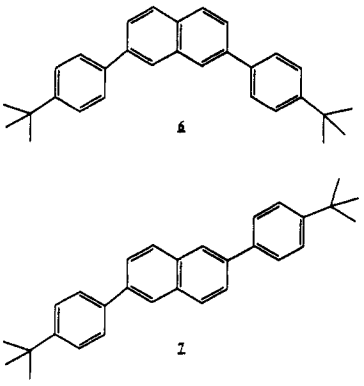

acceleration, by binding a bent transition state more readily than it binds a linear starting material. If this can be achieved, the resulting catalysis will put cyclodextrin dimers even more clearly into close resemblance to antibodies.

Acknowledgment. Support of this work by the NIH and the Office of Naval Research is gratefully acknowledged.

Synthesis and Reactions of Enantiomerically Pure Molybdenum π-Complexes of 2*H*-Pyran. A General Approach to the Enantiospecific Synthesis of *cis*-2,5-Disubstituted 5,6-Dihydro-2*H*-pyrans and *cis*-2,6-Disubstituted Tetrahydropyrans

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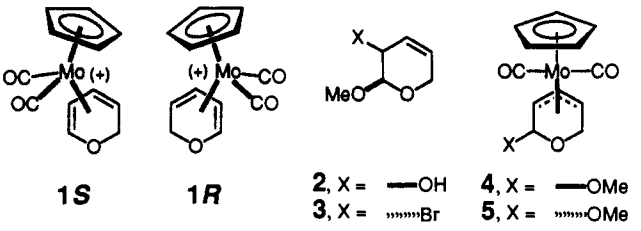
Although transition-metal π-complexes of unsaturated hydrocarbons have been investigated extensively for their applications to organic synthesis, there have been surprisingly few studies of the synthetic potential of isolated transition-metal π-complexes of unsaturated heterocycles.[2-6] Transient palladium species have been utilized in a variety of carbohydrate synthesis applications.[7-13] We describe herein the enantiospecific synthesis of both enantiomers of (η^5-cyclopentadienyl)(dicarbonyl)(η^4-2*H*-pyran)molybdenum tetrafluoroborate (**1S** and **1R**)[14] from D- and L-arabinose, respectively, and the use of these reactive electrophiles in an enantiospecific synthesis of *cis*-2,6-disubstituted tetrahydropyrans and *cis*-2,5-disubstituted 5,6-dihydro-2*H*-pyrans.



1S **1R** **2**, X = —OH **3**, X = ···Br **4**, X = —OMe **5**, X = ···OMe

(5*S*,6*R*)-5-Hydroxy-6-methoxy-5,6-dihydro-2*H*-pyran (**2**), readily available on a large scale from D-arabinose,[15] was converted into the allylic bromide **3** on reaction with $PPh_3/CBr_4/R_4NBr$ (92% yield, four isomeric allylic bromides formed, 91% selectivity for **3**). Following precedent established by Faller and Pearson,[16,17] **3** was converted into (η^5-cyclopentadienyl)(dicarbonyl)-[(2*R*,3*R*)-(3,4,5-η)-2-methoxy-5,6-dihydro-2*H*-pyran-5-yl]molybdenum (**4**) in 72% yield by treatment with $Mo(CH_3CN)_3(CO)_3$ in acetonitrile followed by LiC_5H_5. Treatment of **4** with HBF_4 in diethyl ether led to a low yield of the desired cation **1S**; however, prior epimerization of **4** to the exo isomer **5** (cat. *p*-TSA, CH_2Cl_2, MeOH) followed by ionization with HBF_4 in ether gave **1S** in 88% yield.[18] The enantiomeric molybdenum complex **1R** was prepared in an identical fashion from L-arabinose.

The enantiomerically pure cationic molybdenum complexes **1S** and **1R**, although stable and handled without special precautions, were potent electrophiles and reacted with a wide range of nucleophiles exclusively at the terminus of the coordinated diene adjacent to the oxygen (Table I). Nuclear Overhauser enhancement experiments allowed assignment of nucleophile stereochemistry as anti to the metal. The range of carbon nucleophiles that participated in efficient reaction is particularly noteworthy. In addition to high-yield carbon–carbon bond formation with a stabilized carbanion such as sodio malonate, good yields of products were obtained with unstabilized enolates of simple esters and keto imines and from simple organometallics such as Grignard reagents and lithium organometallics. All three levels of carbon hybridization were accommodated in the nucleophilic addition. The products (**6**) were formed with a minimum of 96% enantiomeric excess.[19]

The value of the enantiomerically pure molybdenum cations **1S** and **1R** in enantiospecific synthesis was demonstrated in two ways. The preparation of both enantiomers of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**7**) is shown in Scheme I, the *S*,*S* isomer being a component of the scent gland secretion of *Viverra civetta*.[9,20-29] Allyl molybdenum complex **6b** (Table I, entry 2) was converted into cationic diene complex **8**, which underwent high-yield addition of $LiCH_2COOMe$ leading to formation of the cis-disubstituted molybdenum allyl **9a**. After hydrolysis of the methyl ester **9a** to the carboxylic acid **9b**, demetalation produced an approximate 1:1 mixture of olefin re-

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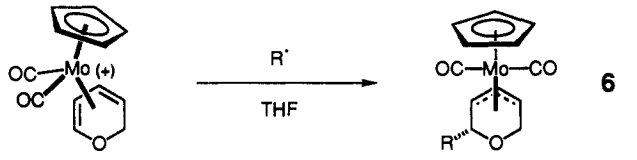
Table I. Reaction of (η^5-Cyclopentadienyl)(dicarbonyl)(η^4-2*H*-pyran)molybdenum Tetrafluoroborate with Nucleophiles[a]



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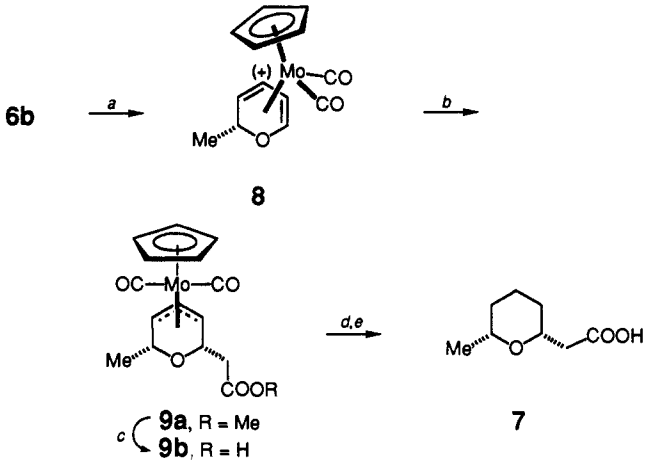
entry	R^-	compd	R	yield, %
1	$LiBDEt_3$	**6a**	D	62
2	MeLi	**6b**	Me	56
3	MeMgI	**6b**	Me	80
4	p-$CH_3C_6H_4MgBr$	**6c**	p-tolyl	82
5	$NaCH(COOEt)_2$	**6d**	$CH(COOEt)_2$	90
6	$LiCH_2COOMe$	**6e**	CH_2COOMe	76
7	$LiCH_2(C{=}NC_6H_{11})CH_3$	**6f**	CH_2COCH_3[b]	68
8	$CH_2{=}CHMgBr$	**6g**	$CH{=}CH_2$	64
9	$C_4H_9C{\equiv}CLi$	**6h**	$C{\equiv}CC_4H_9$	66

[a] Reaction conditions: lithium reagents were added at −78 °C and quenched after 15 min; Grignard reagents were added at −78 °C, and the reaction mixture was allowed to warm to 0 °C and then quenched; sodio malonate was added at 0 °C, and the reaction mixture was allowed to warm to room temperature. [b] After hydrolysis of the imine.

Scheme I[a]

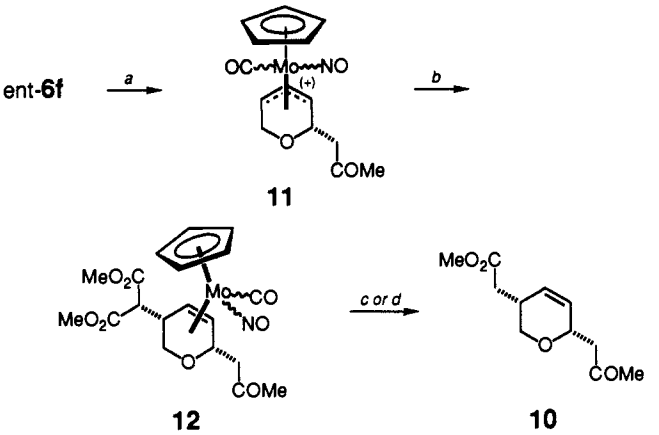


[a] (a) $Ph_3C^+PF_6^-/CH_2Cl_2/0$ °C, 92%; (b) $LiCH_2COOMe$/THF/−78 °C, 92%; (c) KOH/MeOH/H_2O/reflux/15 min, 93%; (d) $CF_3COOH/CHCl_3$/room temperature/14 h, 84%; (e) H_2/PtO_2/EtOAc/room temperature/1.5 h, 90%.

gioisomers (3,4- and 4,5-dehydro **7**). Catalytic hydrogenation then provided (−)-(*R,R*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**7**), $[\alpha]^{25}_{589} = -36.2°$ (*c* 0.87, C_6H_6) in >90% ee.[30] The same sequence of reactions was initiated with **1R** and gave the naturally produced (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (*ent*-**7**) in >90% ee,[30] $[\alpha]^{25}_{589} = +32.2°$ (*c* 0.81, C_6H_6) {lit.[21] $[\alpha]^{22}_D = +31.97°$ (*c* 1.2, C_6H_6)}.

Both enantiomers of methyl [2-(2-oxopropyl)-5,6-dihydro-2*H*-pyran-5-yl]acetate (**10**), a compound of demonstrated utility in the enantiospecific synthesis of monic acid derivatives,[31] were prepared from the respective enantiomers of the acetonyl derivative **6f** (Table I, entry 7) as shown in Scheme II for the 2*S*,5*R* isomer. For example, *ent*-**6f** was converted into the cationic molybdenum nitrosyl allyl **11** which was formed as a mixture of diastereomers epimeric at molybdenum.[16,17,32] The crude mixture reacted with

Scheme II[a]



[a] (a) $NO^+BF_4^-/CH_3CN/-20$ °C; (b) $NaCH(COOMe)_2$/THF/−30 to 0 °C, 63% overall; (c) DMSO/NaCl/H_2O/170 °C/3 h, 60%; (d) $Ce(NH_4)_3(NO_3)_6$/NaOAc/acetone/0 °C/2 h, 99%, then 4-aminothiophenol/Cs_2CO_3/DMF/80 °C/15 min, 75%.

sodio malonate, providing a diastereomeric mixture of olefin complexes **12**.[33] Subsequent demetalation and decarbomethoxylation could be conducted thermally in one step (DMSO containing NaCl and H_2O, 170 °C), providing **10** in 60% yield, >96% ee,[19] $[\alpha]^{25}_{589} = -70.0°$ (*c* 0.36, $CHCl_3$) {lit.[31] $[\alpha]^{18}_D = -65.4°$ (*c* 0.21, $CHCl_3$)}. Alternatively, product **10** could also be obtained stepwise by demetalation with $Ce(NH_4)_3(NO_3)_6$/NaOAc (quantitative) followed by decarbomethoxylation according to the procedure of Keinan (75%).[34] The other enantiomer of **10** was synthesized accordingly (>96% ee,[19] $[\alpha]^{25}_{589} = +69.7°$ (*c* 0.46, $CHCl_3$)).

In summary, an enantiospecific route to cis-disubstituted dihydro- and tetrahydropyrans has been developed. The ready availability of both enantiomers of (η^5-cyclopentadienyl)(dicarbonyl)(η^4-2*H*-pyran)molybdenum tetrafluoroborate (**1**) and the broad range of nucleophiles that react with **1** should allow concise and enantiospecific synthetic routes to various substituted dihydro- and tetrahydropyrans. Full details of the current study will be published shortly.

Acknowledgment. This investigation was supported by Grant No. GM43107, awarded by the Institute of General Medical Sciences, DHHS. We acknowledge the use of a VG-S mass spectrometer purchased through funding from the National Institutes of Health, S10-RR-02478, and 300-MHz and 360-MHz NMR instruments purchased through funding from the National Science Foundation, NSF CHE-85-16614 and NSF CHE-82-06103, respectively.

Supplementary Material Available: Full synthetic details and spectroscopic and analytical characterization of all compounds, details of the data collection and crystal structure solution for **1S**, and listings of atomic coordinates, thermal parameters, and bond distance and angle data for **1S** (32 pages); observed and calculated structure factors for **1S** (6 pages). Ordering information is given on any current masthead page.

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