry of the aldol products has also been a challenge and, in general, has relied upon the availability of crystalline products.

During our efforts to apply the zinc-mediated chain extension-aldol reaction to the generation of peptide isosteres, we observed a ceric ammonium nitrate (CAN)-initiated oxidative cleavage that resulted in the preparation of substituted γ-lactones.[4] We report herein an investigation of this CAN-mediated oxidative cleavage and its utility for the establishment of stereochemistry in a select group of tandem chain extension-aldol reactions. We also report on the utility of the CAN-mediated oxidation for the rapid and stereocontrolled access to substituted γ-lactones and, in particular, a member of the phaseolinic acid family of natural products.[5]

SCHEME 1. γ-Lactone Formation through CAN Oxidation



The general strategy for γ-lactone formation is illustrated in Scheme 1. Treatment of methyl 4-methoxyacetoacetate **1** with the Furukawa reagent,[6] derived from diethylzinc and diiodomethane, results in the formation of a chain-extended organometallic **2**, which can act as a latent enolate and trap a variety of electrophiles. When the latent enolate was used to capture acetone, the tandem chain extension-aldol product **3** was present as a mixture of open and closed (hemiketal) forms. Treatment of the aldol product **3** with aqueous ceric ammonium nitrate (CAN) provided the corresponding γ-lactone **4**.[7] Similarly, a mixture of aldol products (**5** and **6**) was produced through capture of benzaldehyde with the same enolate. The ratio and identity of diastereomers produced in this tandem chain extension-aldol reaction was difficult to estimate from NMR analysis of the crude reaction material due to the appearance of hemiketal isomers and/or the open chain form for each diastereomer. Separation of the major isomer of the aldol reaction and comparison to the NMR spectra of the crude reaction material revealed a diastereomeric ratio of 3:1. While the stereochemical assignment of the major diastereomer (**5**) as either the *syn* or the *anti* aldol product was not possible at this stage, it was apparent that the presence of the methoxy group diminished the *syn*-selectivity in the aldol reaction, since the 3:1 diastereomeric ratio was significantly poorer than the average

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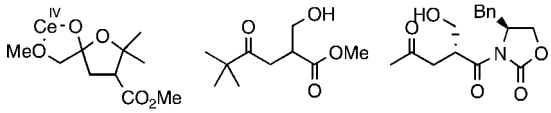
10.1021/jo801258h CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/12/2008

(10:1 *syn*:*anti*) diastereoselectivity observed in the reactions of unsubstituted acetoacetate starting materials.[2] The reason for this poorer diastereoselection is not clear, although zinc-complexation with the methoxy group and disruption of selective (*Z*)-enolate formation may play a role. The major aldol stereoisomer **5** was reacted with CAN to provide the known γ-lactone **7**,[8] which indicated that the major stereoisomer of the aldol reaction was, in fact, the *syn* aldol product. When the crude aldol reaction mixture (3:1, *syn*:*anti*) was treated with CAN, a similar mixture of diastereomeric lactones[8] was produced, which indicates that little epimerization was taking place in the oxidative cyclization.

A proposed mechanism for the oxidation involves single electron-mediated cleavage of a cerium complexed hemiketal **9**. Oxidative cleavage of monomethylated 1,2-diols by CAN has been reported previously.[9] The appearance of hemiketal forms in the aldol products (i.e. **3**) presents a similar 1,2-dioxygenated functionality for the cleavage. The necessity of the α-heteroatom for the oxidative cleavage was confirmed by the preparation of aldol products **10** and **11**, which were unreactive and returned starting material upon exposure to CAN. Furthermore, no oxidative cleavage was observed with substrates lacking the α-hydroxymethyl (aldol-derived) substituents.

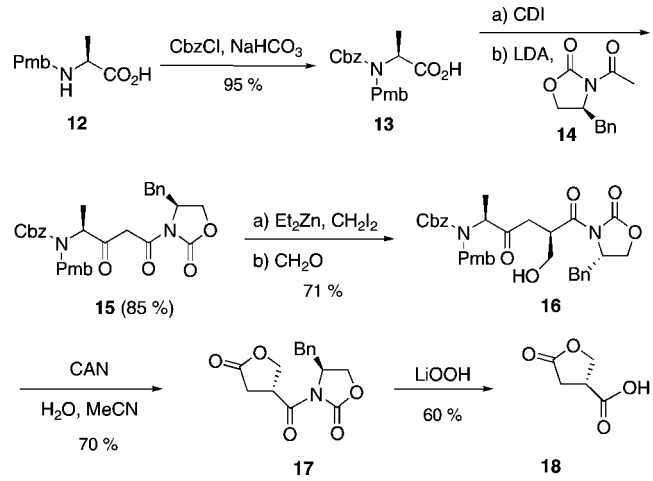


9 **10** **11**

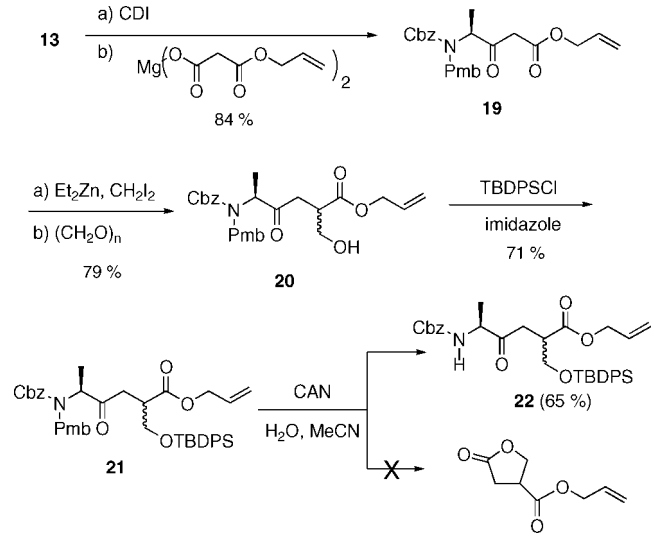
Substrates for the chain extension-aldol reaction that contained nitrogen atoms α to the ketone were also studied. Our interest in developing a stereocontrolled approach to ketomethylene-containing peptide isosteres provided additional motivation for the study of these compounds.[10] Reductive alkylation of alanine with anisaldehyde provided compound **12**,[11] which was further protected with a Cbz group. The use of two nitrogen-protecting groups was necessary to prevent quenching of the intermediate enolate in the tandem chain extension-aldol reaction. Formation of the β-keto imide **15** was accomplished through a mixed Claisen reaction utilizing an acyl imidazole (Scheme 2). The chain extension-aldol reaction took place with high diastereoselectivity; however, the stereochemistry of the product **16** could not be assigned. Oxidative cleavage of the aldol product with CAN proceeded cleanly to provide the γ-lactone **17**, which demonstrated that an α-nitrogen can facilitate the oxidative cleavage. Removal of the oxazolidinone with lithium hydrogen peroxide provided the known (*S*)-γ-lactone **18**,[12] which allowed the assignment of the stereoselectivity of the aldol reaction.

Compound **19** was also generated from the alanine derivative **13** by application of the Masamune acylation procedure[13] (Scheme 3). A tandem chain extension-aldol reaction of allyl ester **19** provided two inseparable aldol products **20** in a 1:1 ratio, which were subsequently protected with a TBDPS group.

SCHEME 2. CAN Oxidation of Alanine Derivative



SCHEME 3. Unsuccessful Lactone Formation of TBDPS Ether



Exposure of the silyl ether **21** to CAN resulted in the removal of the Pmb group, but did not result in oxidative cleavage and formation of a γ-lactone. This result lends strong support to the assertion that hemiketal formation is essential for the oxidative cleavage. Even though a small concentration of the ketone hydrate might be expected under the aqueous reaction conditions, no oxidative cleavage of **21** was observed over the course of 8 h.

We recently reported a variation on the chain extension reaction in which substituted diiodomethanes are used to generate the carbenoid.[14] Use of this substituted carbenoid results in the formation of β-substituted γ-keto esters in one step from β-keto ester starting materials. The use of substituted diiodomethanes as reagents in a tandem chain extension-aldol reaction had not been explored; however, we anticipated that oxidative cleavage of the proposed aldol products with CAN would provide rapid access to the phaseolinic acid family of natural products.[5]

As expected, treatment of methyl 4-methoxyacetoacetate (**1**) with a carbenoid derived from 1,1-diiodoethane[15] provided a

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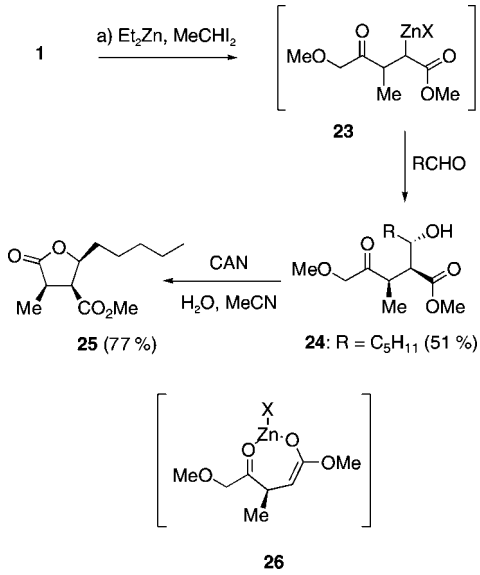
SCHEME 4. Formation of 3,4,5-Trisubsituted-γ-lactone



chain-extended organometallic **23** that could be trapped with hexanal (Scheme 4). A complex mixture of products, due to the appearance of hemiketal forms, was observed. Chromatographic separation provided the aldol product (**24**), as a mixture of open chain and hemiketal forms, in 51% yield. Upon exposure of the aldol product to aqueous CAN, the cis,cis-stereoisomer **25** was produced in 77% yield. Structural assignment was confirmed by comparison to previously published spectral data of the phaseolinic acids.[16] The cis relationship between the methyl substituent and the carboxyester group can be rationalized due to facial bias on a zinc-complexed (*Z*)-enolate (**26**); however, the preference for the *anti*-aldol product, which leads to a cis relationship in the hemiketal and lactone systems, was unanticipated. Whether the change in selectivity to favor formation of the aldol product (**24**) is due to a decreased bias for *Z*-enolate intermediacy, due to a reversal in aldehyde facial selectivity, or due to the operation of an alternate (open) transition state is unclear, although the substituent at the β-position of the intermediate enolate is clearly playing a role. The role that the β-substituent plays in stereocontrolled tandem chain extension-aldol reactions is under investigation in our group.

In conclusion, a rapid method for the assembly of substituted γ-lactones has been developed. The reaction sequence relies upon a zinc carbenoid-mediated tandem chain extension-aldol reaction and a CAN-mediated oxidative cleavage. While the oxidative cleavage is only applicable to aldol products that have heteroatoms α to the ketone and are capable of forming γ-lactols, the CAN-mediated reaction was shown to be useful in the identification of *syn*- or *anti*-aldol stereochemistry through conversion to the corresponding γ-lactones. The assignment of stereochemistry in a diastereoselective tandem chain extension-aldol reaction was made possible through the application of the CAN-mediated cleavage reaction. Lastly, the rapid assembly of naturally occurring γ-lactones, even those with α-alkyl substituents, was accomplished through application of these sequential transformations.

Experimental Section

Representative experimental details are given below.

Methyl 5-Hydroxy-5-(methoxymethyl)-2,2-dimethyltetrahydrofuran-3-carboxylate (3). An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, and rubber septum, charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen. The flask was put in an ice bath and diethylzinc (1 M solution in hexanes) (3.0 mmol, 3.0 mL) was added via syringe followed by slow addition of diiodomethane (3.3 mmol, 0.26 mL) via syringe over 5 min. The resulting solution was allowed to stir for approximately 10 min. Methyl 4-methoxyacetoacetate (1.0 mmol, 0.13 mL) was added via syringe over 5 min and the mixture was allowed to stir for an additional 30 min. Acetone (2.0 mmol, 0.15 mL) was added via syringe over 1 min and the reaction mixture was monitored by TLC (15:2, hexanes:ethyl acetate) until starting material was consumed. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 30 mmHg) to give a yellowish liquid. The crude reaction product was purified by flash chromatography (15:2, hexanes:ethyl acetate) to yield 0.14 g (63% yield) of product as a mixture of hemiketal anomers. IR (neat) 3437, 2979, 2829, 2250, 1721, 1445, 1366, 1105, 978, 916, 818, 732, 647, 533 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H, minor isomer), 3.71 (s, 3H, major isomer), 3.52−3.38 (m, major (2H) and minor (2H) isomers), 3.45 (s, 3H, minor isomer), 3.43 (s, 3H, major isomer), 3.29 (dd, 1H, J = 11.8, 7.2 Hz, major isomer), 2.93 (dd, 1H, J = 8.5, 4.2 Hz, minor isomer), 2.54−2.07 (m, major (2H) and minor (2H) isomers), 2.32 (m, 1H), 2.12 (dd, 1H, J = 12.9, 7.2 Hz), 1.54 (s, 3H, major isomer), 1.35 (m, 3H, minor isomer), 1.32 (s, 3H, minor isomer), 1.09 (s, 3H, major isomer). ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.5, 172.4, 105.2, 103.5, 84.3, 83.8, 77.5, 59.8, 53.4, 52.4, 52.1, 37.6, 37.3, 30.7, 29.6, 25.5, 24.6. HRMS (FAB+) *m/z* calcd for $C_{10}H_{17}O_4$ [M − OH] 218.1127, found [M − OH] 201.1134.

Methyl 2,2-Dimethyl-5-oxotetrahydrofuran-3-carboxylate (4). An oven-dried, one-necked, 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with acetonitrile (8 mL), water (2 mL), and the acetone aldol product (0.84 mmol, 0.18 g). Ceric ammonium nitrate (CAN) (3.37 mmol, 1.85 g) was added and the solution was allowed to stir at room temperature. The reaction progress was monitored by TLC (5:1, hexanes:ethyl acetate) until starting material was consumed (approximately 1 h). Water (5 mL) was added and the solution was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40 mmHg) to give 0.12 g (83% yield) of a slightly colored liquid. Purification of the crude reaction mixture was not necessary. IR (neat) 3110, 2939, 2677, 1741, 1671, 1576, 1427, 1371, 1293, 1124, 997, 937, 844, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.26 (dd, 1H, J = 9.3, 8.7 Hz), 3.15 (dd, 1H, J = 18.0, 9.3 Hz), 2.80 (dd, 1H, J = 18.0, 8.6 Hz), 1.62 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.6, 170.6, 86.3, 52.9, 50.5, 32.3, 28.5, 23.4. HRMS (FAB+) *m/z* calcd for $C_8H_{13}O_4$ [M + H] 173.0814, found [M + H] 173.0827.

Methyl 5-Hydroxy-5-(methoxymethyl)-4-methyl-2-pentyltetrahydrofuran-3-carboxylate (24). An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar and rubber septum, charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen. The flask was put in an ice bath and methyl 4-methoxyacetoacetate (**1**) (1.0 mmol, 0.13 mL) was added via syringe followed by the slow addition of diethylzinc (1 M solution in hexanes) (5.0 mmol, 5.0 mL) via syringe and the mixture was allowed to stir for 10 min. 1,1-Diiodoethane (5.0 mmol,

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0.39 mL) was added via syringe over 5 min. The resulting solution was allowed to stir for approximately 2 h. Hexanal (2.0 mmol, 0.25 mL) was added via syringe over 1 min and the reaction mixture was monitored by TLC (15:2, hexanes:ethyl acetate) until starting material was almost completely gone (about 45 min). The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 30 mmHg) to give a pale-yellowish liquid. The crude reaction product was purified by flash chromatography (15:2, hexanes:ethyl acetate) to yield 0.14 g (51% yield) of aldol product **24**. IR 3434, 2937, 2353, 1714, 1449, 1386, 1200, 1124, 1006 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (s, 1H), 4.02 (dt, 1H, $J = 7.3$, 5.9 Hz), 3.75 (s, 3H), 3.45−3.39 (m, 2H), 3.42 (s, 3H), 3.08 (dd, 2H, $J = 6.8$, 6.8 Hz), 2.76 (pentet, 1H, $J = 7.1$ Hz), 1.23−1.71 (m, 8H), 1.06 (d, 3H, $J = 7.2$ Hz), 0.88 (br t, 3H, $J = 6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.2, 105.3, 80.7, 74.4 59.9, 52.7, 52.3, 40.3, 32.5, 32.0, 26.1, 22.7, 14.2, 10.3. HRMS (FAB+) *m*/*z* calcd for $C_{14}H_{25}O_4$ [M − OH] 257.1753, found [M − OH] 257.1749.

***cis*,*cis*-Methyl 4-Methyl-5-oxo-2-pentyltetrahydrofuran-3-carboxylate (25).** An oven-dried, one-necked, 25-mL round-bottomed flask was equipped with a magnetic stir bar and charged with acetonitrile (4 mL), water (1 mL), and compound **24** (0.19 mmol, 0.05 g). Ceric ammonium nitrate (CAN) (0.77 mmol, 0.42 g) was added and the mixture was allowed to stir. The reaction progress was monitored by TLC (4:1, hexanes:ethyl acetate) until starting material was almost completely gone (about 6 h.). Water (2 mL) was added and the solution was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40 mmHg) to give 0.03 g (77% yield) of a slightly colored liquid. IR 2951, 2867, 1779, 1736, 1634, 1559, 1444, 1378, 1345, 1275, 1180, 1131, 995, 876, 797, 769, 631, 594, 475, 453, 434 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (dt, 1H, $J = 8.5$, 5.1 Hz), 3.74 (s, 3H), 3.33 (dd, 1H, $J = 7.5$, 5.1 Hz), 2.92 (pentet, 1H, $J = 7.2$), 1.75 (m, 1H), 1.62−1.49 (m, 3H), 1.35−1.28 (m, 4H), 1.24 (d, 3H, $J = 7.1$ Hz), 0.88 (br t, 3H, $J = 6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.7, 170.3, 79.4, 52.0, 50.9, 39.4, 31.6, 31.1, 25.7, 22.6, 14.1, 10.6. HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{21}O_4$ [M + H] 229.1440, found [M + H] 229.1441.

Acknowledgment. We thank the National Institutes of Health (R15 GM060967-02) and the University of New Hampshire for their financial support.

Supporting Information Available: Experimental procedures for the preparation of **5**, **6**, **7**, **8**, **10**, **11**, **13**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, and **22** and ^1H and ^{13}C NMR spectra for **3**, **4**, **5**, **6**, **7**, **8**, **10**, **11**, **13**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801258H