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Organo-Manganese η^2-Auxiliary Directed Reactions: A Diastereoselective Approach to 2,3-Allenols

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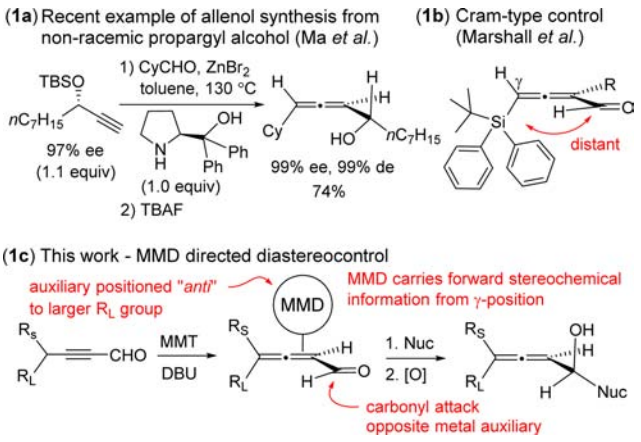
Supporting Information

ABSTRACT: Propargyl aldehydes underwent isomerization to allenyl aldehydes under mildly basic conditions when complexed to an organo-manganese auxiliary using methylcyclopentadienyl manganese tricarbonyl (MMT). This traceless auxiliary magnifies the axial chirality of the allene moiety, allowing for highly diastereoselective additions to the aldehyde carbonyl and subsequent access to an array of 2,3-allenols. Using this strategy, a nitrile-substituted 2,3-allenol was prepared and efficiently converted to Hagen's gland lactone.

Lately, functionalized allenes have taken on increased importance as intermediates in organic synthesis.[1,2] This is particularly true for 2,3-allenyl alcohols, which have been utilized as versatile building blocks in synthesis.[3] Practical methods to synthesize these alcohols are continually emerging and mostly entail the coupling of propargylic reagents with aldehydes and ketones.[4] For example, Ma and co-workers recently developed an enantio- and diastereoselective synthesis of axially chiral α-allenols from TBS-protected chiral propargylic alcohols, aldehydes, and a commercially available prolinol followed by desilylation (Scheme 1a).[5] With a growing number of methods to produce nonracemic allenes,[6] we envisioned that an alternative route to allenyl alcohols could be achieved by exploiting the axial chirality of an allene moiety to control point chirality in the installment of the carbinol center.

Scheme 1. New Approach to 2,3-Allenols



One of the goals in this approach was to increase the diversity of nucleophilic reagents that can be used to construct allenols. The main challenge in this strategy is the control of facial selectivity in the addition of nucleophile to carbonyl. This is a recurring problem with axially chiral motifs such as allenes where the chirality extends over three carbons. In this system, Cram-type control of carbonyl additions is rendered difficult due to the remoteness of the γ-substituents. Indeed, an extensive study by Marshall revealed that only a very bulky γ-organosilyl group (TBDPS) is capable of directing attack of a carbonyl at the α-position (Scheme 1b).[7] However, this approach limits the method to γ-silyl-substituted allenes since the auxiliary is not easily removed.

We reasoned that an η^2-auxiliary might be used to transmit stereochemical information from the remote γ-position of an allenyl aldehyde to a site closer to the center of nucleophilic attack (Scheme 1c). The use of metal auxiliaries has been well established to achieve facial selectivity.[8] We have previously described a neutral η^2-complexed organo-manganese auxiliary for the mild and stereoselective synthesis of functionalized allenes.[9] The inexpensive[10] methylcyclopentadienyl manganese dicarbonyl (MMD) auxiliary, when complexed to allenes, forms air-stable compounds that are easily isolated using silica gel chromatographic methods.[11] Under mild light activation (365 nm), methylcyclopentadienyl manganese tricarbonyl (MMT) is complexed to an alkynyl aldehyde and easily isomerized to MMD-complexed allene. Critical to our design of this system was the known propensity of the MMD auxiliary to complex with an α,β-bond of allenyl aldehydes in an orientation "anti" to larger group (R) at the γ-position (Scheme 1c). Oriented in

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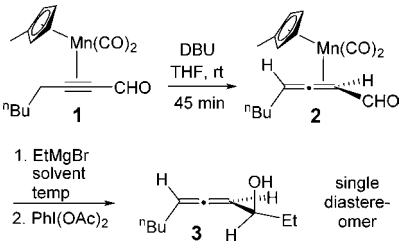
this position, the bulky MMD auxiliary should impede nucleophilic attack on one face of the carbonyl leading to diastereoselective product formation. Importantly, MMD can then be removed under mild oxidative conditions thus serving as a traceless auxiliary.[12] In the present work, we describe our first step toward the stereoselective synthesis of allenols focusing our attention on the issue of diastereocontrol with an application to the concise total synthesis of Hagen's gland lactone.

We began our study with complex **2** which was obtained via treatment of the MMD complexed alkyne isomer **1** with a stoichiometric aount of DBU.[9b,c] It was quickly observed that reactions of complex **2** led to single diastereomer products in diethyl ether even with ethyl magnesium bromide, a relatively small nucleophile. This same outcome was realized under a variety of conditions though lower temperatures led to diminished yields (Table 1). Using our previously reported

Table 1. Optimization of Diastereoselective Grignard Additions with 2



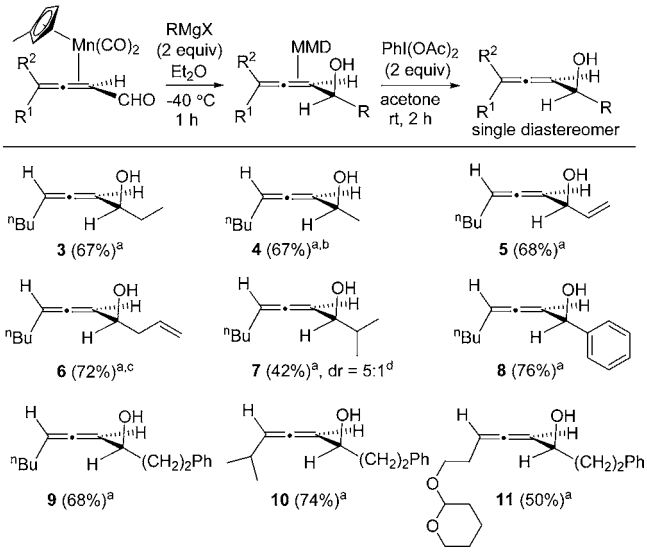
entry	temp (°C)	solvent	EtMgBr (equiv)	time, h	yield of **3**[a] (%)
1	−78	Et_2O	1.0	5	13
2	−78	Et_2O	1.5	5	12
3	−78	Et_2O	2.5	1	46
4	−78	THF	2.5	1	33[b]
5	−40	Et_2O	2.0	1	58
6	−40	Et_2O	2.2	0.65	67
7	0	Et_2O	2.2	1	18

[a]Two-step isolated yield. [b]Diastereoselectivity is 15:1.

mild oxidative MMD removal protocol,[9a] an optimal two-step yield of 67% of compound **3** was realized when more than 2 equiv of Grignard reagent was used at −40 °C (Table 1, entry 6).

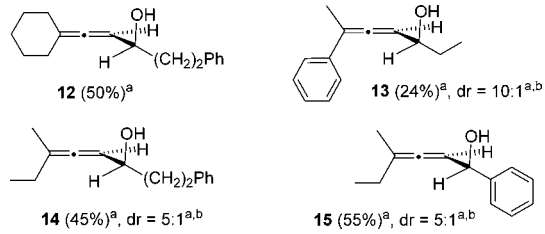
To examine the scope of this allenol synthesis method, several organo-magnesium reagents were reacted with variously substituted MMD-complexed allenals (Schemes 2 and 3). To our delight, single diastereomer products were observed with most nucleophilic reagents ranging in reactivity and molecular size. The two-step yields for γ-monosubstituted substrates were uniformly good except with an isopropyl Grignard reagent (Scheme 2, product **7**) most likely due to its steric bulk. We next sought to extend this method to γ-disubstituted allenyl aldehydes. In these cases, the MMD orientation should be "*anti*" to the larger γ-substituent. Not surprisingly, a substrate containing phenyl and methyl substituents led to relatively high diastereoselectivity (Scheme 3, product **13**). Presumably, the MMD auxiliary preferred to assume a position *anti* to the phenyl group in this case. However, we were surprised to observe a 5:1 diastereoselectivity in the present reaction with an allenyl aldehyde substrate containing γ-methyl and ethyl substituents (leading to product **14**). This auxiliary appears to be sensitive to even relatively minor steric differences.

Scheme 2. Access to Disubstituted Allenols



[a]Two-step isolated yields; only a single diastereomer was produced unless indicated otherwise. [b]Allenol **4** was also obtained using MeLi. [c]Allenol **6** was also obtained using an allyl zinc reagent. [d]All diastereomeric ratios were determined by ^{1}H NMR.

Scheme 3. Access to Trisubstituted Allenols



[a]Two-step isolated yields. [b]All diastereomeric ratios were determined by ^{1}H NMR

Additionally, we note that this protocol tolerates a variety of nucleophilic Zn and Li reagents. For example, the Barbier allylation of complex **2** to afford allenol **6** proved highly selective. Importantly, this approach further allowed us to construct an allenol with a functionalized nucleophile such as an alkyl nitrile. Initially, the acetonitrile anion[13] was produced using *n*-BuLi (at −78 °C in THF) and then reacted with complex **2** followed by MMD removal.These conditions produced adduct **16** as a single diastereomer though in rather poor 2-step yields (40%). A higher yield was observed when the acetonitrile anion was generated via metal halogen exchange between α-iodoacetonitrile and isopropylmagnesium bromide (Scheme 4).

We are intrigued by the unique potential of functionalized 2,3-allenols to serve as efficient building blocks in natural product synthesis. With access to allenol **16**, we endeavored to develop an exceptionally short and diastereoselective synthesis of wasp-derived, Hagen's gland lactone **19**.[14] Although nearly a dozen total syntheses of **19** have been reported, the majority of these are chiron-based approaches often involving the use of less accessible starting materials, protecting groups in otherwise lengthy and poorly diastereoselective routes.[15] Our own synthesis began with a stereospecific cyclization[16] of allenol **16** in the presence of $AgNO_3$ to form 2,5-dihydrofuran **17**

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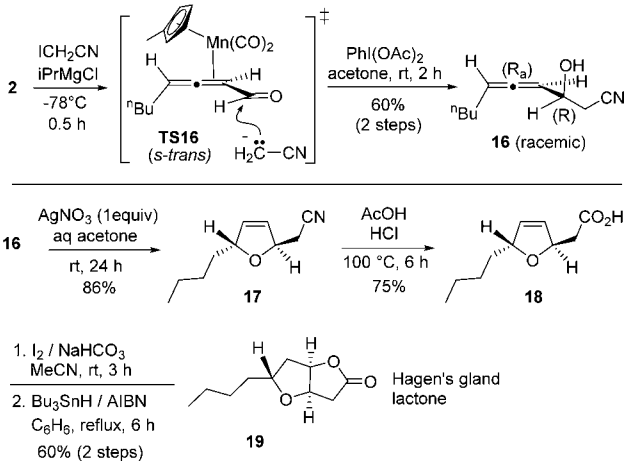
Scheme 4. Acetonitrile Addition and Synthesis of Hagen's Gland Lactone



which, upon acid-catalyzed hydrolysis of the nitrile group, delivered a carboxylic acid **18** derivative in decent yield (Scheme 4). The latter was well poised for iodolactonization which was affected by $I_2/NaHCO_3$ in acetonitrile. Subsequent reductive deiodination under Bu_3SnH/AIBN conditions afforded Hagen's gland lactone **19** in excellent overall yield. This material was identical to the reported characterization data for Hagen's gland lactone[14] thus confirming unambiguously the relative configuration of precursor allenol **16**. We believe this highly concise synthesis of Hagen's gland lactone also provides a new entry to the large class of furofuranone-based natural products.[17]

The relative configuration and high diastereoselectivity of product **16** and other allenols generated by the present method can be explained in terms of facial selectivity afforded by the MMD auxiliary as depicted in transition state **TS16** (Scheme 4). Complex **2** prefers an *S-trans* conformation[18] where bulky MMD occupies a position *anti* to large γ group (nBu in allenal **2**). Crystallographic studies also reveal this conformational preference in a 1,3-diformylallene manganese complex.[11d,e] On the basis these observations, we propose a *Re*-face addition on the carbonyl of **2** (and related complexes) to produce allenol **16** after MMD removal in the (R,R)-relative configuration (Scheme 4).

In conclusion, the MMD auxiliary was successfully utilized to direct nucleophilic 1,2-additions to allenyl aldehydes to give highly substituted 2,3-allenols. This directing strategy applies to several organometallic nucleophiles leading to single diastereomeric allenol products in most cases. MMD auxiliary amplifies the directing effect of γ-substituents and can discriminate even relatively small size differences in that position (e.g., methyl vs ethyl). This inexpensive and readily available manganese auxiliary was introduced and removed under very mild conditions. A similar stereoselective outcome was observed with an acetonitrile addition to afford an allenol that was further elaborated to give Hagen's gland lactone efficiently.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Maity, P.; Lepore, S. D. *J. Am. Chem. Soc.* **2009**, *131*, 4196.
(2) For examples, see: (a) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (c) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.
(3) Cyclization applications: (a) Alcaide, B.; Almendros, P. *Acc. Chem. Res.* **2014**, *47*, 939. (b) Ma, S.; Fu, C.; Li, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 6511. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (d) Kong, W.; Fu, C.; Ma, S. *Chem. Commun.* **2009**, 4572. (e) Campo, D. M. T.; Almendros, P.; Alcaide, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4501. (f) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943. Intermediates in synthesis: (g) Santos, D.; Ariza, X.; Garcia, J.; Lloyd-Williams, P.; Martínez-Laporta, A.; Sánchez, C. *J. Org. Chem.* **2013**, *78*, 1519. (h) Li, Q.; Jiang, X.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 466. (i) Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441. (j) Petri, A.; Schneekloth, J.; Mandal, A.; Crews, C. *Org. Lett.* **2007**, *9*, 3001. (k) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194. (l) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (m) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. Preparation of 1,3-dienes: (n) Sabbasani, V. R.; Mamidipalli, P.; Lu, H.; Xia, Y.; Lee, D. *Org. Lett.* **2013**, *15*, 1552. (o) Alcaide, B.; Almendros, P.; Luna, A.; Prieto, N. *J. Org. Chem.* **2012**, *77*, 11388. (p) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. Other applications: (q) Li, S.; Miao, B.; Yuan, W.; Ma, S. *Org. Lett.* **2013**, *15*, 977. (r) Ma, S.; Gu, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6182. (s) Jonasson, C.; Trost, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2063. (t) Lautens, M.; Delanghe, M. H. P. *J. Org. Chem.* **1993**, *58*, 5037.
(4) From propargylic organometallic reagents: (a) Park, C.; Lee, H. P. *Org. Lett.* **2008**, *10*, 3359. (b) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496. (c) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (d) Lin, M.; Loh, T. *J. Am. Chem. Soc.* **2003**, *125*, 13042. (e) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550. (f) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392. From alkyl oxiranes: (g) Miura, T.; Shimada, M.; Ku, S.-Y.; Tamai, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7101. (h) Mendez, M.; Furstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355. (i) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 4893. (j) Aurrecoechea, J. M.; Alonso, E.; Solay, M. *Tetrahedron* **1998**, *54*, 3833. From propargyl substrates with a leaving group: (k) Mikami, K.; Yoshida, A.; Matsumoto, S.; Feng, F.; Matsumoto, Y.; Sugino, A.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1995**, *36*, 907. From allenyl carbonyls: (l) Kong, W.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2008**, *6*, 4587. (m) Chen, B.; Lu, Z.; Chai, G.; Fu, C.; Ma, S. *J. Org. Chem.* **2008**, *73*, 9486. (n) Andemichael, Y. W.; Gu, Y. G.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 794. Other: (o) Mundal, A. D.; Lutz, E. K.; Thomson, J. R. *J. Am. Chem. Soc.* **2012**, *134*, 5782. (p) Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138.
(5) (a) Ye, J.; Fan, Wu.; Ma, S. *Chem.—Eur. J.* **2013**, *19*, 716. (b) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S. *Org. Lett.* **2012**, *14*, 1346. (c) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

DOI: 10.1021/ol503757h
Org. Lett. 2015, 17, 900−903

(6) (a) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. *Nat. Chem.* **2013**, *5*, 240. (b) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212.
(7) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1993**, *58*, 3233.
(8) For examples, see: (a) Wong, H.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 7517. (b) Chordia, M. D.; Dean Harman, W. *J. Am. Chem. Soc.* **2000**, *122*, 2725. (c) Schinzer, D.; Barmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1678.
(9) (a) Bhowmick, M.; Lepore, S. D. *Org. Lett.* **2010**, *12*, 5078. (b) Lepore, S. D.; Khoram, A.; Bromfield, D. C.; Cohn, P.; Jairaj, V.; Silvestri, M. A. *J. Org. Chem.* **2005**, *70*, 7443. (c) Manganese−allenyl aldehyde complexes form as *exo* (major) and *endo* (minor) isomers (see the Supporting Information). The use of DBU is critical to achieve complex **2** as the *exo* isomer exclusively where *exo* refers to an *anti*-relationship between MMD and larger group at the γ-position..
(10) In this work, the η^2-auxiliaries are derived from methylcyclopentadienyl manganese tricarbonyl (MMT) which is still used as an antiknocking agent in many countries and can be purchased for ∼ $1/g from several vendors.
(11) (a) Frank-Neumann, M.; Martina, D.; Neff, D. *Tetrahedron: Asymmetry* **1998**, *9*, 697. (b) Frank-Neumann, M.; Neff, D.; Nouali, H.; Martina, D.; Cian, A. D. *Synlett* **1994**, *8*, 657. (c) Frank-Neumann, M.; Brion, F. *Angew. Chem., Int. Ed.* **1979**, *18*, 688. (d) Giffard, M.; Gentric, E.; Touchard, D.; Dixneuf, P. *J. Organomet. Chem.* **1977**, *129*, 371. (e) Giffard, M.; Dixneuf, P. *J. Organomet. Chem.* **1977**, *85*, C26.
(12) Zhang, Z.; Lepore, S. D. *Tetrahedron Lett.* **2002**, *43*, 7357.
(13) (a) Knochel, P.; Zhang, Z.; Fleming, F. F. *Org. Lett.* **2004**, *6*, 501. (b) Lo, S. W. C.; Lo, K. C. P.; Lo, M. K.; Carlier, R. P. *J. Org. Chem.* **1997**, *62*, 6316.
(14) (a) Rodney, A. F.; Pullaiah, K. *J. Org. Chem.* **2012**, *77*, 9357. (b) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; Konig, W. A.; Kitching, W. *J. Org. Chem.* **2001**, *66*, 7487.
(15) (a) Lone, A. M.; Bhat, B. A.; Shah, W. A.; Mehta, G. *Tetrahedron Lett.* **2014**, *55*, 3610. (b) Gharpure, S. J.; Nanda, L. N.; Shukla, M. K. *Eur. J. Org. Chem.* **2011**, 6632. (c) Paz-Morales, E.; Melendres, R.; Sartillo-Piscil, F. *Carbohydr. Res.* **2009**, *344*, 1123. (d) Banda, G.; Chakravarthy, I. E. *Tetrahedron: Asymmetry* **2006**, *17*, 1684. (e) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 743. (f) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; Konig, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479.
(16) (a) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.
(17) Hayes, P. Y.; Chow, S.; Rahm, F.; Bernhardt, P. V.; De Voss, J. J.; William, K. *J. Org. Chem.* **2010**, *75*, 6489.
(18) (a) Gladysz, A. J.; Arif, M. A.; Liu, Y.; Dalton, M. D.; Agbossou, F.; Wang, Y. *Organometallics* **1993**, *12*, 2699. (b) A $^3J_{HH}$ value of >5.2 Hz indicates a dominant *s-trans* conformation, and a value of <3.8 Hz indicates a dominant *s-cis* conformation. We found $^3J_{HH}$ 7.8 Hz, indicating *s-trans*.

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