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PREPARATIONS OF BICYCLICLACTOLS FROM ALLYL AND/OR HOMOALLYL PROPARGYL ACETAL-COBALT COMPLEXES AND ITS APPLICATION TO THE FORMAL SYNTHESIS OF (±) LOGANINE

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Abstract : *3-oxa-2-alkoxy bicyclo [3,3,0]-oct-5-en-7-ones and 3-oxa-2-alkoxy bicyclo [4,3,0]-non-5-en-7-ones were efficiently prepared from the corresponding bis(allyl or homoallyl)propargyl acetal-cobalt complexes in the presence of trimethylamine N-oxide. This methodology was successfully applied to the formal synthesis of* (±) *loganine.*

Recent advances in Pauson-Khand reaction have revealed the latent synthetic applicability and expanded the limit of this powerful cyclization. For example, finding of new promoters, such as silica gel,[1] tertiaryamine N-oxide[2a,b] and DMSO[3] and concomitant development of design of new synthetic strategies have made this cyclization one of the primary choices among synthetic tools.

Many examples of the preparation of carbobicyclic,[4] oxabicyclic[5] and azabicyclic[6] systems from the corresponding carbon, oxygen and nitrogen bridged enyne substrates *via* the Pauson-Khand reaction and their applications to the natural products synthesis have appeared in the literature. Until very recently, however, the preparations of higher oxidation state analogs, such as bicyclic-lactones and/or lactams, were hampered by the deflection of the reaction pathway with electron deficient alkynes and/or alkenes. The diene products were obtained instead of cyclopentenones under the usual thermal condition. Lately Krafft and coworkers[8] forced the cyclization with the electron deficient alkynes by using N-methylmorpholine-N-oxide as a promoter with limited degree of success.

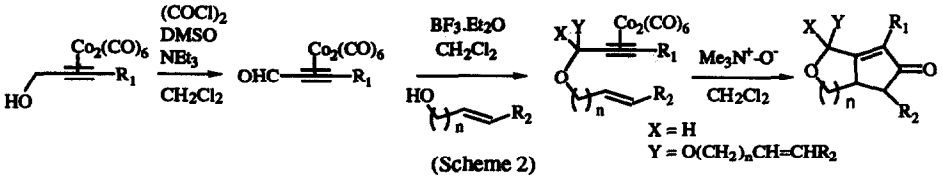
a) X, Y = O
b) X = H, Y = O(CH2)nCH=CHR2

(Scheme 1)

Since the products of higher oxidation state, such as bicyclic lactones (**2a**) and lactols (**2b**), can be directly served as pivotal intermediates for the biologically active natural products,[9] we tried to devise a rather general synthetic route to the higher oxidation state products *via* the alkylated lactol analogs, which can be obtained relatively easily[2a,5c] and oxidized to the higher oxidation state, if necessary.

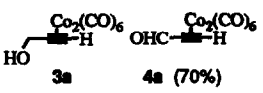
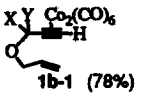
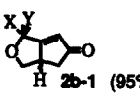
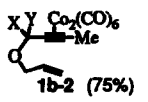
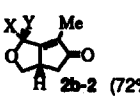
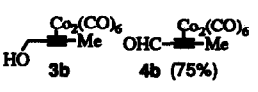
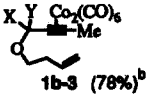
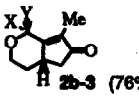
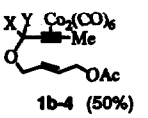
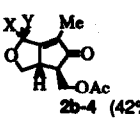
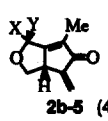
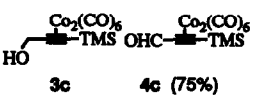
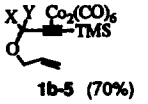
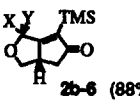
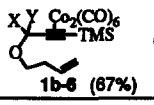
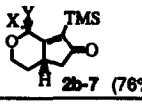
Our synthetic route starting from the easily obtained propargyl alcohol-cobalt complexes (**3**) included

three main features, such as a facile oxidation of propargyl alcohol-cobalt complexes,[10] an acetallization of the resultant propargyl aldehyde-cobalt complexes (4) and amine N-oxide promoted cyclization (Scheme 2). The oxidations of propargyl alcohol-cobalt complexes to aldehydes were succesfully carried out under the condition described by Swern.[11a] This oxidation proceeded uneventfully for the most of the alcohol-cobalt complexes in good to exellent yield. One notable thing in this reaction is that the oxidation of a terminally unsubstituted propargylic alcohol-cobalt complex (3a) produced a propargyl aldehyde-cobalt complex (4a), which is difficult to obtain by usual ways,[11b] in 70% yield. Since carbonyl on cobalt are tolerant to various nucleophiles,[12] this can be used as a surrogated propargyl aldehyde. The acetallization of the propargylic aldehyde-cobalt complexs were best effected with excess (5eq) of allyl and/or homoallyl alcohols in the presence of borontrifluoride etherate (50-78% yield) in dichloromethane or in benzene. This two step sequence provided a general route to allyl and/or homoallyl propargyl acetal-cobalt complexes in a wide range of substrates, especially good for the low molecular weight propargyl aldehydes.



(Scheme 2)

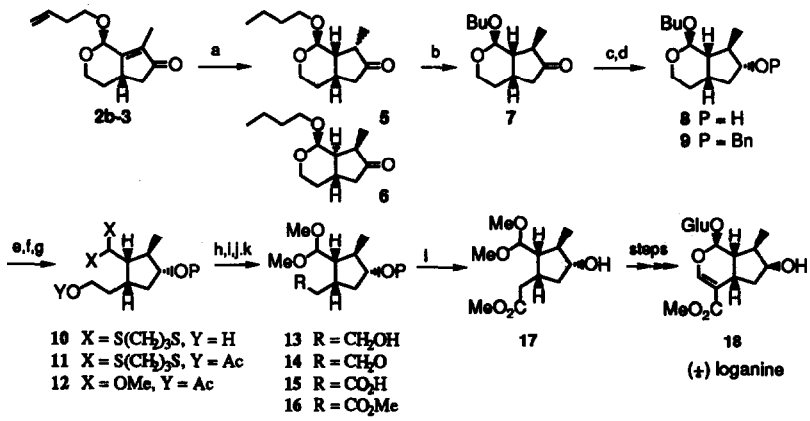
Table 1. Examples of the Three Steps Operations to Bicyclolactols

entry	compounds 3	compounds 4	compounds 1b [a]	compounds 2b
1			 1b-1 (78%)	 2b-1 (95%, α:β = 1:2) X = H Y = $OCH_2CH=CH_2$
2			 1b-2 (75%)	 2b-2 (72%) X = H Y = $OCH_2CH=CH_2$
3	 3b	4b (75%)	 1b-3 (78%)[b]	 2b-3 (76%, α:β = 1:14) X = H Y = $O(CH_2)_2CH=CH_2$
4			 1b-4 (50%)	 2b-4 (42%)  2b-5 (43%) X = H Y = $OCH_2CH=CHCH_2OAc$
5	 3c	4c (75%)	 1b-5 (70%)	 2b-6 (88%) X = H Y = $OCH_2CH=CH_2$
6			 1b-6 (67%)	 2b-7 (76%) X = H Y = $O(CH_2)_2CH=CH_2$

a. BF_3 etherate/CH_2Cl_2, -78°C, b. BF_3 etherate/benzene, -78°C

Finally treatment of complexes (**1b**) in dichloromethane with trimethylamine N-oxide[13] produced the desired cyclopentenones (**2b**) in excellent yields with high diastereoselectivities (Table1). Diastereoselectivities are unusually high compared to that of carbacyclic analogs and simply reflect the size of the substituents on the propargyl group (TMS>Me>H). Homoallyl analogs (entry 3 and 6) are equally effective to allyl analogs to build [5.6] fused bicyclc systems. The complication of products distribution in entry 4 is largely due to the facile elimination of acetate group from the product (**2b-4**) in the presence of trace of acid. Terminally unsubstituted propargyl acetal-cobalt complex (entry 1) proceeded the cyclization efficiently to our pleasant surprise even though the diastereoselectivity is relatively low.

Further manipulation of these intermediates may lead to the synthesis of biologically important natural products, specially iridoids, and we proved this notion by formal systhesis of (±) loganine as described in Scheme 3. Hydrogenation of (**2b-3**) produced ketones as a mixture of (**5**) and (**6**) with 11 to 1 ratio in 97% yield, where major isomer derived by the hydrogenation from convex face. The stereochemistry of the product (**5**)[14] was fully assigned without any ambiguieties by the aid of spectroscopic means, mainly nOe experiments. A compound (**5**) was subjected to the epimerization condition (NaOMe(cat) in MeOH) for the complete conversion into (**7**). Reduction of ketone (**7**) occured stereospecifically to afford an alcohol (**8**), whose stereochemistry should be inversed in the later stage. After protecting of the free hydroxyl group , opening of cyclic acetal was detoured through a thioacetal (**10**) because of the trouble in the direct methyl acetallization. A thioacetal (**11**) was transacetallized efficiently with MeOH by the aid of bis(trifluoroacetate)iodobenzene.[13] Subsequent oxidation of a free alcohol (**13**) to the carboxylic acid (**15**) followed by the treatment of diazomethane gave an intermidiate (**16**). Deprotection of benzyl group by hydrogenolysis produced a compound (**17**), which was converted to (±) loganine previously.[18]



Scheme 3

a) H_2, Pd/C, rt, 12hr, 97%. b) NaOMe(0.13M)/MeOH, 0°C, 2days, 90%. c) $NaBH_4$, MeOH, rt, 0.5hr. d) NaH, BnBr, DMF, rt, 2hr (94% over 2steps). e) HS-$(CH_2)_3$-SH (1.6eq), BF_3Et_2O/CH_2Cl_2, -15°C(1h), 0°C, 5h, 89%. f) Ac_2O, DMAP (cat), TEA, CH_2Cl_2, rt, 30min, 100%.[15] i) NMO, TPAP (cat), CH_2Cl_2, 4A molecular sieves, rt, 2h[16] j) $KMnO_4$, ^tBuOH-$KHPO_4$ buffer, 0°C, 2min.[17] k) CH_2N_2, ether (71% over 3steps). l) H_2, Pd/C, EtOH, rt, 20hr,100%

In conclusion, we have devised an efficient route to propargyl acetal-cobalt complexes, even for the low molecular weight homologues, from the propargyl alcohol-cobalt complex, which were converted to bicycliclactols. And we have demonstrated the usefulness of this sequence of reactions by the formal synthesis of (±) loganine. Further application to the natural product systhesis will be reported in due course.

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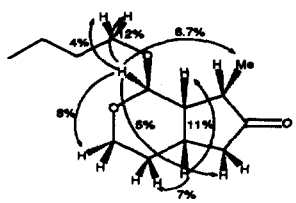
13. TMANO should be dried carefully for the maximum yield of the cyclization. We have removed water from TMANO azeotropically with benzene then sublimed (150 C/10^{-1} torr).

14. **Spectral Data for Compound (5)**; ^{1} **H NMR** (300MHz, $CDCl_3$); 0.91 (3H, t, J=7.3Hz), 1.14 (3H, d, J=7.1Hz), 1.23-1.65 (6H. m), 1.83-1.94 (1H, m), 2.14 (1H, dd, J=18.8 and 9.2Hz), 2.29-2.44 (2H, m), 2.59-2.65 (1H, m), 3.35 (1H, dt, J=9.3 and 6.7Hz), 3.55 (1H, ddd, J=11.9, 9.5 and 3.0Hz), 3.78-3.91 (2H, m), 4,28 (1H, d, J=6.5Hz). ^{13} **C NMR** (75MHz, $CDCl_3$); 11.74, 14.10, 19.64, 27.14, 31.38, 32.03, 40.85, 43.46, 47.49, 59.58, 68.33, 99.79, 220.09 **IR** (neat); 1740 cm^{-1}, **HRMS**; m/e calculated for $C_{13}H_{22}O_3$, 226.1563; Observed 226.1567



N.O.E. Experimental Data

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