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Complementary Diastereoselective Reduction of Cyclic γ-Keto Acids: Efficient Access to Trisubsituted γ-Lactones

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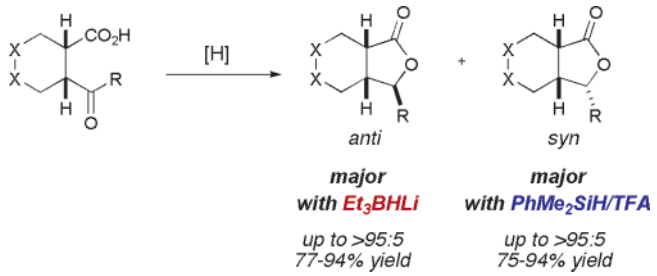
ABSTRACT



Complementary reduction conditions have been identified that provide ready access to each respective diastereomer of bi- and tricyclic, trisustituted γ-lactones starting from the corresponding cyclic γ-keto acids. Subjection of cyclic γ-keto acids to silane reagents in the presence of trifluoroacetic acid provides all *syn*-γ-lactones, while reduction with trialkylborohydrides furnishes the *syn*,*anti*-γ-lactones. The conditions are mild and provide the product lactones in good yields and modest to excellent selectivity.

New methods for the synthesis of the lactone moiety continue to be an area of intense investigation due to its synthetic utility and its prevalence in biologically significant natural products.[1] In particular, γ-butyrolactones represent an equivalent to 4-hydroxycarbonyl compounds, also known as homoaldol products.[2] Among the multitude of approaches devised for the synthesis of γ-lactones,[3,4] the synthesis of trisubstituted derivatives still represents a formidable challenge.[5] We have recently developed complementary approaches to γ-keto acid derivatives[6] using alkylative anhydride desymmetrization as well as asymmetric Stetter reactions.[7] Herein, we report the complementary diastereoselective reduction of γ-keto acids bearing a cyclic backbone providing ready access to trisubstituted γ-lactones.

Substrate-directed reactions represent a powerful method for the introduction of new stereochemical elements into

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(3) For a review, see: Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377−1395.

(4) For recent representative examples, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208. (c) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143−4145. (d) Floreancig, P. E.; Wang, L. *Org. Lett.* **2004**, *6*, 4207−4210. (e) Fukuzawa, S.; Miura, M.; Saitoh, T. *J. Org. Chem.* **2003**, *68*, 2042−2044. (f) Chhor, R. B.; Nosse, B.; Sörgel S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260−270. (g) Buchwald, S. L.; Speilvogel, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 3500−3501. (h) Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457−6458.

(5) For selected approaches, see: (a) Barros, M. T.; Burke, A. J.; Lou, J.-D.; Maycock, C. D.; Wahnon, J. R. *J. Org. Chem.* **2004**, *69*, 7847−7850. (b) Evans, D. A.; Wu, J.; Masse, C. E.; MacMillian, D. W. C. *Org. Lett.* **2002**, *4*, 3379−3382. (c) Hong, S.-p.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19−21. (d) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675−678. (e) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071−4074. (f) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848−7855.

(6) For a review on the synthetic utility of 1,4- and 1,5-keto acids, see: Csende, F.; Stajer, G. *Heterocycles* **2000**, *53*, 1379−1419.

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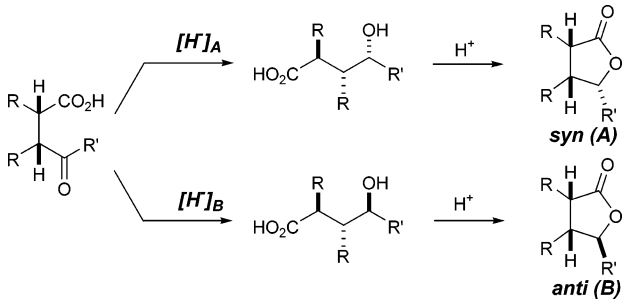
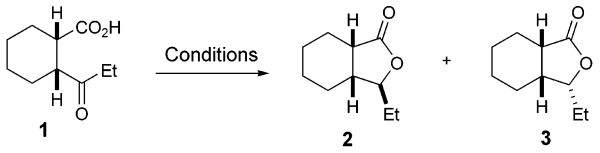
molecules containing preexisting stereocenters.[8] Although reductions of β-hydroxyacids are well developed, relatively few examples applying this concept to the reduction of γ-keto acids have appeared.[9] Several reports have detailed the diastereoselective reduction of cyclic[10] and acyclic[11] 1,4-keto acid derivatives providing the product lactones in good yield and selectivity. We envisioned that treatment of the 4-oxo-carboxylic acids with a particular reducing agent ($[H^-]_A$) would potentially provide the *syn*-lactone **A**, while treatment of the starting material with a separate hydride source ($[H^-]_B$) may supply the paired *anti*-lactone **B** (Scheme 1).

Scheme 1



Our initial efforts to discover a set of conditions that provide access to each diastereomer focused on reducing agents known to participate in substrate-directed reduction manifolds (Table 1). Alkyl aluminum hydrides have been shown to reduce acyclic 1,4-keto acids with high levels of stereocontrol.[11] Reduction of *cis*-cyclohexyl keto acid **1** with DIBAL-H at low temperature followed by cyclization afforded the desired lactone in modest yield and selectivity favoring *syn*-lactone **3** (entry 1).[12] Silanes have seen application as hydride sources usually under acidic conditions and have been shown to be effective for the reduction of α-hydroxyketones.[13] In the event, treatment of keto acid **1**

Table 1. Reducing Agent Screen



entry	conditions	yield (%)	**2:3**[a]
1	DIBAL-H THF, −78 °C	64	25:75
2	Et_3SiH TFA/CH_2Cl_2 (1:3), 0 °C	54	20:80
3	$PhMe_2SiH$ TFA/CH_2Cl_2 (1:3), 0 °C	90	7:93
4	Et_3BHLi THF, −78−23 °C	83	85:15
5	s-Bu_3BHLi THF, −78−23 °C	65	75:25

[a] Diastereomeric ratios determined by ^1H NMR.

with Et_3SiH under acidic conditions provided an isomeric mixture of the desired lactones in modest yield but improved selectivity favoring **3** in an 80:20 ratio (entry 2). Increasing the steric demand of the silane source in the form of $PhMe_2$-SiH leads to a dramatic increase in both reaction efficiency and selectivity, supplying **3** in a 93:7 ratio (entry 3).[14]

With efficient entry to the syn diastereomer, we turned our attention to the search for conditions that would favor the corresponding anti isomer. Lithium trialkylborohydrides had been shown to provide the *anti*-lactones in similar systems.[10] Subjection of keto acid **1** to 2.4 equiv of Super-Hydride (Et_3BHLi) in THF provided the desired products after cyclization in 83% yield and an 85:15 ratio favoring *anti*-lactone **2** (entry 4). Increasing the steric bulk of the reducing agent resulted in reduced selectivity (entry 5).

Having identified two discrete reducing agents that provide complementary diastereomers of the product γ-butyrolactones in synthetically useful selectivities, we sought to examine the effects of backbone architecture (Table 2). Unsaturation present in the cyclohexyl ring has little effect on the selectivity or efficiency of the reaction. Super-Hydride reduction of cyclohexenyl keto acid **4** provides the corresponding anti product in a 79:21 ratio, while silane reduction favors the syn product as a 90:10 mixture (entry 1). Tetrasubstituted olefin-containing keto acid **5** and benzofused oxoacid **6** undergo smooth reduction under both conditions, supplying each respective isomeric lactone in slightly elevated selectivity (entries 2 and 3). Keto acids bearing bicyclic [2.2.1] and [2.2.2] backbones also efficiently participate in the reaction manifold. Upon reduction with the silane system, saturated and unsaturated bicyclic keto acids **7**−**10** afford the expected *syn*-lactones in uniformly high yield and selectivity. When keto acids **7**−**10** are subjected

(7) (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174−175. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 10248−10249. (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* In press. (d) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (e) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934−1936. (f) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876−8877. (g) Rovis, T. *Chemtracts* **2003**, *16*, 542−553.

(8) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (b) Sailes, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1785−1805.

(9) (a) For enantioselective reduction of prochiral keto acids using boranes, see: Ramachandran, P. V.; Brown, H. C.; Pitre, S. *Org. Lett.* **2001**, *3*, 17−18. Ramachandran, P. V.; Pitre, S.; Brown, H. C. *J. Org. Chem.* **2002**, 67, 5315−5319. (b) For enzymatic methods, see: Forzato, C.; Gandolfi, R.; Molinari, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2001**, *12*, 1039−1046 and references therein.

(10) (a) Fujiwara, Y.; Kimoto, S.; Okamoto, M. *Chem. Pharm. Bull.* **1975**, *23*, 1396−1403. (b) Miyano, S.; Abe, N.; Fujisaki, F.; Sumoto, K. *Heterocycles* **1987**, *26*, 1813−1826. (c) Pourahmady, N.; Eisenbraun, E. J. *J. Org. Chem.* **1983**, *48*, 3067−3070.

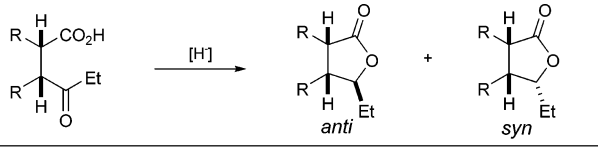
(11) (a) Frenette, R.; Kakushima, M.; Zamboni, R.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1987**, *52*, 304−307. (b) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1991**, *56*, 3083−3089. (c) Satoh, M.; Washida, S.; Takeuchi, S.; Asaoka, M. *Heterocycles* **2000**, *52*, 227−236. (d) Fernandez, A.-M.; Paquevent, J.-C.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007−4014.

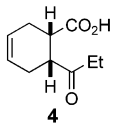
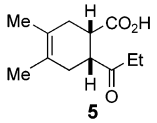
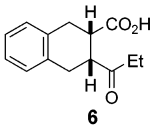
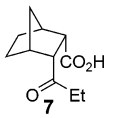
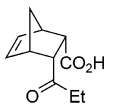
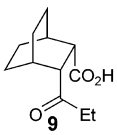
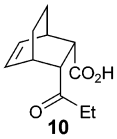
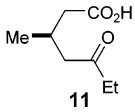
(12) Relative stereochemistry was determined by NOE experiments.

(13) For an excellent review, see: Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063-2192.

(14) This effect has been observed in other reduction manifolds; see: Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415−5421.

Table 2. Substrate Scope



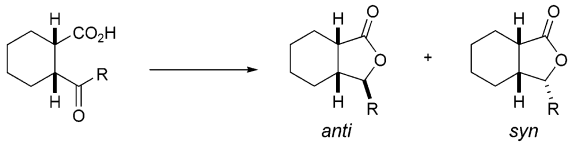
entry	substrate	conditions[a,b]	yield (%)[c]	*anti* : *syn*[d]
1	 **4**	Et_3BHLi	94	79 : 21
		$PhMe_2SiH$	88	10 : 90
2	 **5**	Et_3BHLi	87	81 : 19
		$PhMe_2SiH$	75	7 : 93
3	 **6**	Et_3BHLi	92	79 : 21
		$PhMe_2SiH$	82	8 : 92
4	 **7**	Et_3BHLi	88	75 : 25
		$PhMe_2SiH$	87	5 : >95
5	 **8**	Et_3BHLi	83	53 :47
		$PhMe_2SiH$	82	5 : >95
6	 **9**	Et_3BHLi	90	62 : 38
		$PhMe_2SiH$	94	5 : >95
7	 **10**	Et_3BHLi	87	47 : 53
		$PhMe_2SiH$	91	5 : >95
8	 **11**	Et_3BHLi	77	55 : 45
		$PhMe_2SiH$	NR	--

[a] Reaction conducted in the presence of 2.4 equiv of Et_3BHLi in THF from −78 °C to ambient temperature for 4 h. [b] Reaction conducted in the presence of 1.2 equiv of $PhMe_2SiH$ in 3:1 CH_2Cl_2/TFA from 0 °C to ambient temperature for 14 h. [c] Isolated yield. [d] Diastereomeric ratios determined by ^1H NMR.

to lithium trialkylborohydride reduction, the product lactones are isolated in good yields but the selectivity is eroded with the exception of substrate **7** (entries 4−7). Finally, submission of the acyclic δ-keto acid **11** to silane reduction fails to yield any reduced product, while Super-Hydride affords the product δ-lactone in good yield slightly favoring the formation of the syn diastereomer (entry 8).

Next, we focused our attention on the effect the ketone substituent may have on the course of the reaction (Table 3). Methyl keto acid **12** provides the corresponding *anti*-lactone when subjected to Super-Hydride in modest yield and selectivity. Silane reduction of **12** efficiently provides

Table 3. Effect of Ketone Substituents

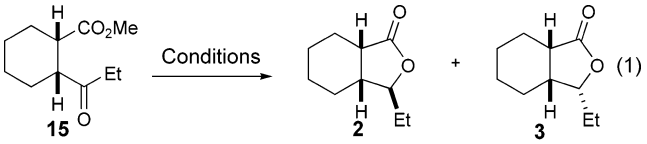


	substrate	yield (%)[b]	anti:syn[c]
Et_3BHLi[a]	Me (**12**)	75	86:14
	Et (**1**)	83	85:15
	*i*Pr (**13**)	85	95:5[d]
	Ph (**14**)	83	>95:5
$PhMe_2SiH$/TFA[a]	Me (**12**)	82	5:>95
	Et (**1**)	90	7:93
	*i*Pr (**13**)	78	8:92[d]
	Ph (**14**)	91	50:50

[a] See Table 2. [b] Isolated yield. [c] Diastereomeric ratios determined by NMR. [d] Diastereomeric ratio determined by GC.

the complementary *syn*-lactone in >95:5 selectivity (entry 1). The branched *iso*-propyl oxo acid **13** effciently affords each respective lactone in excellent yield and high diastereoselectivity (entry 3). Aromatic ketones also participate in the reaction. Phenyl keto acid **14** undergoes a highly selective reduction under Super-Hydride conditions, supplying the *anti*-lactone in superb yield.[10c] Unfortunately, when keto acid **14** is reduced with the $PhMe_2SiH$/TFA system, the product lactone is produced as a 1:1 mixture of diastereomers. We attribute the low selectivity to an epimerization event of the benzylic stereocenter under the acidic reaction conditions that presumably proceeds via an S_N1-type ionization pathway.[15]

To this point, all of the reductions had been performed on keto acid derivatives. Although we reasoned that the carboxylic acid was acting as a directing or activating group in light of the low selectivity and reactivity of acyclic keto acids (vide infra), we could not rule out simple conformational effects being responsible for the observed results. To delineate between these two possibilities, keto ester **15** was subjected to each of the respective reaction conditions (eq 1). Super-Hydride reduction of methyl ester **15** provided an 85% yield of a 75:25 mixture of isomeric lactones favoring *syn*-lactone **3**. Subjection of keto ester **15** to standard reaction conditions provides an 89:11 mixture of lactones favoring *syn* **3**, but in dramatically reduced yield.



The acid functionality plays a fundamental role in the silane reduction process as that of an activator at least.

We have performed some initial calculations[16] that suggest that the acid functionality participates in a hydrogen bond to the ketone in the minimized structure. We suggest that activation of this ketone by TFA protonation proceeds via this conformer allowing hydride to attack from the sterically more accessible front face (A in Figure 1). Correspondingly,

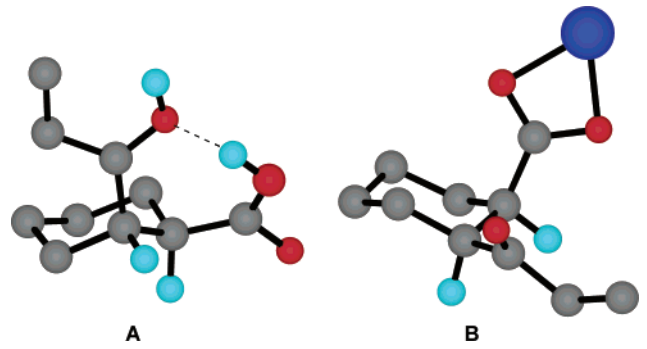


Figure 1.

the formation of the lithium carboxylate under the reaction conditions plays a crucial role in the stereochemical course of hydride delivery when using $LiBHEt_3$, as evidenced by the turnover in selectivity observed with ester substrates. A calculation suggests that structure B in Figure 1 is the lowest energy conformer, which, upon addition of hydride to the sterically more accessible distal face relative to the carboxylate, would afford the observed major diastereomer. However, we caution that this conclusion should be considered tenuous at best since the minimized structure is only about 0.7 kcal/mol more stable than a structure involving rotation about the cyclohexyl/ketone carbonyl bond, which exposes the other diastereoface to attack. This small difference in energy may be responsible for the modest selectivities we observe in many of these reactions.

In conclusion, we have identified a set of complementary reducing conditions to afford either diastereomer of trisubstituted lactone starting from the γ-keto acids bearing cyclic backbones. We observe increased selectivity with increasing steric bulk on the ketone. We further note that the carboxylic acid functionality is a key element of this reaction, controlling facial selectivity in Et_3BHLi reductions and affecting reactivity in silane reductions.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) See ref 10c. (b) For similar observations in the context of Mitsunobu displacements, see: Hillier, M. C.; Desrosiers, J.-N.; Marcoux, J.-F.; Grabowski, E. J. J. *Org. Lett.* **2004**, *6*, 573−576.

(16) Geometry optimizations were performed at the PM3 level (Spartan, Wavefunction, Inc., Irvine, CA).