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Synthesis of Bicyclic α-Methylene Butyrolactones via Alkoxycarbonylation of Molybdenum-Propargyl Compounds

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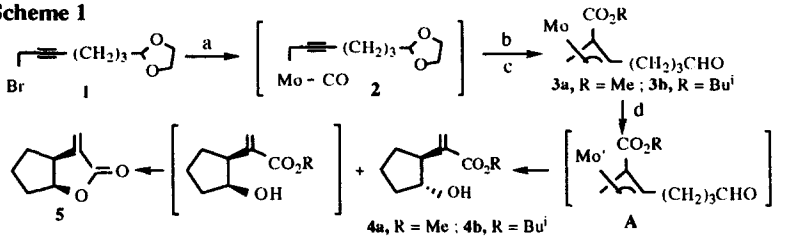
Abstract: Syntheses of various bicyclic α-methylene butyrolactones from functionalized propargyl bromides were carried out in short steps; the overall yields are reasonable. The key step involves alkoxycarbonylation of molybdenum-propargyl compounds.

α-Methylene butyrolactones are important structural units for many natural products especially terpenes that often exhibit biological activity.[1-2] Efficient syntheses of bicyclic and tricyclic α-methylene butyrolactones in various forms are challenging.[3-5] One successful route to bicyclic α-methylene butyrolactones involves intramolecular acid- or metal-mediated annulation of β-ethoxycarbonylallylsilanes and -bromides with tethered aldehydes;[4-5] a drawback of this method is the tedious synthesis of starting β-ethoxycarbonylallylic compounds. Here, we report the utilization of $CpMo(CO)_3Na$ to mediate the synthesis of various fused α-methylene butyrolactones from more readily available bromopropargyl aldehydes.[6]

The overall synthetic route is depicted in Scheme 1. In a typical reaction, treatment of bromopropargyl compound **1** with $CpMo(CO)_3Na$ delivered molybdenum-η^1-propargyl species **2**. We reported previously that transition-metal-η^1-propargyl species underwent alkoxycarbonylation reaction in the presence of Bronsted acid.[7] Subsequent treatment of **2** with p-toluenesulfonic acid catalysts (0.20 equiv.) in ROH (R = Me, Bu^i), followed by hydrolysis, afforded molybdenum-π-allyl species **3a** and **3b** in 70% and 78% yields respectively based on propargyl bromides. To achieve the syntheses of α-methylene-butyrolactones, compounds **3a-3b** were sequentially treated with $NOBF_4$ and MX (MX = NaI, LiCl) in CH_3CN, yielding the derivatives of $CpMo(NO)X(\pi\text{-allyl})$[8] (X = Cl, I) **A** that functions as an allyl anion to induce intramolecular cyclization in the absence of Lewis acid. After 24 hours at appropriate temperatures, workup of the solution gave a mixture of *trans*-cyclopentanol **4a-4b** and *cis*-α-methylene butyrolactones **5** that were further separated on a silica column. The configurations of **4a-4b** and **5** were determined by proton NOE effect, and their ^1H NMR spectral data were identical to those of authentic sample.[3]

Scheme 1



Mo=CpMo(CO)$_2$, Mo'=CpMo(NO)X (a) CpMo(CO)$_3$Na (1.0 equiv), 0 °C, THF, 3 h (b) p-TSA (0.2 equiv.)/ ROH (c) acetone/water/p-TSA (0.2 equiv.) (d) $NOBF_4$ (1.0 equiv)/CH_3CN; MX (2.0 equiv.)

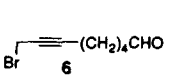
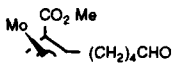
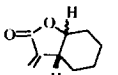
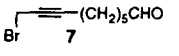
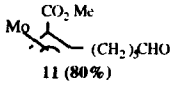
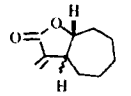
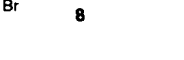
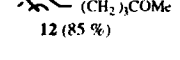
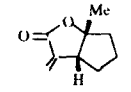
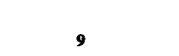
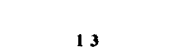
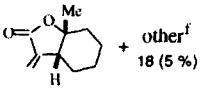
Entry	π-allyl	MX	Temp.	products (isolated Yields)
1	**3a**	NaI	23 °C	**5** (50%), **4a** (12%)
2	**3b**	NaI	23 °C	**5** (39%), **4b** (23%)
3	**3a**	LiCl	23 °C	**5** (13%), **4a** (51%)
4	**3a**	NaI	0 °C	**5** (63%), **4a** (2%)
5	**3a**	LiCl	0 °C	**5** (61%), **4a** (3%)

One unique feature of this method is that two sites can be modified for stereocontrol of the products: (1) the alkoxy group of π-allyl compounds (2) the halide of the CoMo(NO)X core. Scheme 1 presents results based on these modifications. Each reaction was performed at least twice, and the yields in Scheme 1, reflect an average of two runs with a distribution range within 2 %. Regarding alkoxy groups, methoxy **3a** is better than isobutoxy **3b** in the *trans*-stereoselection at 23 °C (entries 1-2). When **3a** is used in the reaction, *trans*-cyclopentanol **4a** is the preferable product (entry 3) in contrast with the NaI case (entry 1) under the same conditions. When the reaction temperature was 0 °C, both LiCl and NaI yielded *cis*-fused lactone **5** exclusively (entries 4-5). This temperature effect reflects a very small difference in the energies of activation for *cis/trans* stereoselection of the primary cyclopentanol products.

As the starting bromopropargyl aldehydes are readily prepared, we expanded the scope of this method to synthesize of α-methylenebutyrolactone fused with varied carbocyclic rings. The results are summarized in Table 1. The η^1-propargyl species generated from CpMo(CO)3Na and **6-9** were directly transformed into π-allyl complexes **10-13** by p-toluenesulfonic acid/CH_3OH. The resulting π-allyl complexes were subsequently treated with $NOBF_4$ and MX at appropriate temperatures to induce intramolecular cyclization, ultimately yielding bicyclic α-methylenebutyrolactone **14-17** in reasonable yields. Entries 1-2 show the aldehyde substrates **6-7** used for syntheses of α-methylenebutyrolactones fused with six- and seven-membered rings **14-15**; *trans*-fused isomers were the major products in both cases. The *trans*-selectivity of **15** is more pronounced at 5 °C (entry 2). Although CpMo(NO)X(π-allyl) failed to react with ketones,[8] intramolecular allylmolybdenum-ketone addition proceeded very smoothly (entries 3-4); both cases favor *cis*-stereoselection when NaI is used. When chloro replaced iodo, a *cis*- and *trans*-isomeric mixture of six-

membered carbocyclic ring **17** was obtained in a 3:2 ratio. In entry 4, the biproduct 2-iodomethyl-8-oxo-non-2-enoic acid methyl ester **18** was isolated in 5% yield together with **17**.

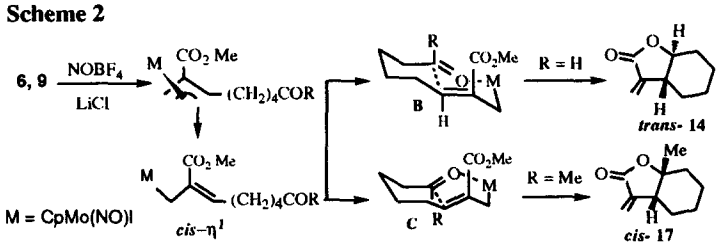
Table 1. Isolated Yields of Mo-π-allyl Compounds and Fused α-Methylenebutyrolactones.

Entry	Substrate[a]	π-Allyl [b,c]	MX/Temp.	Lactones[d,e]
1	 **6**	 **10** (80 %)	NaI / 23 °C	 **14** *cis* 8%; *trans* 55%
2	 **7**	 **11** (80%)	NaI / 23 °C (5 °C)	 **15** *cis* 14%; *trans* 48% (*cis*-6%; *trans* 56%)
3	 **8**	 **12** (85 %)	NaI / 23 °C	 **16** *cis* 70%
4	 **9**	 **13** (88 %)	NaI / 23 °C	 **17** *cis* 62%, *trans* 2 %;
5	**9**	**13**	LiCl / 23 °C	**17** *cis* 38%, *trans* 26%

[a]Equimolar ratios of $CpMo(CO)_3Na$ and propargyl bromide were used. [b]These organometallic compounds were purified on a silica column [c]Isolated yields after chromatographic purification. [d]Isolated yields after purification with preparative silica TLC. [e]Yields are estimated based on molybdenum-allyl compounds. [f]This byproduct was identified as 2-iodomethyl-8-oxo-non-2-enoic acid methyl ester.

Scheme 2 rationalizes the stereochemical course for the [4,3,0] fused lactones **14** and **17** that follow *trans*- and *cis*-stereoselections respectively. Complexes of CpMo(NO)X(π-allyl) are prone to π -> σ dissociation[8] to leave a vacant site that coordinates organic carbonyls to form a chairlike conformation represented by **B**. This process tend to yield a *trans*-fused isomer of **14** consistent with our observation. When a ketone replaces the aldehyde as in the case of **9**, the methyl group (R = Me) of **B** suffers 1,3-diaxial interactions with CO_2Me; the resulting product **17** is expected to follow *cis* -selectivity via a boatlike transition structure **C**. Such bicyclic transition structures account not only for the stereochemistries of **14** and **17** but also for those of bicyclic fused lactones **5**, **15** and **16**.

Scheme 2



In summary, we have developed an efficient method for synthesis of fused α-methylenebutyrolactones based on bromopropargyl aldehydes; the key step involves alkoxycarbonylation of an molybdenum propargyl intermediate. Stereochemical courses of allylmolybdenum-carbonyl addition can be rationalized based on bicyclic transition states.

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