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Asymmetric Total Synthesis of (+)-Aphanamol I Based on the Transition Metal Catalyzed [5 + 2] Cycloaddition of Allenes and Vinylcyclopropanes

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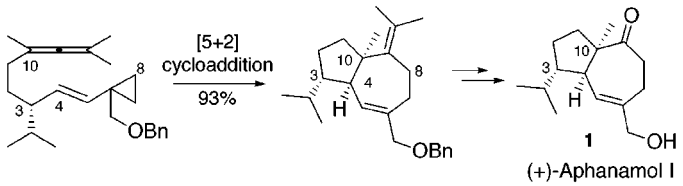
ABSTRACT



A concise asymmetric total synthesis of (+)-aphanamol I is described, based on the transition metal catalyzed [5 + 2] allenyl–vinylcyclopropane cycloaddition. The key cycloaddition precursor is convergently assembled from (*R*)-(+)-limonene and cyclopropane diester through a novel decarboxylative dehydration reaction. The metal-catalyzed [5 + 2] cycloaddition of this precursor proceeds with complete *chemo*, *endo/exo*, and *diastereo*selectivity in *93%* yield, representing an effective general route to bicyclo[5.3.0]decane derivatives.

A significant program in our laboratory is directed at the design and development of new metal-catalyzed [m + n] cycloadditions that in the absence of catalyst would be difficult or impossible to achieve. This effort has thus far produced the first examples of metal-catalyzed intramolecular [4 + 4] cycloadditions of bis-dienes and [4 + 2] cycloadditions of dienes and π-systems[1] and two new processes involving the metal-catalyzed [5 + 2] cycloadditions of vinylcyclopropanes[2] and [6 + 2] cycloadditions of vinylcyclobutanones.[3] The further development of these reactions

(1) For [4 + 4] cycloadditions, see: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678−4679. Wender P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904−5906. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089−1094. For more recent studies, see: Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino A, Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908−4909. Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251−6282. Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, *S1*, 951−953. For [4 + 2] cycloadditions, see: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432−6434. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824−825. Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255−1275. For more recent studies, see: Jolly, R. S.; Luedtke. G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965−4966. McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145−6154. O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443−445. Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075−2078. Gilbertson, S. R.; Hoge, G. S.; Genov, D. G.; *J. Org. Chem.* **1998**, *63*, 10077−10080.

(2) For intramolecular [5 + 2] cycloadditions with alkynes, see: Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. For more recent reports, see: Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442−10443. Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089−2092. Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379−2380. For intermolecular [5 + 2] cycloadditions with alkynes, see: Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Org. Lett.* **2000**, *2*, 1609−1611. For intramolecular [5 + 2] cycloadditions with alkenes, see: Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940−1941. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203−7220. For intramolecular [5 + 2] cycloadditions with allenes, see: Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349. Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137−139.

(3) Wender, P. A.; Correa, A. G.; Sato. Y.; Sun, R. *J. Am. Chem. Soc.* In press.

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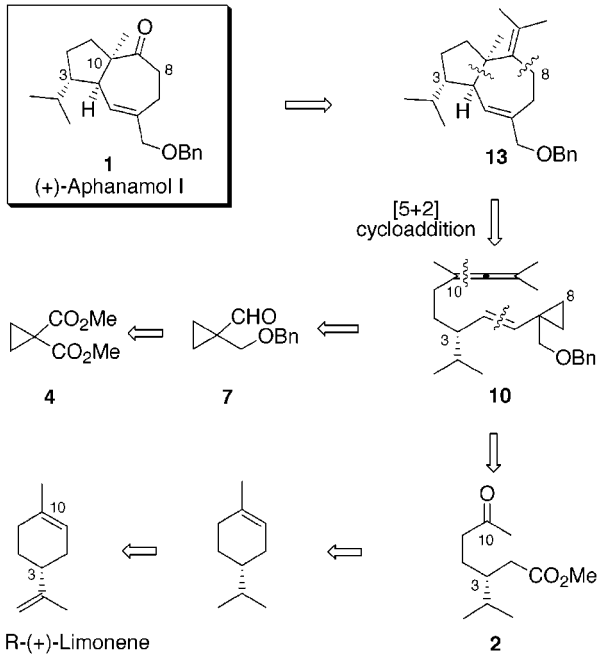
requires the evaluation of changes in the metal, ligands, reaction conditions, and substrates on the course and efficiency of the reaction and most importantly an examination of their utility in complex molecule synthesis. In this Letter, we report an investigation of the metal-catalyzed [5 + 2] cycloaddition directed at the asymmetric synthesis of (+)-aphanamol I, a compound that incorporates structural features common to a variety of designed and natural targets.

(+)-Aphanamol I (**1**) (Scheme 1) is a novel hydroazulene-type sesquiterpene isolated in 1984 as a minor toxic principle from the fruit peel of *Aphanamixis grandifolia*.[4] It has been the subject of several synthesis studies resulting thus far in noteworthy total syntheses by the groups of Mehta,[5a] Wickberg,[5b] and Harmata.[5c]

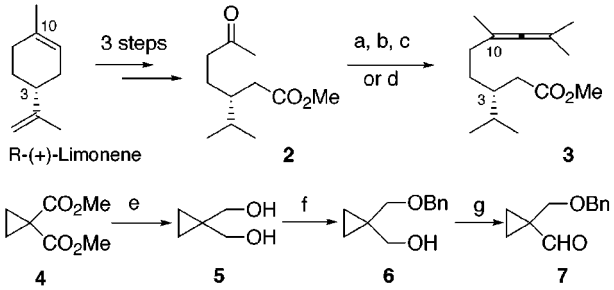
Scheme 1



Our own strategy for the synthesis of (+)-aphanamol I was designed to investigate a previously untested [5 + 2] cycloaddition of vinylcyclopropanes with a tetrasubstituted allene and the degree to which a stereogenic center in the tether subunit would control stereogenesis at the cycloadduct ring fusion positions (Scheme 1: **10** → **13**). An attractive aspect of this plan is that the key cycloaddition precursor **10** could potentially arise from the convergent union of cyclopropanecarboxaldehyde **7** and ketoester **2**, whose functionality and stereochemistry are derivable from commercially available (*R*)-(+)-limonene. The cyclopropane subunit **7** can be conveniently generated from commercially available cyclopropane diester **4**.

(4) Nishizawa, M.; Inoue, A.; Hayashi, Y.; Satrapradja, S.; Kosela, S.; Iwashita, T. *J. Org. Chem.* **1984**, *49*, 3660−3662.
(5) (a) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765−5775. (b) Hanssen, T.; Wickberg, B. *J. Org. Chem.* **1992**, *57*, 5370−5376. (c) Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997**, *38*, 7985−7988.

Scheme 2

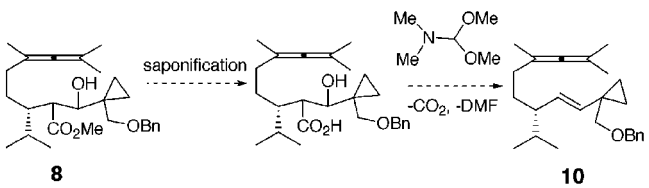


a) 1-Bromopropene: *n*-BuLi, 1.6:2.2, THF, -78°C; b) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, rt; c) Me_2CuLi, THF, -78 °C, 69% for 3 steps; d) 2eq 2-methyl-1-propenyl magnesium bromide, $(Cp)_2TiCl_2$, THF, -40°C to rt, 51%; e) $LiAlH_4$, THF, reflux, 99%; f) NaH, BnBr, DMF, -10°C, 79%; g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C, 90%.

As shown in Scheme 2, execution of this plan started with methyl ester **2**, obtained in three steps from (*R*)-(+)-limonene as described by Kitahara and Mori.[6] Treatment of **2** with propynyllithium, generated in situ,[7] gave a tertiary propargyl alcohol which was immediately protected as the tertiary acetate by DMAP-catalyzed acylation.[8] S_N2'-addition of the Gilman reagent to the propargyl acetate worked remarkably well, furnishing the allene ester **3** in 69% yield over three steps.[9] Direct transformation of **2** to **3** can also be accomplished in one step (51%) by using a titanium-mediated allenylation.[10] The coupling partner for **3**, namely the cyclopropanecarboxaldehyde **7**, was generated through a straightforward three-step sequence from commercially available diester **4**, involving $LiAlH_4$ reduction,[11] followed by a benzyl protection and Swern oxidation.

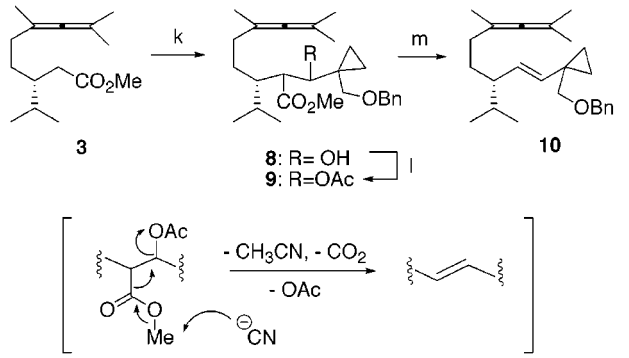
Initial attempts to form the key cycloaddition precursor **10** through condensation of the dianion of the acid derived from **3** with aldehyde **7** and decarboxylative dehydration of the resultant product were unsuccessful.[12] Consequently, the anion derived from allene ester **3** was first condensed with aldehyde **7** to generate the aldol adduct **8** as a diastereomeric mixture in 81% yield. This mixture was then converted to the corresponding acetates **9** which upon treatment with NaCN in DMSO at 130 °C gave the desired cycloadduct

(6) Kitahara, T.; Mori, K. *J. Org. Chem.* **1984**, *49*, 3281−3285.
(7) Suffert, J.; Toussaint, D. *J. Org. Chem.* **1995**, *60*, 3550−3553.
(8) Steglich, W.; Höfle, G. *Angew. Chem., Intl. Ed. Engl.* **1969**, *8*, 981.
(9) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289−3292.
(10) Petasis, N. A.; Hu, Y.-H. *J. Org. Chem.* **1997**, *62*, 782−783.
(11) Wright, M. E.; Allred, G. D. *J. Org. Chem.* **1993**, *58*, 4122−4126.
(12) Another approach called for a saponification of the aldol adduct **8** and subsequent treatment of the product with dimethyl DMF acetal to effect a decarboxylation elimination to produce **10**. However, various saponification conditions gave either no reaction or induced a retro-aldol reaction.



precursor **10** in 51% over two steps. A reasonable mechanism for this novel transformation is given in Scheme 3.[13]

Scheme 3

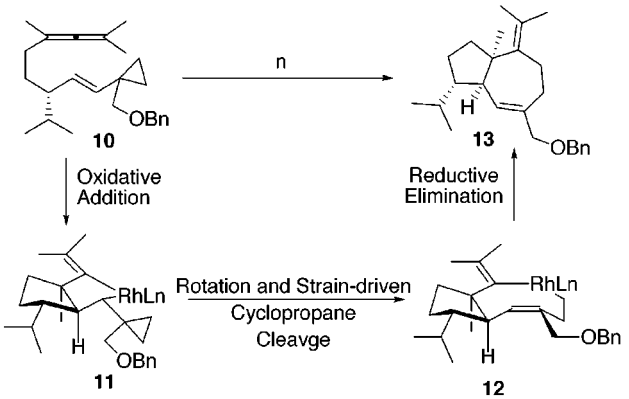


k) 1.2eq LDA, THF, -78°C, **7**, 81%; l) Ac_2O, NEt_3, DMAP, CH_2Cl_2, rt; m) NaCN, DMSO, 130°C, 2 steps, 51%.

With a reliable route to **10** secured, we turned our attention to the key intramolecular [5 + 2] cycloaddition process. Initial attempts to effect the cycloaddition with Wilkinson's catalyst in the presence or absence of silver triflate additives were unsuccessful.[14] We had previously introduced another catalyst for these [5 + 2] cycloadditions, $[Rh(CO)_2Cl]_2$,[15] and were pleased to find in the present case that it worked exceptionally well even at 0.5 mol %, *providing the desired cycloadduct **13** with apparently complete chemo, exo/endo, and diastereoselectivity in excellent yield (93%).*

The stereochemical outcome of this reaction is consistent with our previously described mechanistic hypotheses for these metal-catalyzed [5 + 2] cycloadditions as shown in Scheme 4 for one mechanism class.[16] According to this

Scheme 4

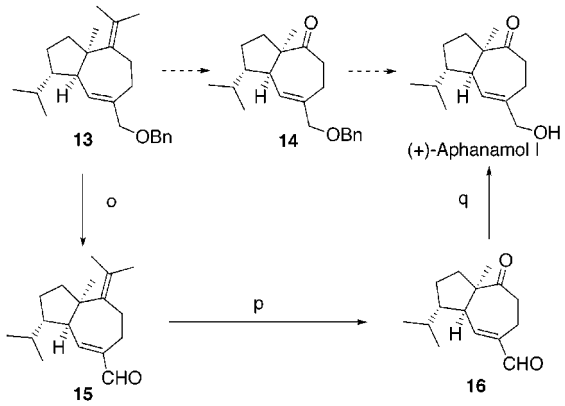


n) 0.5 mol% $[Rh(CO)_2Cl]_2$, 0.1M, Toluene, 110°C, 30 min, 93%

process, the catalyst could reversibly coordinate to either π-face of alkene **10**. One of the two diastereomeric complexes would then produce the cis-fused metallabicyclic intermediate **11** with the large isopropyl substituent preferentially on the less encumbered exo face. Cleavage of the cyclopropane bond and reductive elimination would provide the observed product **13**. The other diastereomeric complex of **10** and catalyst would for steric reasons either not proceed to the metallabicyclic stage or would not progress beyond that point.

Completion of the synthesis of (+)-aphanamol I (Scheme 5) required the selective cleavage of the arguably more

Scheme 5



o) 5 eq DDQ, CH_2Cl_2:H_2O (10:1), rt, 87%; p) (i) O_3/ CH_2Cl_2, -78°C, (ii) Me_2S, 61%; q) $NaBH_4$, MeOH, $CeCl_3$·$7H_2O$, 0°C, 97%.

electron rich exocyclic double bond of **13** to give **14**, followed by a simple benzyl deprotection. However, direct ozonolysis of cycloadduct **13** cleaved the less hindered endocyclic double bond selectively.[17] This problem was eventually solved by oxidizing the allylic benzyl ether directly to α,β-unsaturated aldehyde **15** using an excess of DDQ.[18] This served to reduce electron density in the endocyclic double bond and allow for selective cleavage of the exocyclic double bond with ozone. Luche reduction of the resultant ketoaldehyde **16** furnished (+)-aphanamol I in excellent yield (97%). The spectral data and optical rotation of the final product are identical to the reported values in all respects.[4,5]

(13) An alternative mechanism would be the formation of a β-lactone by the attack of the free acid on the acetate, followed by a decarboxylation reaction.

(14) No reaction occurred with Wilkinson's catalyst. Wilkinson's catalyst with AgOTf as additive caused fast isomerization of the allene to produce dienes.

(15) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164−4165.

(16) We have previously proposed two general mechanistic classes for the [5 + 2] cycloaddition which are differentiated by the timing of cyclopropane opening and CC bond formation. For space consideration, only one is partially illustrated here, that being a path in which CC bond formation precedes cyclopropane cleavage. For additional discussion on the mechanism, see ref 2.

(17) Treatment of cycloadduct **13** with *m*CPBA selectively epoxidized the more electron rich exocyclic double bond. However, cleavage of the resultant epoxides gave complex mixtures. Other direct oxidative cleavage procedures involving reagents, such as $OsO_4/NaIO_4$ and RuO_4, gave sluggish reactions with poor conversions, presumably due to the steric hindrance of the alkene.

(18) Mori, K.; Tomioka, H.; Fukuyo, E.; Yanagi, K. *Liebigs Ann. Chem.* **1993**, *6*, 671−682.

In summary, our synthesis produced (+)-aphanamol I in 10 steps from known methyl ester **2** (13 steps overall) in 13.6% yield. In addition, this work established several new advances regarding the scope and utility of Rh(I)-catalyzed [5 + 2] cycloadditions. First, the cycloaddition of substrate **10** served as the first example of a tetrasubstituted allenyl−vinylcyclopropane [5 + 2] cycloaddition. Second, this study established that excellent control of relative stereochemistry can be achieved with appropriate tether substitution. Third, a novel method to generate vinylcyclopropanes was developed. Finally, this study provides a flexible and efficient strategy for accessing substitutionally complex bicyclo[5.3.0]-decane derivatives, a structural motif common to a range of significant natural and nonnatural compounds.

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Supporting Information Available: IR, NMR, and mass spectroscopic data for compounds **1**−**3**, **5**−**10**, and **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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