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Total Synthesis

A Short Synthesis of Aphanamol I in Both Racemic and Enantiopure Forms

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Dedicated to Professor Andrew B. Holmes, mentor and friend

Abstract: A short synthesis of the biologically active sesquiterpene natural product (+)-aphanamol I in both racemic and enantiopure forms is reported. Key steps include: a catalytic enantioselective conjugate addition, an oxidative radical cyclization, and a ring-expanding Claisen rearrangement.

(+)-Aphanamol I **1** is a sesquiterpene natural product isolated as one of the minor toxic principles from the fruit peel of the timber tree *Aphanamixis grandifolia* by Nishizawa and co-workers.[1,2] (+)-Aphanamol I contains a core bicyclo[5.3.0]decane (hydroazulene) a common structural motif embedded in a large number of terpenoid natural products.[3] There have been a number of notable syntheses of aphanamol I from the groups of Mehta,[4,5] Wickberg,[6] Harmata[7] and Wender.[8,9] To date all of the asymmetric syntheses of aphanamol I have used limonene as the chiral pool starting material, and featured various key steps, including: a diastereoselective acyclic Claisen rearrangement and an enone-olefin cyclization,[4,5] a photochemical cycloaddition followed by a Grob-type fragmentation,[6] and a rhodium-catalyzed [5+2] cycloaddition of an allene with a vinylcyclopropane,[8] whereas Harmata's synthesis of racemic aphanamol I featured a key [4+3] allyl cation/diene cycloaddition to construct the core bicyclo[5.3.0]decane.[7] Herein we report a short and highly efficient catalytic enantioselective synthesis of (+)-aphanamol I, which features a catalytic asymmetric conjugate addition of an acetylene to an α,β-unsaturated aldehyde, an oxidative γ-lactone annulation and a ring-expanding Claisen rearrangement as key steps.[10–12] This strategy provides rapid access to the key [5.3.0]-bicyclic decane structural motif from which the natural product was readily prepared and provides a platform for the synthesis of other hydroazulene natural products.

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Embedded within the carbon framework of aphanamol I **1** is the retron for the Claisen rearrangement.[13] Application of this retrosynthetic transformation leads to the [3.3.0]-bicyclic enol ether **2**, which would be readily prepared from the corresponding [3.3.0]-bicyclic lactone **3** following methylenation (Figure 1).[12] We have recently used oxidative radical methodology for the synthesis of [3.3.0]-bicyclic lactones by the cyclization of 4-pentenyl malonates.[14,15–19] Application of such an oxidative radical cyclization to an appropriately functionalized 4,6-heptadienyl malonate **4** should yield the corresponding alkenyl-substituted [3.3.0]-bicyclic lactone **3**. Based on the Beckwith–Houk model[20,21] for 5-*exo*-trig radical cyclizations and our own previous experience, we would predict that the oxidative radical cyclization would proceed through the pre-transition state assembly **5** with the *iso*-propyl group residing in a *pseudo*-equatorial position of the chair-like transition state with minimization of allylic strain. Preparation of the dienyl malonate such as **4** in enantioenriched form was to be achieved using the beautiful catalytic enantioselective conjugate addition methodology recently reported by Nishimura and Hayashi,[22,23] with the requisite diene being formed by a hydroboration–Suzuki cross-coupling sequence.

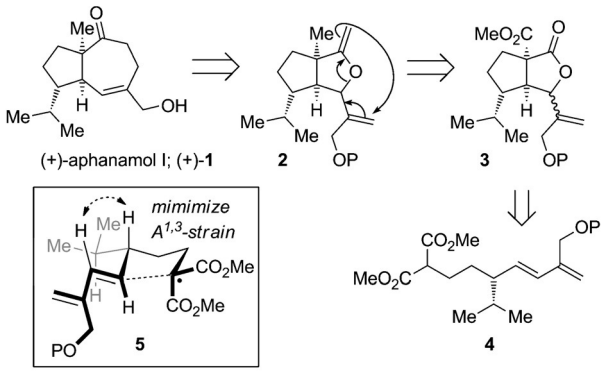
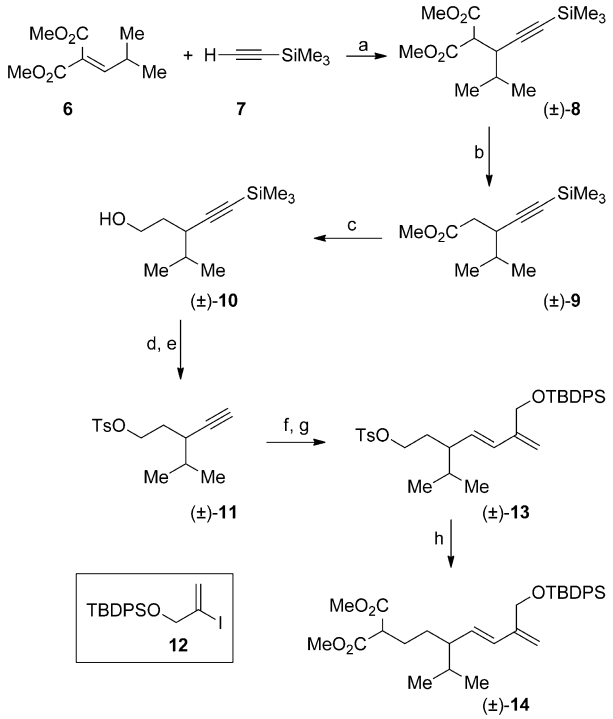
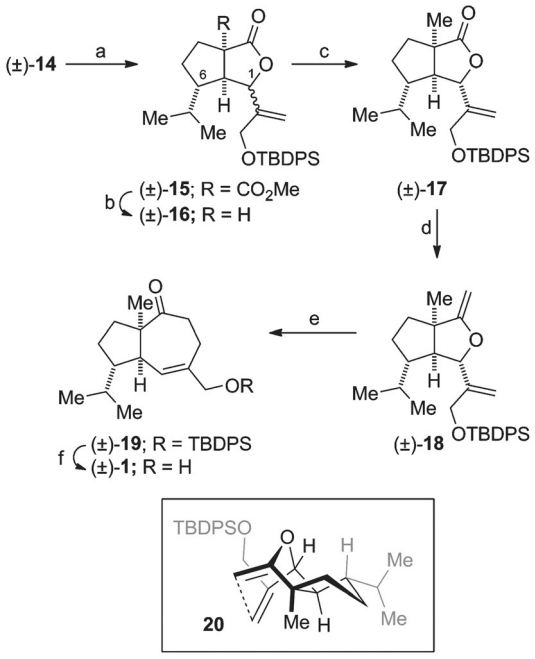


Figure 1. Retrosynthetic analysis of (+)-aphanamol I (+)-**1**; P = protecting group.

Our initial studies focused on developing a synthesis of aphanamol I in racemic form so that we could determine the effectiveness of the previously unreported oxidative radical cyclization of 4,6-heptadienyl malonates for the synthesis of vinyl-substituted [3.3.0]-bicyclic lactones. The synthetic route to racemic aphanamol I (±)-**1** began with the conjugate addition of (trimethylsilyl)acetylene **7** to the unsaturated malonate



Scheme 1. Synthesis of cyclization substrate (±)-**14**. a) CH_3CH_2MgBr, 0.1 mol% CuCl, THF, 0 °C–RT, 94%; b) LiCl, water, DMF, 150 °C, 81%; c) $LiAlH_4$, Et_2O, 0 °C–RT, 93%; d) 1 M Bu_4NF, THF, RT, 92%; e) *p*-$CH_3C_6H_4SO_2Cl$, pyridine, CH_2Cl_2, RT, 87%; f) catecholborane, THF, 70 °C 18 h; g) **12**, 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 M LiOH, THF, 40 °C, 4 h, 79% (two steps); h) $CH_2(CO_2CH_3)_2$, NaH, DMF, THF, 80 °C, 1.5 h, 76%. TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran, DMF = dimethylformamide.

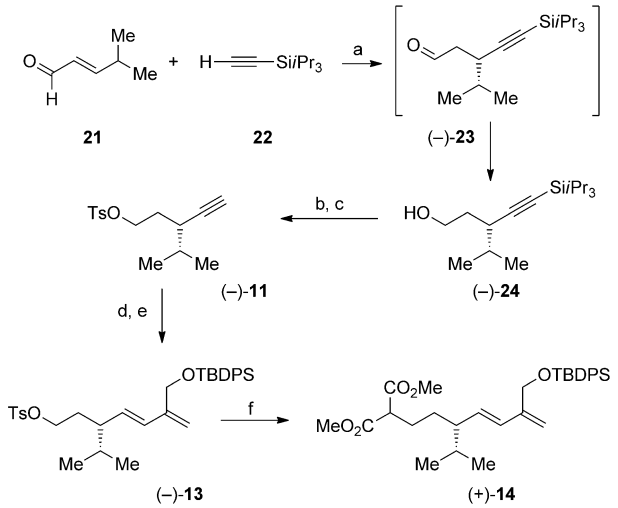


Scheme 2. Synthesis of aphanamol I in racemic form. a) Manganese(III) acetate, copper(II) triflate, acetonitrile, reflux, 89%, 6:1 d.r. at C-1; b) LiCl, water, DMF, 150 °C, 65% (±)-**16a** major diastereomer, 8% (±)-**16b** minor diastereomer; c) CH_3I, $((CH_3)_3Si)_2NLi$, THF, −78 °C, 90%; d) $Cp_2Ti(CH_3)_2$, toluene, reflux, 89%; e) xylene, reflux, 76%; f) Bu_4NF, THF, 86%. Cp = cyclopentadienyl.

6[24] to give (±)-**8** in 94% yield using the procedure of Ohno and Tanaka[25] (Scheme 1). Krapcho decarboxylation of the malonate (±)-**8**[26] gave the ester (±)-**9**, which, on reduction with lithium aluminum hydride, provided the primary alcohol (±)-**10** in good yield. The alcohol (±)-**10** was converted into the corresponding tosylate and the alkyne protecting group was removed using tetra-*n*-butylammonium fluoride giving (±)-**11**. Hydroboration of the terminal alkyne in (±)-**11** with catechol borane followed by Suzuki–Miyaura cross-coupling under standard conditions using the readily prepared iodide **12**[27] gave the diene (±)-**13** in 79% yield.[28] Alkylation of dimethyl malonate with the tosylate (±)-**13** gave the cyclization substrate (±)-**14**. After brief optimization we found that exposure of the dienyl malonate (±)-**14** to our usual oxidative radical cyclization conditions, manganese(III) acetate and copper(II) triflate in acetonitrile, delivered the [3.3.0]-bicyclic γ-lactones (±)-**15** in 79% yield (Scheme 2).[29] The lactones (±)-**15** were isolated as a 6:1 mixture of inseparable C-1 diastereomers.[30,31] The oxidative radical cyclization most likely takes place via the pre-transition state assembly **5** (P = OTBDPS) with the *iso*-propyl group and the diene occupying *pseudo*-equatorial positions in the chair-like transition state. The adduct allylic radical so formed then undergoes oxidative lactonization to deliver the product as a mixture of diastereomers at the lactone stereocenter. Krapcho decarboxylation[26] of (±)-**15** gave the corresponding lactones (±)-**16**, which could be separated by flash chromatography and were individually characterized allowing assignment of their relative configurations by ^{1}H NMR NOE experiments. Alkylation of the major diastereomer (±)-**16a** was readily achieved using methyl iodide and lithium bis(trimethylsilyl)amide giving the γ-lactone (±)-**17**. The alkylated lactone (±)-**17** was readily converted into the corresponding *exo*-cyclic enol ether (±)-**18** on exposure to dimethyltitanocene in toluene at reflux.[32] Heating the enol ether (±)-**18** in xylene at reflux induced the desired Claisen rearrangement to provide the two-carbon ring-expanded product (±)-**19** in 76% yield. Deprotection of the silyl ether provided aphanamol I in racemic form (86%). The ^{1}H and ^{13}C NMR data of our synthetic material were in excellent with agreement with that of the natural product[1] and previously reported data on synthetic samples.[6,8]

The Claisen rearrangement to form the [5.4.0]-bicyclic ketone (±)-**19** is precedented from the work of Haramata and most likely proceeds through a concerted [3,3]-sigmatropic rearrangement from a chair-like pre-transition state assembly related to that depicted in Scheme 2 (**20**) with the isopropyl group occupying a pseudo-equatorial position.[33,34]

Having established a thirteen-step route to aphanamol I in racemic form, we sought to develop a synthesis of the natural product in enantioenriched form. This was reduced to the preparation of the cyclization substrate (**14**) in enantioenriched from. Nishimura, Hiyashi, and co-workers recently reported a beautiful enantioselective rhodium-catalyzed conjugate addition of (triisopropylsilyl)acetylene to α,β-unsaturated aldehydes to give β-alkynylated aldehydes in high yields and enantiomeric excesses.[22] They had prepared the enantiomer of the aldehyde (−)-**23** (Scheme 3) in 88% yield and 99% *ee* on

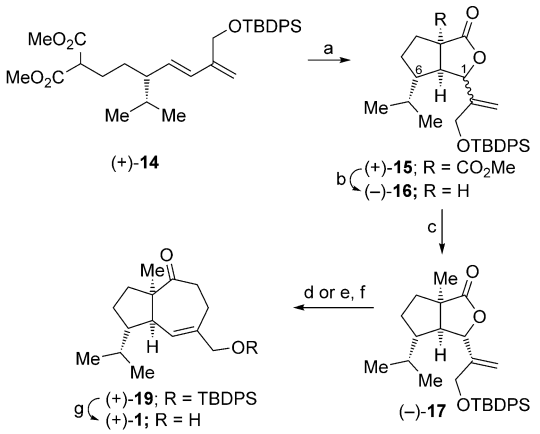


Scheme 3. Catalytic enantioselective synthesis of cyclization substrate (+)-**14**. a) 2.5 mol% [{Rh(OAc)(C_2H_4)$_2$}$_2$], 6.0 mol% (*S*)-DTBM-segphos, CH_3OH, 40 °C, 24 h, then $NaBH_4$, RT, 30 min., 78%, 99% *ee*; b) Bu_4NF, THF, 0 °C–RT, 67%; c) *p*-$CH_3C_6H_4SO_2Cl$, pyridine, −20 °C–RT, 87%; d) catecholborane, THF, 70 °C, 18 h; e) **12**, 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 M LiOH, THF, 40 °C, 4 h, 87%; f) $CH_2(CO_2CH_3)_2$, NaH, THF, 80 °C, 1.5 h, 84%. DTBM-segphos = 5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole.

a 0.2 mmol scale. Following the reported procedure,[22] but using (*S*)-DTBM-segphos in place of (*R*)-DTDM-segphos, as well as working up the reaction with sodium borohydride, gave the alcohol (−)-**24** in 78% yield and 99% *ee* on a 7.0 mmol scale.[35] A similar synthetic route was used to convert the alkyne (−)-**24** into (+)-aphanamol I (+)-(**1**) with similar yields. Thus, the alcohol (−)-**24** was readily converted into the enantiopure cyclization substrate (+)-**14**[36] using a Suzuki cross-coupling as a key step. Exposure of the cyclization substrate (+)-**14** to manganese(III) acetate and copper(II) triflate gave the [5.3.0]-bicyclic γ-lactones (+)-**15** in 74% yield (Scheme 4). As in the racemic series, the lactones (+)-**15** were isolated as a 6:1 mixture of inseparable C-1 diastereomers. Krapcho decarboxylation of the lactones (+)-**15** allowed separation of the C-1 diastereomeric lactones (−)-**16**. The major diastereomer (−)-**16a** was readily converted into the methyl-substituted lactone (−)-**17** on treatment with lithium bis(trimethylsilyl)amide and methyl iodide. As in the racemic series, methylenation of the lactone gave the corresponding enol ether, which, on heating in xylene, gave the desired [5.3.0]-bicyclic ketone (+)-**19** (65% over two-steps). Alternatively we found that addition of Celite™ post-methylenation followed by continued heating in toluene at 150 °C gave a one-pot synthesis of the [5.3.0]-bicyclic ketone (+)-**19** in 74% yield (see Scheme 4).

Deprotection of the silyl ether with buffered tetra-*n*-butylammonium fluoride gave (+)-aphanamol I (+)-**1** in quantitative yield. The ^1H and ^{13}C NMR data of our synthetic material were in excellent agreement with that of the natural product and previously reported data on synthetic samples.[1,6,8,37]

In summary, we have developed a synthesis of the biologically active natural product aphanamol I in both racemic and enantiopure forms using a catalytic enantioselective conjugate addition of a silylated alkyne to an α,β-unsaturated aldehyde, an oxidative radical cyclization, and a ring-expanding Claisen rearrangement as key steps. Further applications of oxidative radical cyclizations for the synthesis of complex natural products will be reported in due course.



Scheme 4. Completion of the synthesis of (+)-aphanamol. a) Manganese(III) acetate, copper(II) triflate, acetonitrile, reflux, 74%; b) LiCl, DMF, water, 150 °C, 75% major diastereomer, 12% minor diastereomer; c) CH_3I, $((CH_3)_3Si)_2NLi$, THF, −78 °C, 90%; d) Cp_2TiMe_2, toluene, 110 °C, then add Celite™, 150 °C, 74%; e) $Cp_2Ti(CH_3)_2$, toluene, reflux, 84%; f) xylene, reflux, 77%; g) Bu_4NF, CH_3CO_2H, THF, 0 °C–RT, quant.

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Keywords: aphanamol · Claisen rearrangement · conjugate addition · radical cyclization · total synthesis

[1] M. Nishizawa, A. Inoue, Y. Hayashi, S. Sastrapradja, S. Kosela, T. Iwashita, *J. Org. Chem.* **1984**, *49*, 3660 – 3662.
[2] Throughout the manuscript solid and broken bold lines will be used for racemic compounds with two or more sterocenters and solid and broken wedges will be used for enantiopure compounds, see: H. Maehr, *J. Chem. Educ.* **1985**, *62*, 114 – 120.
[3] A search using REAXYS® indicated more than 4500 natural products contain the hydroazulene motif. Many of these natural products are terpenes.
[4] G. Mehta, N. Krishnamurthy, S. R. Karra, *J. Chem. Soc. Chem. Commun.* **1989**, 1299 – 1300.
[5] G. Mehta, N. Krishnamurthy, S. R. Karra, *J. Am. Chem. Soc.* **1991**, *113*, 5765 – 5775.
[6] T. Hansson, B. Wickberg, *J. Org. Chem.* **1992**, *57*, 5370 – 5376.
[7] M. Harmata, K. W. Carter, *Tetrahedron Lett.* **1997**, *38*, 7985 – 7988.
[8] P. A. Wender, L. Zhang, *Org. Lett.* **2000**, *2*, 2323 – 2326.
[9] For a synthesis of aphanamol II, see: Y. Shizuri, S. Yamaguchi, Y. Terada, S. Yamamura, *Tetrahedron Lett.* **1986**, *27*, 57 – 60.
[10] For examples of ring-expanding Claisen rearrangements for the synthesis of fused bicyclic medium-ring ketones, see: a) W. A. Kinney, M. J. Coghlan, L. A. Paquette, *J. Am. Chem. Soc.* **1984**, *106*, 6868 – 6870; b) W. A. Kinney, M. J. Coghlan, L. A. Paquette, *J. Am. Chem. Soc.* **1985**, *107*, 7352 – 7360.

[11] For a recent review of [3,3]-sigmatropic rearrangements in the total synthesis of natural products, see: E. A. Ilardi, C. E. Stivala, A. Zakarian, *Chem. Soc. Rev.* **2009**, *38*, 3133 – 3148.
[12] The specific thermal rearrangement of a [3.3.0]-bicyclic enol ether to yield a [5.3.0]-bicyclic ketone finds precedent from the work of Haramata who demonstrated this ring-expanding Claisen rearrangement as an aid to the structure assignment of the products of a Lewis acid catalyzed [4+3] cycloaddtion reaction, see: M. Harmata, C. B. Gamlath, C. L. Barnes, D. E. Jones, *J. Org. Chem.* **1995**, *60*, 5077 – 5092.
[13] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis* John Wiley & Sons, New York, **1989**.
[14] The formation of [3.3.0]-bicyclic lactones from pentenyl malonates using manganese(III) acetate was first reported by Ernst and Fristad, see: a) A. B. Ernst, W. E. Fristad, *Tetrahedron Lett.* **1985**, *26*, 3761 – 3764; the use of copper(II) acetate in such reactions was first reported by Curran and Snider, see: b) D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider, M. A. Dombroski, *J. Am. Chem. Soc.* **1991**, *113*, 6607 – 6617.
[15] A. C. Chany, L. B. Marx, J. W. Burton, *Org. Biomol. Chem.* **2015**, *13*, 9190 – 9193.
[16] A. W. J. Logan, S. J. Sprague, R. W. Foster, L. B. Marx, V. Garzya, M. S. Hallside, A. L. Thompson, J. W. Burton, *Org. Lett.* **2014**, *16*, 4078 – 4081.
[17] A. W. J. Logan, J. S. Parker, M. S. Hallside, J. W. Burton, *Org. Lett.* **2012**, *14*, 2940 – 2943.
[18] J. J. Davies, T. M. Krulle, J. W. Burton, *Org. Lett.* **2010**, *12*, 2738 – 2741.
[19] L. H. Powell, P. H. Docherty, D. G. Hulcoop, P. D. Kemmitt, J. W. Burton, *Chem. Commun.* **2008**, 2559 – 2561.
[20] A. L. J. Beckwith, C. H. Schiesser, *Tetrahedron Lett.* **1985**, *26*, 373 – 376.
[21] K. N. Houk, M. N. Paddonrow, D. C. Spellmeyer, N. G. Rondan, S. Nagase, *J. Org. Chem.* **1986**, *51*, 2874 – 2879.
[22] T. Nishimura, T. Sawano, T. Hayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 8057 – 8059; *Angew. Chem.* **2009**, *121*, 8201 – 8203.
[23] For a recent example of the use of Nishimura and Hayashi's methodology in total synthesis, see: T. M. Brütsch, P. Bucher, K. H. Altmann, *Chem. Eur. J.* **2016**, *22*, 1292 – 1300.
[24] We used the Knoevengal procedure described by Cardillo for the preparation of **6**, see: G. Cardillo, S. Fabbroni, L. Gentilucci, M. Gianotti, A. Tolomelli, *Synth. Commun.* **2003**, *33*, 1587 – 1594.
[25] We followed the procedure of Ohno and Tanaka and co-workers who prepared the dibenzylmalonate analogue of (±)-**8**, see: H. Ohno, Y. Takeoka, Y. Kadoh, K. Miyamura, T. Tanaka, *J. Org. Chem.* **2004**, *69*, 4541 – 4544.
[26] A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahnhen Jr., A. J. Lovey, W. P. Stephens, *J. Org. Chem.* **1978**, *43*, 138 – 147.
[27] The vinyl iodide **12** was prepared by hydroiodination of propargyl alcohol according to the procedure of Ishii and co-workers: a) S. Irifune, T. Kibayashi, Y. Ishii, M. Ogawa, *Synthesis* **1988**, 366 – 369; followed by silylether formation. The *tert*-butyldimethylsilyl ether equivalent of **12** is a known compound: b) M. T. Lai, D. Li, E. Oh, H. W. Liu, *J. Am. Chem. Soc.* **1993**, *115*, 1619 – 1628.
[28] The diene (±)-**13** was assigned the (*E*)-geometry on the basis of ^{1}H NMR coupling constant analysis ($J_{4,5} = 16$ Hz).
[29] For reviews of manganese(III) acetate in organic synthesis, see: a) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339 – 363; b) G. G. Melikyan, *Org. React.* **1997**, *49*, 427 – 675; c) Ayhan S. Demir, M. Emrullahoglu, *Curr. Org. Synth.* **2007**, *4*, 321 – 351; d) J. W. Burton, **2012**, in *Encyclopedia of Radicals in Chemistry, Biology and Materials* (Eds.: C. Chatgilialoglu and A. Studer), John Wiley & Sons Ltd, Chichester, UK, pp. 901 – 942; e) M. Mondal, U. Bora, *RSC Adv.* **2013**, *3*, 18716 – 18754.
[30] The relative configuration was assigned on the basis of ^{1}H NMR NOE experiments: see the Supporting Information.
[31] The ^{1}H NMR of **15** indicated the presence of another component, which we have been unable to characterize, but is possibly a C-6 diastereomer. The ratio of this component to the major C-1 diastereomer **15a** is approximately 20:1.
[32] N. A. Petasis, E. I. Bzowej, *J. Am. Chem. Soc.* **1990**, *112*, 6392 – 6394.
[33] For reviews of the Claisen rearrangement, see: a) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423 – 1452; b) A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939 – 3002.
[34] Given that the [5.3.0]-bicyclic ketone (±)-**19** is the sole product isolated from the rearrangement reaction its formation is unlikely to be the result of a diradical mechanism. For an example of the related Cope rearrangement, which appears to proceed via a diradical mechanism, see: H. Ito, S. Takeguchi, T. Kawagishi, K. Iguchi, *Org. Lett.* **2006**, *8*, 4883 – 4885.
[35] The enantiomeric excess of the alcohol (−)-**24** was determined by chiral HPLC analysis (Chiralcel OD column) of the corresponding benzoate ester, see the Supporting Information.
[36] The enantiopure cyclization substrate (+)-**14** had close to zero optical rotation on the sodium "D"-line but a significant positive rotation when measured on one of the mercury lines at 365 nm..
[37] The optical rotation of our synthetic (+)-aphanamol I was in agreement with those of Wickberg (ref. [6]) and Wender (ref. [8]) and was approximately half value of that of the isolated natural product (ref. [1]), see the Supporting Information. Wickberg (ref. [6]) has previously discussed the discrepancy between the optical rotations of synthetic and natural (+)-aphanamol I and noted that: "it is not uncommon that natural terpenoids occur as mixtures of enantiomers, and this could explain the higher specific rotation" of the synthetic material.

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