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A short approach to trisubstituted γ-butyrolactones

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Abstract—The dihydroxylation of unsaturated aldol adducts with catalytic OsO_4 and NMO occurs under very mild conditions and with moderate to excellent levels of diastereoselectivity to give trisubstituted γ-butyrolactone derivatives.

1. Introduction

Chiral substituted γ-butyrolactones are present in the structures of a wide variety of natural products with potential pharmacological applications. The diversity of their biogenetic origins suggests that this structure may be one of the key elements in their biosynthesis.[1]

Because of their importance as chiral building blocks for the synthesis of compounds with important biological activities, such as antimumor, antibiotic, antifungal, and antibacterial, the stereocontrolled synthesis of trisubstituted γ-butyrolactones represent an attractive objective for synthetic organic chemists.[2,3]

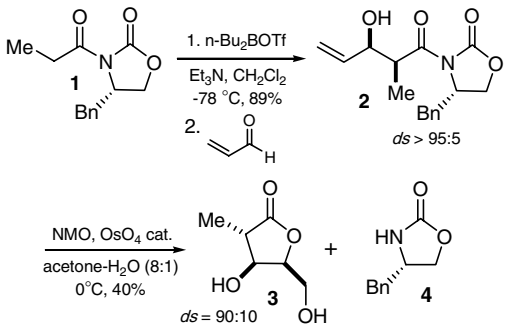
Here we report, a novel methodology for the construction of γ-butyrolactones, via a diastereoselective osmylation of unsaturated *syn*-aldol adducts. This synthetic methodology involves two steps: (i) the preparation of the enantiopure aldol adduct and (ii) the dihydroxylation reaction followed by in situ lactonization. Despite the widespread application of the aldol reaction in synthesis, to the best of our knowledge, this is the first direct application of unsaturated aldol adducts in the synthesis of γ-butyrolactones via an osmylation/lactonization sequence.[3]

2. Results and discussion

The synthesis of butyrolactones began with the asymmetric aldol addition of the boron enolate derived from *N*-propionyloxazolidinone **1** with acrolein to give the corresponding aldol adduct **2** in 89% yield (ds >95:5) (Scheme 1).[4] The next step involved treatment of the aldol adduct with catalytic amounts of osmium tetroxide and NMO in acetone/H_2O as solvent. We were very pleased to find that dihydroxylation of aldol adduct **2** under these conditions led directly to γ-butyrolactone **3** in 40% yield and 90:10 diastereoselectivity for the two-step sequence (dihydroxylation and lactonization). The chiral auxiliary **4** was easily recovered.

Silylation of aldol **2** with TBSOTf and 2,6-lutidine gave **5** in 89% yield (Scheme 2). Treatment of **5** with catalytic amounts of osmium tetroxide and NMO in acetone/H_2O as solvent gave γ-butyrolactone **6** in 42% yield and 90:10 diastereoselectivity for the two-step sequence (dihydroxylation and lactonization).

Both lactones **3** and **6** were smoothly converted to the same lactone **7** on treatment with TBSOTf and 2,6-lutidine in good overall yields. This proved that the same



Scheme 1. Dihydroxylation/lactonization sequence.

Keywords: Dihydroxylation; γ-Lactones; Osmylation reaction; Aldol adducts.
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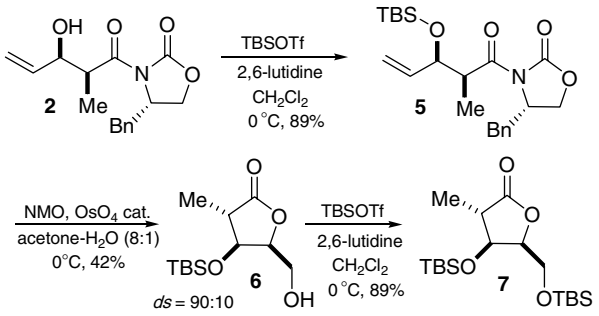
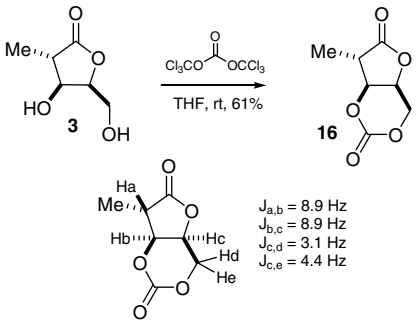


Scheme 2. Synthesis of lactones **6** and **7**.



Scheme 4. Synthesis of cyclic carbonate **16**.

major stereoisomer was obtained with both aldol adducts **2** and **5**.

Treatment of aldol adducts **8**–**11** with catalytic amounts of osmium tetroxide and NMO in acetone/H_2O as solvent led to lactones **12**–**15**, respectively, in good overall yields and moderate to high diastereoselectivities for the two-step sequence (Scheme 3).

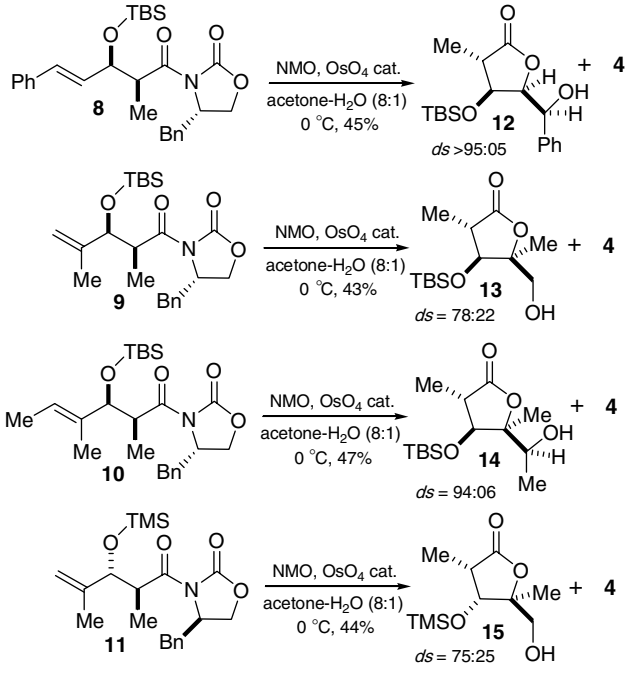
It is noteworthy that aldol adducts **9**–**11** led to lactones **13**–**15**, respectively, with a quaternary stereogenic center being created. The use of *anti*-aldol adduct **11** led only to moderate selectivity (ds = 75:25).

The observed relative stereochemistry of the major isomers **3** and **6** was proved by conversion to the cyclic carbonate **16**, after treatment of lactone **3** with triphosgene (61% yield) followed by coupling constant analysis of its ^{1}H NMR spectrum (Scheme 4). The large vicinal coupling constant of Hb with both Ha and Hc (8.9 Hz) confirmed the trans-diaxial relationship between Hb and Ha as well as the cis relationship between Hb and Hc. The small vicinal coupling constants between Hc with both Hd (3.4 Hz) and He (4.4 Hz) confirmed that there is no trans-diaxial relationship between these hydrogens and unambiguously established the relative stereochemistry of the major isomers (Scheme 4).

The relative stereochemistry for lactones **12**–**15** was determined by coupling constant analysis in their ^{1}H NMR spectra as well as by NOESY experiments (Fig. 1).[5] The illustrated NOESY interactions between Ha/Hd, and Hd with the hydrogens of the *tert*-butyl group (OTBS) together with the coupling constants for Ha/Hb (5.9 Hz) and Hb/Hc (0.7 Hz) confirmed the stereochemistry of lactone **12**.

The NOESY interaction between Ha/Hc, together with the coupling constant for Ha/Hb (9.5 Hz) confirmed the stereochemistry of lactone **13**. NOESY experiments performed on lactones **14** and **15** also supported their relative stereochemistries. For lactone **14**, a NOESY cross-peak was observed for the Ha/OH signals and, for lactone **15**, a NOESY cross-peak was observed for the Ha/Hb and Hb/Hc signals.

In these stereochemical assignments, both the C2–methyl and the C3–OTBS (or OTMS in the case of lac-



Scheme 3. Synthesis of lactones **12**–**15**.

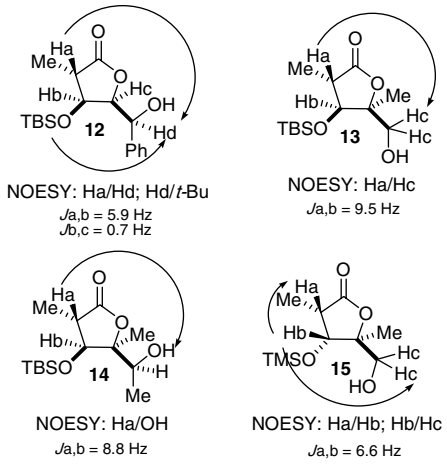


Figure 1. NOESY interactions and coupling constants for lactones **12**–**15**.

tone **15**) stereocenter configurations served as important reference points.[5,6]

3. Conclusions

In summary, we have demonstrated that dihydroxylation of unsaturated *syn*-aldol adducts occurs under very mild conditions and with good levels of diastereoselectivity to give trisubstituted γ-butyrolactone derivatives. The relative and absolute stereochemistries of C2–C3 stereocenters is then established by the nature of the aldol reaction (*syn* or *anti*) and by the resident chirality of the chiral auxiliary as, probably, the oxazolidinone ring plays a dominant role in controlling the conformation of these compounds. This research, in combination with the accessibility of optically pure aldol adducts, may represent a useful entry into the field of natural product synthesis, as this work provides access to trisubstituted 3,4-*cis*-γ-lactones, which are very difficult to construct selectively. Extension of this work to the total synthesis of some naturally occurring γ-lactones as well as studies in order to explain the origin of diastereoselectivity are underway and the results will be described in due course.[6,7]

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6. **Lactone 3**: ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm): 1.31 (d, *J* 7.3 Hz, 3H), 2.66 (dq, *J* 8.8, 7.3 Hz, 1H), 3.72 (dd, *J* 12.8, 4.6 Hz, 1H), 3.94 (dd, *J* 12.8, 2.4 Hz, 1H), 4.01 (dd, *J* 8.8, 7.3 Hz, 1H), 4.18 (ddd, *J* 7.3, 4.6, 2.4 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm): 12.8, 44.9, 61.4, 74.7, 86.0, 179.3; **Lactone 6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.28 (d, *J* 7.3 Hz, 3H), 2.62 (m, 1H), 2.76 (br s, 1H), 3.67 (d, *J* 13.0 Hz, 1H), 3.98 (d, *J* 13.0 Hz, 1H), 4.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): −4.6, −4.1, 12.8, 17.9, 25.6, 44.3, 60.1, 74.2, 84.1, 176.5. **Lactone 7**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.29 (d, *J* 7.4 Hz, 3H), 2.60 (q, *J* 7.4 Hz, 1H), 3.75 (dd, *J* 12.1, 2.6 Hz, 1H), 3.92 (dd, *J* 12.1, 2.2 Hz, 1H), 4.10 (dt, *J* 6.6, 2.2 Hz, 1H), 4.20 (dd, *J* 8.1, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): −5.6, −5.4, −4.8, −4.4, 13.0, 17.8, 18.2, 25.6, 25.8, 44.2, 60.4, 74.1, 84.4, 176.8. **Lactone 12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): −0.14 (s, 3H), −0.07 (s, 3H), 0.83 (s, 9H), 1.16 (d, *J* 7.3 Hz, 3H), 2.56 (dq, *J* 7.3, 5.9 Hz, 1H), 4.30 (dd, *J* 5.9, 0.7 Hz, 1H), 4.37 (dd, *J* 5.9, 0.7 Hz, 1H); 4.72 (d, *J* 5.9 Hz, 1H), 7.30–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): −5.2, −5.1, 8.8, 17.9, 25.6, 39.6, 71.4, 73.6, 89.5, 126.8, 128.8, 128.9, 138.8, 178.4. **Lactone 13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 0.10 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.24 (s, 3H), 1.28 (d, *J* 7.3 Hz, 3H), 2.15 (br s, 1H), 2.67 (dq, *J* 9.5, 7.3 Hz, 1H), 3.47 (d, *J* 12.8 Hz, 1H), 3.72 (d, *J* 12.8 Hz, 1H), 4.25 (d, *J* 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): −4.8, −4.3, 12.7, 16.7, 17.8, 25.6, 42.3, 65.0, 74.5, 86.5, 176.2. **Lactone 14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.21 (s, 3H), 1.26 (d, *J* 7.3 Hz, 3H), 1.28 (d, *J* 6.4 Hz, 3H), 1.95 (br s, 1H), 2.61 (dq, *J* 8.8, 7.3 Hz, 1H), 3.60 (q, *J*

6.4 Hz, 1H), 4.35 (d, *J* 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): −4.6, −4.0, 12.9, 16.5, 17.7, 17.9, 25.6, 42.3, 69.4, 75.7, 84.6, 176.3. **Lactone 15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 0.14 (s, 9H), 1.15 (d, *J* 7.3 Hz, 3H), 1.28 (s, 3H), 2.40 (br s, 1H), 3.04 (dq, *J* 7.3, 6.6 Hz, 1H), 3.59 (d, *J* 12.1 Hz, 1H), 3.69 (d, *J* 12.1 Hz, 1H), 4.33 (d, *J* 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): 0.10, 9.6, 17.9, 41.3, 67.4, 73.4, 88.5, 179.0.

7. Yields refer to chromatographically and spectroscopically homogeneous materials.