Transition-Metal-Mediated Dihydropyran Syntheses. *Exo* Selective Hetero Diels−Alder Reactions of Cobaloxime Dienyl Complexes with Aldehydes

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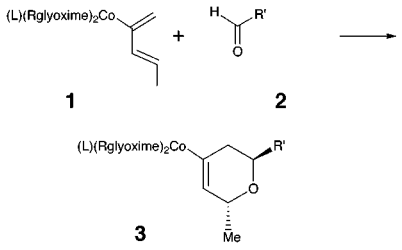
Cobaloxime 1,3-dienyl complex, 2-pyridine bis(dimethylglyoximato)cobalt(III)−(3*E*)-1,3-pentadiene, participates in *exo* selective hetero Diels−Alder reactions with a variety of alkyl and aryl aldehydes. The cobaloxime-substituted cycloadduct products of these reactions can be demetalated to provide diastereomerically pure dihydropyrans with concomitant cobalt recovery. One of the cobaloxime-substituted dihydropyrans has been characterized by X-ray crystallography to prove the *exo* selective nature of the Diels−Alder cycloaddition.

Introduction

Over the last four years, we have prepared cobalt substituted 1,3-dienes (**1**) and examined the rates, regioselectivities, and stereoselectivities of their reactions with dienophiles in Diels−Alder reactions.[1] During this time, Tada and co-workers have reported alternative preparations of some cobaloxime-substituted dienes as well as results of their cycloaddition reactions;[2] other groups have also reported that the alternative strategy of transition-metal substitution in the dienophiles can have a pronounced effect on 4 + 2 cycloaddition diastereoselectivities.[3] The diastereoselectivities of the Diels−Alder reactions of these cobaloxime dienyl complexes **1** are unusual for acyclic dienes in that products arising from *exo* transition states are the major products. We have postulated that this *anti* (*exo*) selectivity is a result of metal ligand set−dienophile steric interactions which disfavor *endo* transition states.

Dihydropyrans are a class of compounds that have proven particularly useful in the synthesis of highly oxygenated acyclic as well as cyclic components of macrocyclic antibiotics[4] and also as precursors in the preparation of C-glycosides.[5] Dihydropyrans are typically prepared via one of two cycloaddition strategies: (1) Lewis acid-catalyzed Diels−Alder reactions of oxygenated dienes with aldehydes developed primarily by Danishefsky's group[6] or (2) inverse electron demand Diels−Alder reactions of α,β-unsaturated acyls with enol ethers.[7,8] This manuscript provides details of our initial studies in dihydropyran synthesis (**3**) utilizing *exo* selective hetero Diels−Alder reactions of cobaloxime dienyl complexes **1** and aldehydes **2**.



Experimental Section

General Methods. For a description of instrumentation and chromatographic adsorbents used see ref 1b. Cobalt chloride hexahydrate used in the preparation of dienyl complexes was purchased from Strem Chemicals and used as received. Dimethylgloxime was purchased from Fischer Scientific and recrystallized from 95% EtOH (12 mL/g) prior to use. Zinc chloride in THF, paraformaldehyde, acetaldehyde,

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benzaldehyde, and trimethylaluminum were purchased from Aldrich Chemicals and used as received. Isobutyraldehyde, nitrobenzaldehyde, and valeraldehyde were purchased from Acros Chemicals and used as received. (3*E*)-1,3-Pentadien-2-yl-(pyridine)bis(dimethylglyoximato)cobalt(III) (**10**),[1b,e] was prepared according to previously described methods. All reactions were performed under an atmosphere of nitrogen unless specified otherwise.

Preparation of [2-Methyl-5,6-dihydro-2*H*-pyran-4-yl]-(pyridine)bis(dimethylglyoximato)cobalt(III) (12a). Diene **10** (200 mg, 0.4598 mmol) was dissolved in dry THF (10 mL) in a flame-dried 25 mL round-bottom flask. Paraformaldehyde (300 mg) and zinc chloride (2.30 mL, 1.15 mmol of a 0.5 M solution in THF) were added. The solution was allowed to stir at 25 °C for 72 h. Ice-cold saturated $NaHCO_3$ was then added. The resulting mixture was extracted with ether, and the combined ether layers were dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was chromatographed on silica (EtOAC) to yield a yellow solid (165 mg, 0.355 mmol, 77%): mp 210 °C dec; ^{1}H NMR ($CDCl_3$): δ 8.60 (d, J = 6.4 Hz, 2H), 7.69 (t, J = 6.0 Hz, 1H), 7.28 (t, J = 6.4 Hz, 2H), 5.06 (s, 1H), 4.14 (m, 1H), 3.68 (m, 1H), 3.49 (td, J = 3.8, 10.8 Hz, 2H), 2.15 (m, 1H), 2.08 (s, 6H), 2.07 (s, 6H), 1.95 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 150.1, 149.8, 137.6, 130.2, 128.3, 125.2, 72.3, 65.8, 33.9, 22.1, 12.2. IR ($CDCl_3$) 3149.3, 2982.0, 2898.3, 1643.7, 1560.0 cm^{-1}. Anal. Calcd for $C_{19}H_{28}CoN_5O_5$: C, 49.04; H, 6.06. Found: C, 48.84; H, 6.07.

Preparation of [*trans*-2-Methyl-6-methyl-5,6-dihydro-2*H*-pyran-4-yl](pyridine)bis(dimethylglyoximato)cobalt-(III) (12b). Diene **10** (300 mg, 0.690 mmol) was dissolved in dry THF (10 mL). Acetaldehyde (0.386 mL, 6.90 mmol) and zinc chloride (4.14 mL, 2.07 mmol of a 0.5 M solution in THF) were added, and the mixture was refluxed for 5 days. The mixture was poured into ice-cold saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified on silica: (1) 1:1 pentane/ether to remove unreacted aldehyde; (2) EtOAC to yield an orange solid (206 mg, 0.430 mmol, 62%); mp 200 °C dec ^{1}H NMR ($CDCl_3$): δ 8.62 (d, J = 6.4 Hz, 2H), 7.69 (t, J = 6.4 Hz, 1H), 7.28 (t, J = 6.6 Hz, 2H), 5.09 (s, 1H), 4.29 (m, 1H), 3.68 (m, 1H), 2.08 (s, 6H), 2.07 (s, 6H), 1.80 (m, 1H), 1.65 (m, 1H), 1.06 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 150.1, 149.7, 149.5, 137.5, 129.2, 125.2, 70.3, 66.3, 40.3, 21.1, 20.6, 12.1. IR ($CDCl_3$): 3154.4, 2983.2, 2901.6, 1646.2, 1559.0 cm^{-1}. Anal. Calcd for $C_{20}H_{30}CoN_5O_5$: C, 50.11; H, 6.31. Found C, 50.24; H, 6.41.

General Procedure for Cycloadditions in the Presence of Sodium Hydride. Diene **10** (200 mg, 0.460 mmol) was dissolved in dry THF (10 mL). NaH (0.0368 g, 1.53 mmol) was added, and the mixture was allowed to stir for 15 min. The aldehyde and zinc chloride in THF were added, and the mixture was refluxed for 5 days. The mixture was poured into ice-cold $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified on silica: (1) 1:1 pentane/ether to remove unreacted aldehyde; (2) EtOAC to yield cycloadduct.

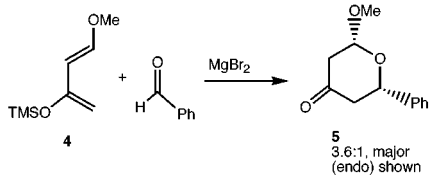
Preparation of *trans*-2-Methyl-6-heptyl-5,6-dihydro-2*H*-pyran (15). Cobaloxime complex **12e** (123 mg, 0.218 mmol) was dissolved in dry THF (10 mL) and treated with $AlMe_3$ (0.218 m l, 0.437 mmol of a 2.0 M solution in hexanes) at 0 °C. The reaction was warmed to 25 °C and stirred for 4 h. Ice−water was added and the mixture was extracted with CH_2Cl_2 to yield a mixture of (pyridine)(dimethylglyoximato)-cobalt(III) methyl and the organic cycloadduct. After removal of the solvent by rotary evaporation, the residue was chromatographed on silica: (1) 4:1 pentane/ether to yield a yellow oil (**15**) (0.030 g, 0.153 mmol, 70%). ^{1}H NMR ($CDCl_3$): δ 5.73 (m, 1H), 5.65 (m, 1H), 4.30 (m, 1H), 3.63 (m, 1H), 1.87 (m, 2H), 0.855 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 131.0, 123.6, 68.5, 67.4, 35.3, 31.9, 31.7, 30.6, 29.3, 25.6, 22.6, 20.0, 14.1. IR ($CDCl_3$) 3155.4, 2958.3, 2929.2, 2858.0, 1653.0, 1569.3 cm^{-1}. EI MS M$^+$ 196(10), 181(10), 163(2), 153(5), 139(8), 112(5), 97-(40), 81(20), 68(100). HREI: m/z calcd for $C_{13}H_{24}O$ 196.1827, found 196.1795. Further elution with EtOAc, followed by solvent removal, yielded (pyr)(dmg)$_2$Co-Me (**18**) (0.075 g, 0.196 mmol, 90%) by ^{1}H NMR comparison to an authentic sample.[1a,b,9]

Preparation of *trans*-2-Methyl-6-phenyl-5,6-dihydro-2*H*-pyran (16). This complex was prepared using the method described above using complex **12f** (124 mg, 0.229 mmol) and $AlMe_3$ (0.229 mL, 0.458 mmol of a 2.0 M solution in hexanes) to yield a yellow oil (**16**) (0.035 g, 0.201 mmol, 88%). ^{1}H NMR ($CDCl_3$): δ 7.29 (m, 5H), 5.87 (m, 1H), 5.75 (m, 1H), 4.72 (dd, J = 5, 7.8 Hz, 1H), 4.46 (m, 1H), 2.28 (m, 2H), 1.32 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 142.5, 131.1, 128.3, 127.4, 127.2 126.3, 123.7, 69.5, 49.1, 29.7, 20.0. IR ($CDCl_3$): 3155.2, 2984.6, 2902.0, 1646.2, 1559.2 cm^{-1}. EI MS M$^+$ 174(20), 159(15), 141-(5), 131(30), 115(15), 107(80), 91(50), 77(30), 68(100). HREI: m/z calcd for $C_{12}H_{14}O$ 174.1045, found 174.1044. Further elution with EtOAc, followed by solvent removal, yielded (pyr)-(dmg)$_2$Co-Me (**18**) (0.064 g, 0.167 mmol, 73%) by ^{1}H NMR comparison to an authentic sample.[1a,b,9]

Preparation of *trans*-2-Methyl-6-(*p*-nitrophenyl)-5,6-dihydro-2*H*-pyran (17). Cobaloxime complex (**12g**) (204 mg, 0.348 mmol) was dissolved in dry THF (15 mL) and treated with $AlMe_3$ (0.348 mL, 0.696 mmol of a 2.0 M solution in hexanes) at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. Ice−water was added, and the mixture was extracted with CH_2Cl_2 to yield a mixture of (pyridine)bis-(dimethylglyoximato)cobalt(III) methyl and the organic cycloadduct. After removal of the solvent by rotary evaporation, the residue was chromatographed on silica: (1) 1:1 pentane/ether to yield a yellow crystalline solid cycloadduct (**17**) (0.063 g, 0.287 mmol, 83%): mp 130 °C dec. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 5.85 (m, 1H), 5.80 (m, 1H), 4.80 (dd, J = 4.5, 8.8 Hz, 1H), 4.49 (m, 1H), 2.25 (m, 2H), 1.30 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 150.1, 147.1, 131.2, 126.8, 123.6, 123.0, 69.7, 68.5, 32.1, 20.0. IR ($CDCl_3$) 3154.5, 2982.2, 2927.8, 2901.9, 1817.0, 1793.1, 1646.3, 1602.4, 1558.9, 1521.8 cm^{-1}. EI MS M$^+$ 219(10), 204-(12), 177(10), 160(15), 149(10), 129(15), 115(10), 89(5), 68(100). HREI: m/z calcd for $C_{12}H_{13}NO_3$ 219.0895, found 219.0890. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 66.53; H, 6.56. Further elution with EtOAC, followed by solvent removal, yielded (pyr)(dmg)$_2$Co-Me (**18**) (0.100 g, 0.261 mmol, 75%) by ^{1}H NMR comparison to an authentic sample.[1a,b,9]

Results and Discussion

Throughout the 1990s, naturally occurring C-glycosides have been the subject of enzymatic, metabolic, and synthetic studies.[10] Many methods for carbon−carbon bond formation at the anomeric carbon have been developed, and C-glycosides are being used as chiral replacements for O-glycosides in situations where a glycosidic linkage not cleavable by hydrolysis is desired.[10] Cycloadditions of aryl and alkyl aldehydes with Danishefsky's diene (**4**) as a hetero Diels−Alder approach to C-glycosides show modest *endo* preferences (**5**) whereas α-alkoxy aldehydes have very high *exo* selectivities.[6b] More highly



4 **5** 3.6:1, major (endo) shown

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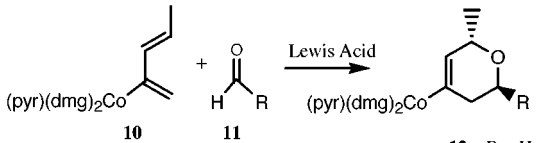
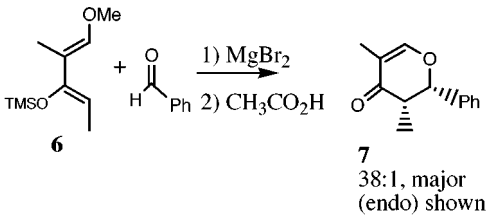
Table 1. Reactions of Aldehydes with 10

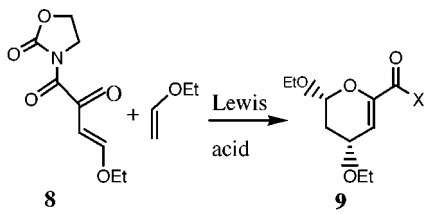


12a, R = H
12b, R = Me
12c, R = iPr
12d, R = *n*-Bu
12e, R = *n*-heptyl
12f, R = Ph
12g, R = *p*-NO_2Ph

entry	Lewis acid	conditions	product	% yield	diastereoselectivity (*exo:endo*/*anti:syn*)
1	$ZnCl_2$	THF/25 °C/72 h	**12a**	77	NA
2	$ZnCl_2$	THF/Δ/120 h	**12b**	62	3:1
3	$ZnCl_2$	THF/Δ/120 h	**12c**	33	4:1
4	$ZnCl_2$	THF/Δ/120 h	**12d**	51	6:1
5	$ZnCl_2$	THF/Δ/120 h	**12e**	48	15:1
6	$ZnCl_2$	THF/Δ/120 h	**12f**	50	10:1
7	$ZnCl_2$	THF/25 °C/96 h	**12g**	73	>20:1
8	$ZnCl_2$	THF/25 °C/96 h/NaH	**12a**	61	NA
9	$ZnCl_2$	THF/Δ/120 h/NaH	**12b**	50	4:1
10	$ZnCl_2$	THF/Δ/120 h/NaH	**12c**	42	3:1
11	$ZnCl_2$	THF/Δ/120 h/NaH	**12d**	45	2:1
12	$ZnCl_2$	THF/Δ/120 h/NaH	**12f**	45	15:1
13	$Zn(OAc)_2$	THF/Δ/3 h	**12a**	45	NA

substituted siloxy dienes (**6**) show a high preference for cis (*endo*) 2,3-disubstituted products (**7**).[6b] Inverse electron demand Diels–Alder reactions that produce pyrans rely either on the use of Lewis acids in conjunction with high pressure for simple acyls[7] or rely on the use of electron-withdrawing groups on the acyls in conjunction with Lewis acids at lower pressure.[8] In general, these reactions show high *endo* preferences leading to *cis*- 2,6- or -2,3-disubstituted dihydropyrans for simple enol ethers. Tietze has very recently reported some *exo* selective cycloadditions using his simple oxazolidine (**8**) activating moiety, but the *exo* selectivitites dropped rapidly when substituted (chiral) oxazolidines were used.[8b]

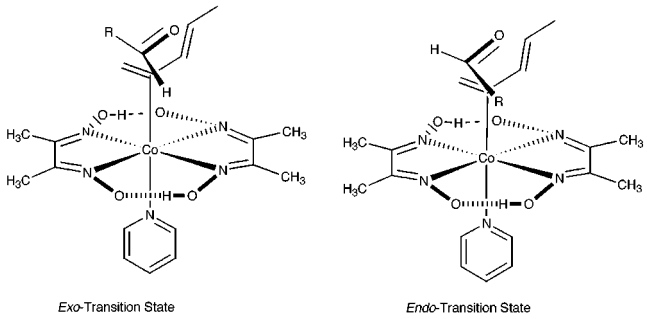




We first surveyed reactions of cobaloxime dienyl complex **10** with benzaldehyde and *p*-nitrobenzaldehyde using a variety of Lewis acids. Since we knew that cobalt–carbon bonds in **10** as well as possible cycloadducts might be sensitive to Lewis acid-mediated decomposition,[1c–e] we wanted to find a Lewis acid capable of catalyzing cycloaddition with a minimum amount of cobalt complex decomposition. Several Lewis acids surveyed proved incapable of catalyzing the desired reaction, and complex **10** was recovered unreacted: (1) $LiBF_4/CH_2Cl_2$ or CH_3CN/25 °C/48–72 h; (2) Et_2AlCl/CH_2Cl_2/-45 °C/4 h; (3) ZnI_2/C_6H_6/25 °C/96 h; (4) $Pd(OAc)_2/CH_2Cl_2$/25 °C/48 h; (5) $MgBr_2$/THF/25 °C/72 h and (6) $Eu(FOD)_3/CH_2Cl_2$/25 °C/48 h. Several other Lewis acids proved too harsh and the cobaloxime was decomposed: BCl_3, BPh_3, BF_3–Et_2O, or Me_2BBr in CH_2Cl_2 at −45 °C over periods from 3 to 24 h. Zinc chloride proved to be the most effective catalyst for the desired hetero Diels–Alder reaction for a variety of aldehydes (**Table 1**, entries 1–6). We have found that formaldehyde, acetaldehyde, isobutyraldehyde, valeraldehyde, caprylaldehyde, benzaldehyde, and *p*-nitrobenzaldehyde all cyclize with **10** using $ZnCl_2$ as a catalyst. The yields of cycloadduct **12** are >50% except in the case of isobutyraldehyde. Formaldehyde and *p*-nitrobenzaldehyde will react at 25 °C whereas the other aldehydes require heating in THF.

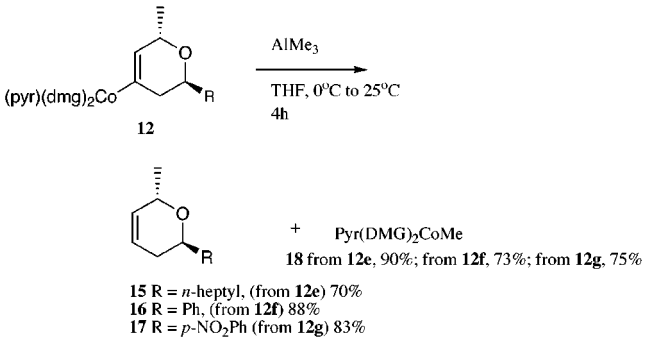
All these reactions proved to be diastereostereoselective, and the *exo* selective nature of these hetero Diels–Alder reactions has now also been proven by X-ray crystallography. The ORTEP of the *p*-nitrobenzaldehyde adduct (**12g**) which has the expected *anti* (*exo*) stereochemistry is provided in the Supporting Information. The cobalt–C(1) bond distance of 1.972(7) Å is typical of cobalt–sp^2 carbon bond lengths we have seen previously (1.954(15)–2.019(6) Å.[1b,c,i] The cobalt-substituted double bond (C_1–C_5) in the dihydropyran (1.329(9) Å) is also within the range of bond lengths (1.293(9)-1.375(12) Å) that we have observed previously for cobalt-substituted alkenes. It should be pointed out that *exo* selective hetero Diels–Alder reactions involving cobaloxime dienyl complexes are *complimentary from a stereochemical standpoint to the known hetero-Diels–Alder reactions outlined above.* We rationalize the preference for products arising from *exo* transition states (**13**) using aldehyde substituent/cobaloxime ligand set steric interactions (**14**) in a manner analogous to what we have previously reported for Diels–Alder reactions of these complexes (Chart 1).[1]

Chart 1



Since we knew that cobaloximes were sensitive to traces of acid, particularly when heated,[1c−e] we tried adding 2 equiv of NaH to **10** (to deprotonate the glyoxime hydroxyls) prior to the addition of aldehydes and Lewis acids (Table 1, entries 7−11). However, the addition of NaH proved to have little effect on the reaction outcomes. When K_2CO_3 was used in place of NaH, the cycloadditions slowed markedly, and essentially 1:1 mixtures of unreacted **10** and cycloadducts **12** were isolated after heating these aldehydes with **10** for 96 h. We also investigated the effect of changing the zinc Lewis acid on reaction outcomes. Zinc hydroxide failed to catalyze the cyclization of **10** with formaldehyde or valeraldehyde. Zinc acetate failed to catalyze the cyclization of **10** with *p*-nitrobenzaldehyde or isobutyraldehyde but did yield some cycloadduct with formaldehyde (Table 1, entry 12). Zinc acetyl acetonate and zinc bis(2,2,6,6-tetramethyl-3,5-heptanedionate) failed to catalyze the cyclization of **10** with *p*-nitrobenzaldehyde.

After settling on zinc chloride as the optimum cycloaddition catalyst, we next turned our attention to demetalation reactions. We placed particular emphasis on discovery of demetalations that yielded dihydropyrans where the diastereoselectivity of the cobaloxime cycloadduct was maintained and the cobaloxime was recovered in a useful form. We had invested considerable effort in developing demetalation reactions that satisfied these criteria for our cobaloxime substituted Diels−Alder cycloadducts,[1] so those known demetalation conditions were applied to these cobaloxime substituted dihydropyrans. As expected, alkyl- and aryl-substituted dihydropyranyl complexes **12e**,**f**,**g** were all cleanly demetalated by $AlMe_3$. This demetalation produced the dihydropyrans **15**−**17** in



good yield and produced the cobaloxime methyl **18** which can be recycled back into the synthesis of **10**.[9] We have discussed the mechanism of this interesting type of demetalation previously.[1h]

In summary, we have now demonstrated that cobaloxime dienyl complexes **10** will participate in *exo* selective hetero Diels−Alder reactions and that the cobaloxime-substituted dihydropyran products **12** can be demetalated to dihydropyrans. The demetalation reactions are noteworthy in that they also yield cobaloximes that can be recycled into the production of **10** in addition to the demetalated organic cycloadduct. Extension of this chemistry to the production of more highly oxygenated pyrans and dihydropyrans will be reported in due course.

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Supporting Information Available: An ORTEP of **12g** and complete characterization data for complexes **12c**−**g** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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