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Rhodium-Catalyzed [5 + 2] Cycloadditions of Allenes and Vinylcyclopropanes: Asymmetric Total Synthesis of (+)-Dictamnol

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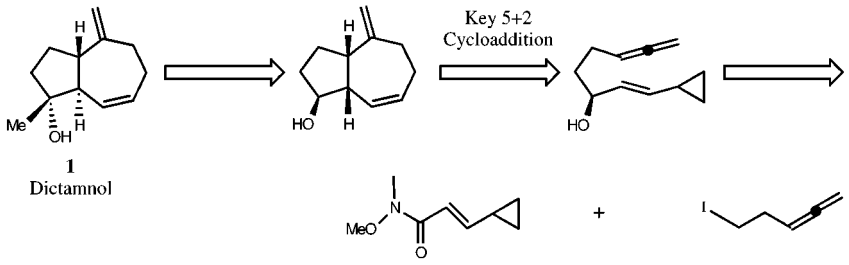
ABSTRACT



The asymmetric synthesis of (+)-dictamnol is described, based on the rhodium catalyzed [5 + 2] cycloaddition of an allene and vinylcyclopropane. This cycloaddition methodology provides the basis for a general and efficient route to various bicyclo[5.3.0]decenes, ring systems common to a wide range of natural and designed compounds of structural and medicinal interest.

We have been investigating the use of metal catalysts to effect reactions that in the absence of catalysts are forbidden or require harsh experimental conditions. This program has thus far produced the first examples of the metal-catalyzed intramolecular [4 + 4] cycloadditions of bis-dienes and the [4 + 2] cycloadditions of dienes and π-systems.[1,2] More recently, we have reported a new reaction for the formation of seven-membered rings based on the [5 + 2] cycloadditions of vinylcyclopropanes and alkynes, alkenes, and allenes.[3] As part of our interest in defining the scope, limitations, and utility of these new reactions, we are exploring the use of the [5 + 2] cycloaddition in total synthesis with an emphasis on developing new and effective routes to commonly encountered ring systems. Dictamnol (**1**) incorporates a core ring system common to a wide range of natural and designed compounds, many representing significant medicinal leads such as the phorbol esters[4] and resiniferatoxin[5] (Figure 1). In this communication, we describe a concise total synthesis of (+)-dictamnol (**1**) that represents a general approach to

(1) For representative examples, see: For [4 + 4] cycloadditions, Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678−4678. Wender, P. A.; Correia, C. R. D.; Ihle, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 5904−5906. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089−1094. For [4 + 2] cycloadditions, 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.* **1995**, *60*, 2962−2963. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824−825. Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255−1275.

(2) 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.

(3) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. 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. Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164−4165. Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.*, in press.

(4) For lead references and the total synthesis, see: Evans, F. J., Ed. *Naturally Occurring Phorbol Esters*; CRC Press: Boca Raton, FL, 1986. Hecker, E.; Schmidt, R. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 377. Wender, P. A.; Kogen, H.; Lee, H.-Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957−8958. Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897−7898.

(5) For lead references and the total synthesis, see: Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976−12977.

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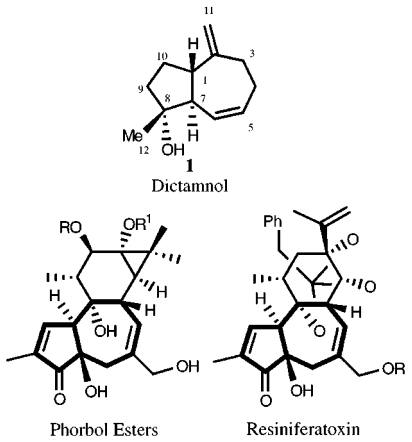
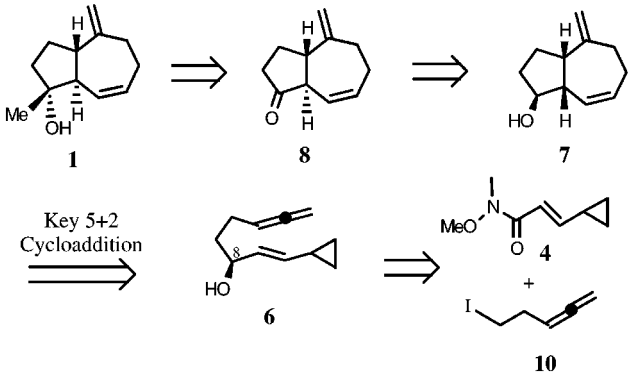


Figure 1.

structures of this type. In addition, this study provides an effective procedure for the construction of cycloaddition precursors (i.e., tethered allenes and vinylcyclopropanes), a test of relative and exo−endo stereoselectivity, and a strategy based on these selectivities that allows for the overall control absolute stereochemistry in synthetic applications.

Dictamnol (**1**) is a trinorguaiane sesquiterpene isolated from the roots of *Dictamnus dascarpus* TURCZ.[6] While dictamnol was originally proposed to have a *cis* ring fusion and a synthesis of the natural isomer was described,[7,8] subsequent synthetic studies by the group of De Groot insightfully revealed that dictamnol contained a *trans* ring fusion.[9] Further evidence on this assignment was provided in a subsequent synthesis by Lange and co-workers in 1997.[10] The approach described herein is based on the observation that ketone **8** is an established precursor of dictamnol.[7] On the basis of the use of the [5 + 2] cycloaddition as a strategy level reaction,[11] this bicyclic compound could potentially be derived from allene-cyclopropane **6** (Scheme 1). In principle,

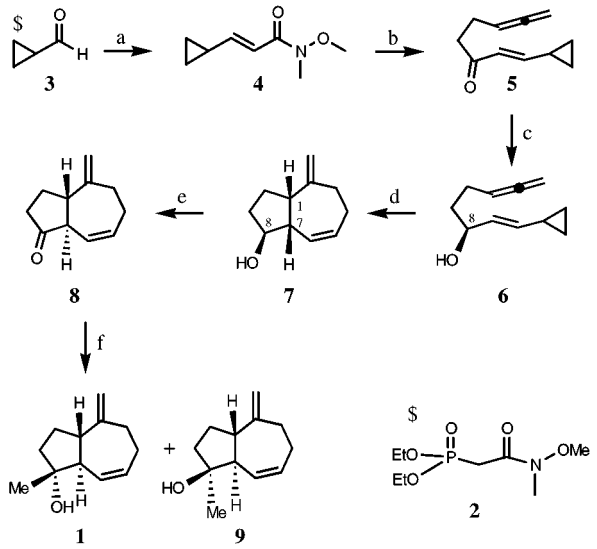
Scheme 1



the corresponding ketone could be used in this step. However, if the absolute stereochemistry of C-8 could be controlled in the formation of **6** and if that stereochemistry could be used in turn to control the ring fusion stereochemistry, an asymmetric synthesis would be realized. We describe below the execution of this plan.

Our synthesis starts with the preparation of the cycloaddition precursor **6** via a convergent approach from commercially available cyclopropanecarboxyaldehyde. Toward this goal, cyclopropanecarboxaldehyde was converted to Weinreb amide **4** in 90% yield under standard Horner−Emmons conditions using a commercially available phosphonoacetate (Scheme 2). Weinreb amide **4** was converted to ketone **5** with the lithium anion of **10** in 82% yield.[12]

Scheme 2



(a) $=Commercially available. **2**, NaH, THF; **3**, RT, 2 h, 90%.
(b) *t*-BuLi, 1-iodo-3,4-butadiene (**10**), Et_2O, -78°C -> RT, 82%.
(c) (*R*)-2-methyl-CBS-oxazaborolidine, BH_3, RT, THF, 78%, 91% ee
(d) 2.5 mol % $[Rh(CO)_2Cl]_2$, dichloroethane, 80 °C, 0.025M, 7 h, 76%.
(e) Dess-Martin periodinane, CH_2Cl_2, 80% (f) MeMgBr, 0 °C, Et_2O, 50% (1:1 of **1**:**9**)

Attempts to cyclize ketone **5** or its acetal were unsuccessful using various rhodium(I) catalysts. In contrast, the unprotected alcohol derived from Luche reduction of **5** served as

(6) Takeuchi, N.; Fujita, T.; Goto, K.; Morisaki, N.; Osone, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1993**, *41*, 923−925.

(7) Koike, T.; Yamazaki, K.; Fukumoto, N.; Yashiro, K.; Takeuchi, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1996**, *44*, 646−652.

(8) The absolute stereochemistry of dictamnol was assigned by independent synthesis starting with chiral dione (*S*)-3,4,8,8a-tetrahydro-8aβ-methyl-2*H*,7*H*-naphthalene-1,6-dione, see ref 7.

(9) Piet, D. P.; Orru, R. V. A.; Jenniskens, L. H. D.; Van de Harr, C.; Van Beek, T. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; De Groot, A. *Chem. Pharm. Bull.* **1996**, *44*, 1400−1403.

(10) Lange, G. L.; Merica, A.; Chimanikire, M. *Tetrahedron Lett.* **1997**, *38*, 6371−6374.

(11) For general approaches to seven-membered ring synthesis, see: ref 2. Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1999; Vol. 5, pp 1−45. Nola, E.; Dzwiniel, T. L.; Schweibert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 9702−9703. Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609.

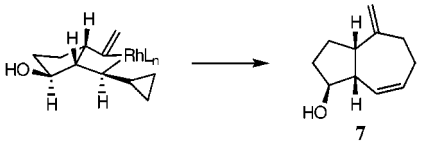
(12) Dauben, W. G.; Shaprio, G. *J. Org. Chem.* **1984**, *49*, 4252−4258. Crandall, J. K.; Ayers, T. A. *J. Org. Chem.* **1992**, *57*, 2993−2995.

an effective substrate for a rhodium(I)-mediated cycloaddition. On the basis of this finding, methods for the asymmetric reduction of ketone **5** were screened. Among these the use of the (*R*)-2-methyl-CBS-oxazaborolidine catalyst with BH_3 proved effective for the asymmetric reduction of prochiral ketone **5**. Alcohol **6** was obtained in 78% yield and in 92% enantiomeric excess.[13,14]

The cycloaddition of alcohol **6** using 10 mol % $Rh(PPh_3)_3Cl$ in toluene (0.01 M) at 90 °C provided cycloadduct **7** in 3 h in 72% yield with high stereoselectivity (8:1).[15] Increasing the concentration of reactants was not possible due presumably to the occurrence of competing oligomerization reactions. Using $[Rh(CO)_2Cl]_2$ in toluene at 80 °C provided comparable yields (70−75%) and reaction times to those obtained using $Rh(PPh_3)_3Cl$. The best cycloaddition conditions involved heating **6** in dichloroethane at 80 °C for 7 h in the presence of commercially available $[Rh(CO)_2Cl]_2$ (2.5 mol %) which provided **7** in 76% yield (9:1 ratio of diastereomers favoring the desired C-8 epimer).[16] It is especially noteworthy that the unprotected alcohol can be used in this reaction and that principally one isomeric cycloadduct is formed. This selectivity is derived from the existing stereochemistry at C-8, which controls stereogenesis at C-1 and C-7.[17]

The stereochemical outcome of the cycloaddition is consistent with the preferential formation and further conversion of a rhodiabicyclo[5.3.0]octane, in which the larger of the C-8 substituents (OH > H) assumes a position on the less encumbered exo face (Scheme 3). Consistent with this

Scheme 3



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analysis, the TBS-protected analogue, in which coordination is excluded, reacts in the presence of 1 mol % $Rh(PPh_3)_3Cl$ in toluene (0.05 M) with even greater selectivity due to the effectively larger size of the C-8 substituent.[18] Upon deprotection of the TBS group, cycloadduct **7** was obtained in 70% yield as a *single* diastereomer (over two steps).

Oxidation of alcohol **7** using Dess−Martin periodinane, followed by exposure of the *cis*-fused ketone to silica gel chromatography, allowed for isomerization to afford *trans*-fused ketone **8** as the sole product isolated in 80% yield. Finally, addition of methylmagnesium bromide to **8** provided a 1:1 mixture of dictamnol (**1**) and *epi*-dictamnol (**9**) in 50% yield.[19] This synthesis produces dictamnol (**1**) in six steps from **3** (nine steps overall) in 9% yield.

This work establishes several new advances bearing on the use of rhodium-catalyzed [5 + 2] cycloadditions. First, it provides a convergent and concise method (2−3 steps) for the preparation of cycloaddition precursors (e.g., allenylvinylcyclopropanes) that can be readily applied to alkynyl and alkenyl systems. Second, it establishes a strategy for the asymmetric synthesis of target rings in which asymmetry introduced in the assembly of the tether is used to control relative stereochemistry during the cycloaddition process. The finding that unprotected hydroxyl groups can be used in the cycloaddition bodes well for economy in design in this and other applications. Finally, this study provides a concise and efficient route to both *cis*- and *trans*-fused 5,7 bicyclic systems and specifically to (+)-dictamnol.

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Supporting Information Available: IR, NMR, and mass spectroscopy data for compounds **1** and **4**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Assignment of stereochemistry of **6** was based on correlation with (+)-dictamnol and analogy to model systems as described by Corey et al.: Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. For an additional use of the model, see: Bach, J.; Berenger, R.; Farras, J.; Garcia, J.; Meseguer, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1995**, *6*, 2683−2686.

(14) The enantiomeric excess of **6** was determined to be 92% by conversion of both enantiomers of **6** to the corresponding (*R*)-mandelate esters and ^1H NMR analysis of the resulting diastereomeric mixture.

(15) The minor isomer is the C-8 epimer of **7**.

(16) For a representative example, $[Rh(CO)_2Cl]_2$ (5 mol %) is added in one batch to a base-washed, oven-dried Schlenk flask under an argon atmosphere and is dissolved in oxygen-free dichloroethane (50 mL). The solution is stirred for 5 min at room temperature, after which allene-vinylcyclopropane **6** (204 mg, 1.24 mmol) is added over 10 s and the solution is heated to 80 °C for 7 h. After cooling, the reaction mixture is filtered through a plug of alumina and concentrated. Flash chromatography (silica gel, 10% ethyl acetate in hexane) gives 154.1 mg of cycloadduct **7** in 76% yield (9:1 ratio of diastereomers favoring the desired C-8 epimer) as a colorless oil.

(17) The relative and absolute stereochemistry of **7** was determined via decoupling and n.O.e. experiments, as well as by conversion to (+)-dictamnol.

(18) The mechanism of the [5 + 2] cycloaddition has not been established and is proposed with the intention of aiding in the rationalization of the stereochemical outcome of the product. For additional discussion on the mechanism, see ref 3.

(19) The NMR data of synthetic (+)-**1** is identical to that reported previously (see refs 6, 7, and 9). In addition, the optical rotation is in agreement with the natural product (+54.2, +55 lit.[6]).