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Diastereoselective Conjugate Additions to π-Allylmolybdenum Complexes: A Stereocontrolled Route to 3,4,5-Trisubstituted γ-Butyrolactones

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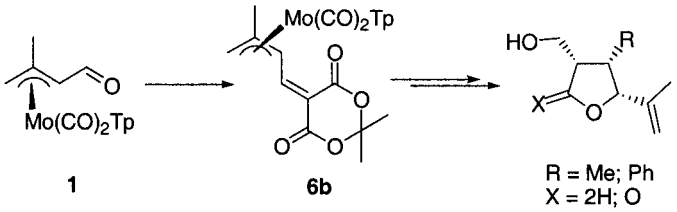
ABSTRACT



π-Allylmolybdenum complex 6b is obtained as a single isomer by Knoevenagel condensation of aldehyde 1 with Meldrum's acid. Conjugate additions of Grignard reagents to Meldrum's acid alkylidene derivative 6b are shown to be completely diastereoselective. Further functional group transformation of the 1,4-adducts, followed by demetalation, leads to trisubstituted tetrahydrofurans and γ-butyrolactones. Whereas the synthesis of tetrahydrofurans (X = 2H) is not completely stereoselective, the γ-butyrolactones (X = O) are obtained with good to excellent diastereoselectivities.

Recently we reported on the construction of hydroxylated tetrahydrofurans and γ-butyrolactones via diastereoselective hydroboration or osmylation reactions of organometallic species having an allylic alcohol or, respectively, an α,β-unsaturated ester (**2**) lateral to a π-allylmolybdenum moiety.[1] Here we extend the scope of our work to the stereocontrolled installation of C−C bonds in π-allyl molybdenum complexes via 1,4-additions to lateral α,β-unsaturated esters, en route to tetrahydrofurans and γ-butyrolactones substituted with hydrocarbon groups.

Initially we attempted to perform Michael additions of higher order organocuprates,[2] $R_2(CN)CuLi_2$, to ester **2**,[1,3] but to our surprise, we obtained only the corresponding saturated ester **3** in 77% yield, regardless of the nature of the alkyl substituent in the nucleophile (Scheme 1). The same result was obtained using simple Me_2CuLi. To the best of our knowledge, this is the first example of complete reduction of the C−C double bond of an α,β-unsaturated ester by organocopperlithium reagents.[4] When the reaction was quenched with D_2O, two deuterium atoms were incorporated in product **4**, one in the α position and one in the β position (Scheme 1). This result suggests that a β-copper enolate intermediate is formed in the reaction and is resistant to reductive elimination, being instead protonated at both α and β positions during the workup. When the reaction mixture was treated with MeI prior to aqueous workup, a Me group

(1) Pearson, A. J.; Mesaros, E. F. *Org. Lett.* **2001**, *3*, 2665.

(2) For a recent review on organocuprate structure and reaction mechanism, see: Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750. For a review on higher order organocuprates, see: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. See also: Hareau, G. P−J.; Koiwa M., Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. Lipshutz, B. H. *Tetrahedron Lett.* **1983**, *24*, 127.

(3) Tp = hydridotris(1-pyrazolyl)borate.

(4) Previous reports of reduced *side* products in reactions involving organocuprates explain the results by the ability of the reagents to undergo thermal β-eliminations (i.e., R = Et, *n*-Pr, *n*-Bu, etc.), generating reactive hydride-copper species: Sahlberg, C.; Claesson, A. *J. Org. Chem.* **1984**, *49*, 9, 4120. House, H. O.; DuBose, J. C. *J. Org. Chem.* **1975**, *40*, 788. Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426. For an example of reduction as a *major* pathway in a Me_2CuLi (no β-elimination possible) reaction with an organic bromide, see: Posner, G. H.; Ting, J.-S. *Tetrahedron Lett.* **1974**, 683.

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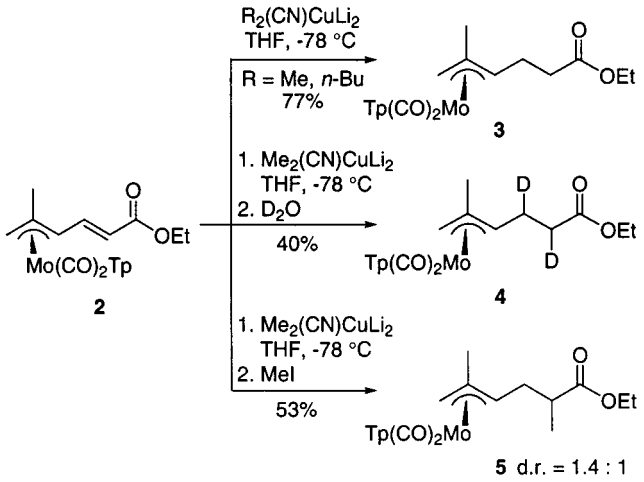
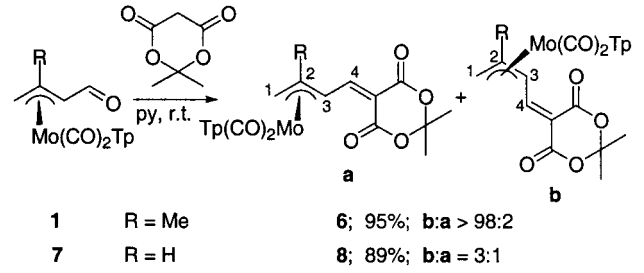
Scheme 1



was attached to the α position, whereas the β position did not react (compound **5**, Scheme 1). Both **4** and **5** were obtained as mixtures of diastereomers, with poor selectivity, rendering these reactions inadequate for synthetic purposes.

At this point we decided to focus our efforts on defining a better Michael acceptor. Therefore, complex **6b** was synthesized by Knoevenagel condensation of aldehyde **1** with Meldrum's acid in pyridine, at room temperature for 6 h.[5] The *syn* π-allylmolybdenum moiety in **1** was converted to an *anti* π-allylmolybdenum system in **6b**, obtained as single product (Scheme 2, R = Me).[6] Stirring **1** in pyridine, at room

Scheme 2

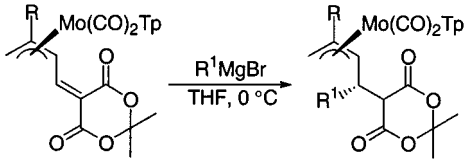


temperature for 6 h, had no effect on the aldehyde stereochemistry, so that the observed inversion in **6b** appears to be a result of a $\pi-\sigma-\pi$ rearrangement occurring either at intermediate stages or in the final product. The confirmation of these hypotheses came from the following experiments. Condensation of **7**[7] with Meldrum's acid gave a mixture of *syn* and *anti* products **8a** and **8b** in a 1:3 ratio (Scheme 2, R = H).[8] Fractional recrystallization provided a mixture of **8b** and **8a** in a 1.5:1 ratio, which was stirred in pyridine for 6 h to give a mixture enriched in **8b** (**8b**:**8a** = 9:1) and then for an additional week to give a mixture of **8b** and **8a** in a ratio greater than 21:1. These findings indicate that condensation of aldehydes **1** and **7** with Meldrum's acid initially gives *syn* products **6a** and **8a**, respectively, which are then converted to their more stable *anti* isomers, **6b** and **8b**, respectively.[9,10] The presence of the Me(2) group in **6** accelerates the equilibration (**8** does not reach the equilibrium within the reaction time, 6 h).

The *syn*/*anti* stereochemistry of **8a** and **8b** was inferred from the ^{1}H NMR vicinal coupling constants of H(3) with H(2) (Scheme 2), and the chemical shift of H(3) in the two isomers.[6] The *anti* configuration of **6b** was confirmed by a NOESY experiment: a cross-peak was present for *anti*-H(1) ↔ H(4) signals, but not for Me(2) ↔ H(4).

Conjugate addition of Grignard reagents to **6b** and **8b** occurred with very good yields and complete diastereoselectivity (Table 1).[5,11] The relative stereochemistry of

Table 1. Diastereoselective 1,4-Addition of Grignard Reagents to **6b** and **8b**



entry	substrate	R	R^1	product	yield (%)
1	**6b**	Me	Me	**9**	95
2	**6b**	Me	Et	**10**	84
3[a]	**6b**	Me	vinyl	**11**	81
4	**6b**	Me	Ph	**12**	96
5[b]	**6b**	Me	allyl	**13**	74[c]
6	**8b**	H	Ph	**14**	97

[a] Grignard reagent was added at −78 °C, and then the reaction mixture was allowed to warm to 0 °C. [b] Reaction was maintained at −78 °C. [c] 51% when reaction was performed at 0 °C.

products **9**−**14** was assigned on the basis of the known mode of attack of the reagent, *anti* to the [Mo(CO)$_2$Tp] moiety,

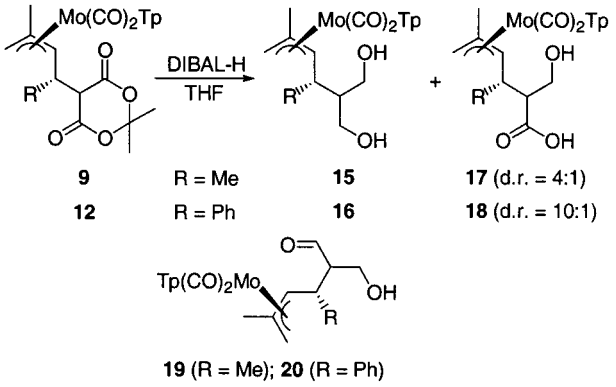
(5) Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151.
(6) Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Payne, S. C.; Semones, M. A.; Liebeskind, L. S. *Organometallics* **1995**, *14*, 4132.
(7) Pearson, A. J.; Neagu, I. B.; Pinkerton, A. A.; Kirschbaum, K.; Hardie, M. J. *Organometallics* **1997**, *16*, 4346.
(8) All diastereomeric ratios reported in this paper are determined by ^{1}H NMR. By ratios of >98:2 we mean that only one isomer was detected.
(9) Although thermal inversion of acyclic (π-allyl)Mo(CO)$_2$Tp complexes and the greater thermodynamic stability of the *anti* isomers versus the *syn* ones are known (ref 6), our results seem to be the first example of a room temperature $\pi-\sigma-\pi$ rearrangement for this type of compound. The role of pyridine in stabilizing the intermediate 16-electron η^1 complex is noteworthy: when a 1:2 mixture of **8a** and **8b** was stirred in Et$_2$O (a poorer donor ligand), no change in ratio was observed in 6 h, and even after 1 week, only a change in ratio to 1:4 was recorded.
(10) *Syn*/*anti* fluxionality has been observed at room temperature for acyclic (π-allyl)Mo(CO)$_2$Tp′ complexes [Tp′ = hydridotris(3,5-dimethyl-1-pyrazolyl)borate]: Chowdhury, S. K.; Nandi, M.; Joshi, V. S.; Sarkar, A. *Organometallics* **1997**, *16*, 1806.
(11) Roush, W. R.; Wada, C. K. *Tetrahedron Lett.* **1994**, *35*, 7351. Larcheveque, M.; Tamagnan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 31. Laabassi, M.; Gree, R. *Tetrahedron Lett.* **1988**, *29*, 611. Donaldson, W. A.; Cushnie C. D.; Guo, S.; Kramer, M. J. *Transition Met. Chem.* **1997**, *22*, 592.

with the substrate in a *s-trans* conformation with respect to the C(3)−C(4) single bond.[1] As expected, with substrates in *anti* configuration, diastereoselectivity was no longer dependent on the Me group at position 2, as opposed to the reactions previously performed on *syn* substrates, where this Me group was essential to shift the conformational equilibrium associated with rotation about the C(3)−C(4) bond toward a *s-trans* conformer.[1,7,12] Thus, addition of PhMgBr to **8b** was also completely diastereoselective (Table 1, entry 6).

To demonstrate potential application of this chemistry to the stereocontrolled synthesis of organic molecules, we explored alternative ways of manipulating the Meldrum's acid moiety in **9**−**14** that will allow for subsequent demetalation.

Typically, this system is hydrolyzed to the corresponding diacid, which is then decarboxylated.[5,11,13] However, only one literature precedent on the reduction of a Meldrum's acid derivative with LAH to a diol was found.[14] After some experimentation we learned that DIBAL-H[15] effects chemoselective reduction, as a function of temperature. Reduction of **9** and **12** at room temperature afforded predominantly diols **15** and **16**, respectively, whereas at −78 °C α-hydroxymethyl acids **17** and **18** were obtained, respectively (Table 2).

Table 2. Results of DIBAL-H Reduction of **9** and **12**



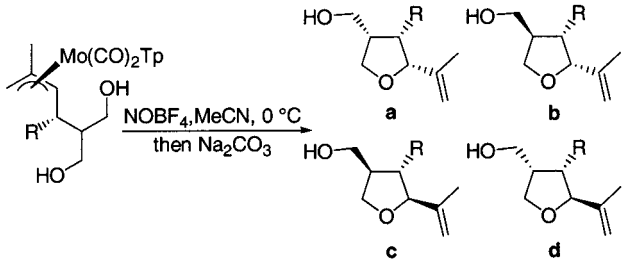
19 (R = Me); **20** (R = Ph)

substrate	R	*T* (°C)	products (yields, %)		
9	Me	rt	**15** (85)	**17** (0)	**19** (7)
9	Me	−78	**15** (2)	**17** (41)	**19** (9)
12	Ph	rt	**16** (84)	**18** (0)	**20** (5)
12	Ph	−78	**16** (2)	**18** (70)	**20** (13)

Residual α-hydroxymethyl aldehydes **19** and **20** were unfortunately present in the reaction mixtures, even when the reduction was performed at room temperature, with a large excess of DIBAL-H.[16] However, the major products were readily separable by chromatography, so that no attempt was made to improve further the chemoselectivity of these reactions. Interestingly, the new chiral center (α position) was generated with good diastereoselectivity in both **17** (4:1) and **18** (10:1). The stereochemistry of this center was not assigned at this stage (see below).

Submitting diols **15** and **16** to the $NOBF_4$ demetalation protocol described earlier[1,17] led in each case to a mixture of all four theoretically possible diastereomers of the substituted tetrahydrofurans **21a**−**d** and **22a**−**d** (Scheme 3),

Scheme 3



15 R = Me **21**; 59 % (67% b.o.r.s.m.); **a**:**b**:**c**:**d** = 10:2:5:1

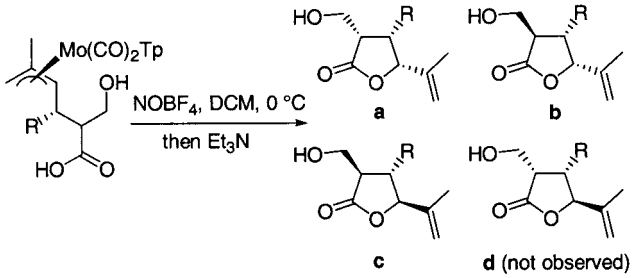
16 R = Ph **22**; 55 % (72% b.o.r.s.m.); **a**:**b**:**c**:**d** = 1:1:2:3

(b.o.r.s.m. = based on reacted starting material)

with poor diastereoselectivity. While both configurations were expected for the center bearing the hydroxymethyl group, as both hydroxyl groups in **15** and **16** can act as nucleophiles, the epimerization of the isopropenyl-bearing center was somewhat surprising, especially in the light of previous results.[1,17,18]

Demetalation of complexes **17** and **18** by an earlier developed lactonization procedure[19] resulted in γ-butyrolactones **23a**−**c** and **24a**−**c**, respectively, with good and excellent diastereoselectivity (Scheme 4).[20] Compound **17**

Scheme 4



17 R = Me **23**; 44%; **a**:**b**:**c** = 31:1:4

18 R = Ph **24**; 67%; **a**:**b**:**c** = 18:1:1

was used as a 4:1 mixture of diastereomers (Table 2), while **18** was successfully fractionated by column chromatography, and only the major isomer was subjected to demetalation. However, epimerization at the acidic α position occurred in both cases (Scheme 4, see structures **a** and **b**).[21]

(12) Pearson, A. J.; Neagu, I. B. *J. Org. Chem.* **1999**, *64*, 2890.

(13) We did not pursue this route at this time because elevated temperatures needed for decarboxylation are known to cause decomposition of π-allylmolybdenum complexes.

(14) Stephen, A.; Wessely, A. *Monatsh. Chem.* **1967**, *98*, 184.

(15) DIBAL-H gave better yields and selectivities than LAH.

(16) Aldehydes **19** and **20** can be readily reduced with $NaBH_4$ to diols **15** and **16**, respectively.

The "stereochemical leakage" at the γ center (structure **c**) is tentatively attributed to a $\pi-\sigma-\pi$ rearrangement of the [(π-allyl)Mo(CO)(NO)Tp]$^+$ intermediates.[22] This hypothesis would explain why poorer diastereoselectivities are observed for the demetalation of **15** and **16** compared to those of **17** and **18** (a carboxylate anion competes more efficiently with the undesired allyl inversion than does a neutral hydroxyl). Demetalation of **18** in DCM at 0 °C gave a mixture of expected[1] diastereomers **24a**, **24b** and the unexpected one, **24c**, in a ratio (**24a**+**24b**):**24c** of 19:1 (7.5:1 in acetonitrile, Scheme 4).[23]

Assuming that **23a** and **24a** are generated under kinetic control, one is tempted to assign the α-hydroxymethyl group in the major diastereomers of **17** and **18** as *anti* to the R group.

Lactones **23d** and **24d** were not detected in the reaction mixtures, presumably because the epimerization of **23c** (or **24c**) is thermodynamically disfavored. Semiempirical calculations (Spartan AM1)[24] showed **24d** to be 2 kcal/mol less stable than **24c** (with both epimers in their lowest energy conformations). The relative stereochemistries of the chiral centers in compounds **21**−**24** were assigned on the basis of the vicinal coupling constants of the protons geminal with hydroxymethyl, methyl (or phenyl), and isopropenyl groups and confirmed by NOE Diff. and NOESY experiments (illustrated for **24a**−**c** in Figure 1).[25,26]

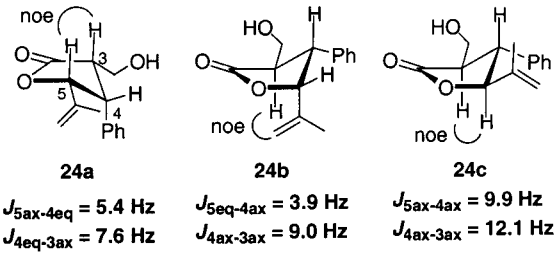


Figure 1. Diagnostic ^{1}H NMR (600 MHz) coupling constants and NOESY cross-peaks in **24a**−**c**, showing the relative configuration for the ring substituents.

The major lactones **23a** and **24a** were isolated by chromatography. *Cis* substituted γ-butyrolactones, known to be difficult to construct selectively,[27] are the core unit of a number of important natural products.[28]

In conclusion, 1,4-additions on 5-alkylidene-1,3-dioxane-4,6-diones attached to a π-allylmolybdenum system are completely diastereoselective. The resulting adducts are converted to γ-butyrolactones with good to excellent diastereoselectivity.

Acknowledgment. We thank the National Institute of General Medical Sciences, National Institutes of Health (GM49221), and Case Western Reserve University for financial support and Dr. Dale Ray of Case Western Reserve University for the NOE experiments.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H NMR and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Lin, S.-H.; Lush, S.-F.; Cheng, W.-J.; Lee, G.-H.; Peng, S.-M.; Liao, Y.-L.; Wang, S.-L.; Liu, R.-S. *Organometallics* **1994**, *13*, 1711.

(18) For a review on tetrahydrofuran synthesis, see: Elliot, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303.

(19) Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446.

(20) For recent examples of (π-allyl)W(CO)$_2$Cp and (π-allyl) Mo(CO)$_2$Cp complexes in γ-butyrolactone synthesis, see: Lin, Y.-L.; Cheng, M.-H.; Chen, W.-C.; Peng, S.-M.; Wang, S.-L.; Kuo, H.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 1781. Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127. Cp = cyclopentadienyl.

(21) Probably catalyzed by Et$_3$N, together with carbonyl activation by coordination to Mo present in side products.

(22) Villanueva, L. A.; Ward, Y. D.; Lachicotte, R.; Liebeskind, L. S. *Organometallics* **1996**, *15*, 4190.

(23) Acetonitrile is a better donor ligand than DCM, so that it stabilizes more efficiently the intermediate η^1 complex required for a competing $\pi-\sigma-\pi$ rearrangement. An improved (**24a**+**24b**):**24c** ratio (15:1) was obtained in acetonitrile as well, at −40 °C.

(24) Hehre, W. J.; Huang, W. W. *Chemistry with Computation*: *An Introduction to SPARTAN*; Wavefunction, Inc.: Irvine, CA, 1995.

(25) Fuchs, B.In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; John Wiley & Sons: New York, 1978; Vol. 10, p 1. Andersson, T.; Berova, N.; Nakanishi, K.; Carter, G. T. *Org. Lett.* **2000**, *2*, 919.

(26) The structures represented in Figure 1 are the calculated minimum energy conformers (Spartan AM1), and they correlate well with the measured ^{1}H NMR coupling constants. These conformations were more stable than the ones with an inverted ring: 4.5 kcal/mol for **24a**, 1 kcal/mol for **24b**, and 2.7 kcal/mol for **24c**.

(27) Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 7097.

(28) Martín, T.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 2503. Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. T. *J. Nat. Prod.* **1999**, *62*, 1565. Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848. Chenevert, R.; Rose, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 2827.