ORGANIC LETTERS

2008
Vol. 10, No. 12
2385−2388

Stereoselective Total Syntheses of Uncommon Sesquiterpenoids Isolated from *Jatropha neopauciflora*

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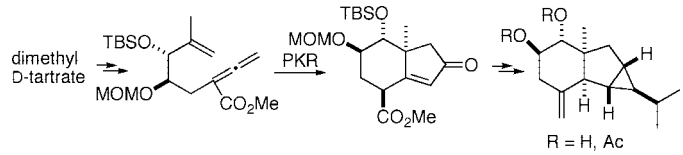
Received March 19, 2008

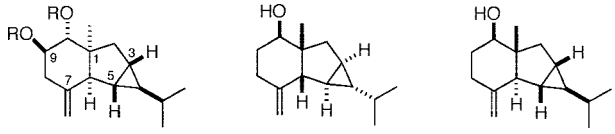
ABSTRACT



The first total syntheses of two tricyclic sesquiterpenes 1 and 2, isolated from *Jatropha neopauciflora*, were completed from dimethyl D-tartrate in a stereoselective manner. The crucial steps in these syntheses involved not only the Rh(I)-catalyzed Pauson−Khand-type reaction of the allenene derivative leading to the exclusive formation of the bicyclo[4.3.0]nonenone framework possessing an angular methyl group but also a highly stereoselective construction of the isopropylcyclopropane ring.

Two uncommon tricyclic sesquiterpenes **1** and **2**, possessing the so-called cycloax-4(15)-ene skeleton, have recently been isolated from *Jatropha neopauciflora*, and their entire structures including the absolute configuration were fully characterized as the (1*S*,3*R*,4*R*,5*R*,6*S*,9*R*,10*R*)-9,10-dihydroxy (or diacetoxy)-1-methyl-4-(1-methylethyl)-7-methylidenetricyclo[4.4.0.0^{3,5}]decane based on their spectroscopic analyses and circular dichroism experiments[1] (Scheme 1). These two sesquiterpenes **1** and **2**

Scheme 1



1: R = H
2: R = Ac

3 **4**

might be regarded as the first natural products having the cycloax-4(15)-ene framework with unambiguous evidence, although the tentative assignment of the cyclopropane-fused *cis*-perhydroindane skeleton of compound **3**,[2] similar to **1** and **2**, based on GC-MS and NMR analysis had already been reported in 2001. The isolation and unambiguous characterization of the related *trans*-perhydroindane natural product **4** with the so-called cyclooppositi-

10.1021/ol800633a CCC: $40.75
Published on Web 05/14/2008

(1) García, A.; Delgado, G. *Helv. Chim. Acta* **2006**, *89*, 16–29.

(2) Kalemba claimed that compound **3** (GC 60% purity) was obtained, accompanied by a mixture of ledol and salviadienol, during their investigation on the constituents of the essential oil of Solidago gigantea. The relative stereochemistry of **3** was deduced by comparison of its NMR spectra with those of the related *trans*-fused natural product **4**, the stereochemistry of which[3,4] had already been established. However, no unquestionable evidence of its structure including the absolute configuration as well as relative stereochemistry can be provided yet. The structure of **3** described in Scheme 1 was cited from the original paper: Kalemba, D.; Marschall, H.; Bradesi, P. *Flavour Fragr. J.* **2001**, *16*, 19–26.

(3) Itokawa, H.; Matsumoto, H.; Mihashi, S. *Chem. Lett.* **1983**, 1253–1256.

(4) (a) Hsieh, Y.-L.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1998**, *47*, 845–850. (b) Fukuda, M.; Ohkoshi, E.; Makino, M.; Fujimoto, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1465–1468.

(5) Biomimetic conversion of epoxygermacrene-D into **4** was reported, see: (a) Yamamura, S.; Niwa, M.; Ito, M.; Saito, Y. *Chem. Lett.* **1982**, 1681–1684. (b) Maurer, B.; Hauser, A. *Helv. Chim. Acta* **1983**, *66*, 2223–2235.

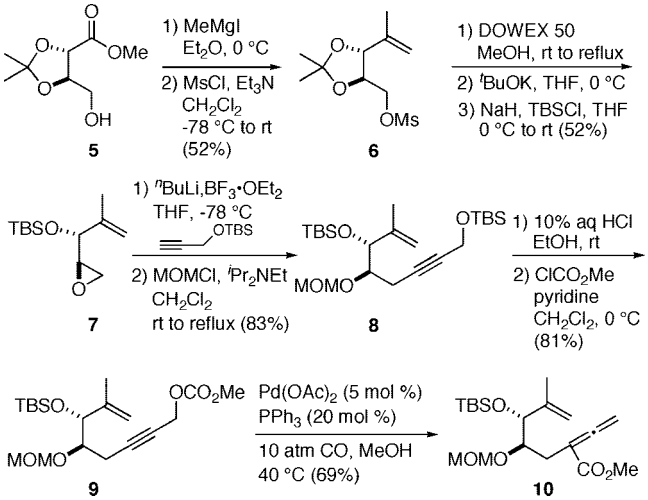
(6) Bulow and Konig reported that the acid-catalyzed rearrangement of germacrene-D produced both the 9,10-deoxygenated derivative of **1** and the 9-deoxygenated congener of **4**: Bulow, N.; Konig, W. A *Phytochemistry* **2000**, *55*, 141–168.

(7) Fox, D. T.; Poulter, C. D. *J. Org. Chem.* **2005**, *70*, 1978–1985.

4(15)-ene skeleton was recorded back in the 1980s,[3] and since then, there have been two additional papers[4] dealing with the isolation of **4**.[5,6] We had much interest in the efficient and stereoselective preparation of these sesquiterpenes, in particular the cycloax-4(15)-ene natural products **1** and **2**, because of their seven contiguous chiral carbon centers involving a quaternary carbon within a relatively small molecule. We now describe the first total syntheses of two uncommon tricyclic sesquiterpene natural products **1** and **2** by taking advantage of the Rh(I)-catalyzed Pauson−Khand-type reaction of the allenene derivative, which produced the bicyclo[4.3.0]nonenone ring system with simultaneous construction of the quaternary carbon center in a highly stereoselective manner.

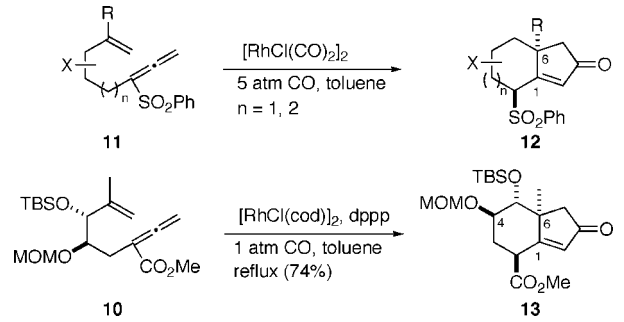
Our tactical feature in this synthesis involved the incorporation of the two chiral centers of D-tartrate into the target molecules. Thus, the known compound **5**,[7] easily derived from dimethyl D-tartrate, was chosen as a starting substrate. Treatment of compound **5** with methylmagnesium iodide gave the diol derivative, subsequent exposure of which to mesyl chloride effected successive mesylation of the primary hydroxyl group and dehydration of the tertiary hydroxyl group leading to the olefin derivative **6** in 52% yield. Deacetonization of **6** under acidic conditions was followed by base treatment to yield the epoxy derivative. The intact secondary hydroxyl moiety was then protected with a *tert*-butyldimethylsilyl (TBS) group to produce **7** in 52% overall yield from **6**. Introduction of a propargyl alcohol moiety was realized upon exposure of **7** to lithium acetylide,[8] adjusted from 3-*tert*-butyldimethylsiloxyprop-1-yne, affording the epoxy ring-opening product, which was subsequently reacted with methoxymethyl (MOM) chloride to produce **8** in 83% yield. The enyne **8** was converted into the carbonate **9** in 81% yield by a selective desilylation and reaction with chloro methyl carbonate. According to Tsuji's procedure,[9] **9** was exposed to $Pd(OAc)_2$ and triphenylphosphine (PPh_3) in MeOH under 10 atm of CO at 40 °C to furnish the allenene **10** in 69% yield (Scheme 2).

Scheme 2



With the allenene **10** for the ring-closing reaction in hand, our endeavors focused on the Rh(I)-catalyzed Pauson−Khand-type reaction of **10**. Recently, we[10] have developed the $[RhCl(CO)_2]_2$-catalyzed intramolecular Pauson−Khand-type [2+2+1] cycloaddition reaction of allenenes **11**(R = H) leading to the bicyclo[5.3.0]dec-1(10)-en-9-one as well as the bicyclo[4.3.0]non-1(9)-en-8-one skeletons **12** (Scheme 3). This procedure was found

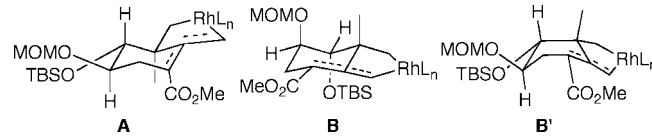
Scheme 3



to be successfully applied to the efficient construction of bicyclo[4.3.0]non-1(9)-en-8-one framework **12** having an alkyl appendage at the ring juncture (C_6-position), whereas the Pauson−Khand reaction of the corresponding enynes is known to generally provide the 6-substituted-bicyclo-[4.3.0]nonenone derivatives such as **12** (R = alkyl) in rather low yields.[11] Thus, the allenene **10** was first exposed to the typical conditions (5 mol % $[RhCl(CO)_2]_2$, 5 atm of CO, toluene, 120 °C),[10] but no desired ring-closed products could be detected in the reaction mixture. Changing the reaction conditions (loading amount of $[RhCl(CO)_2]_2$, CO pressure, solvent, and/or reaction temperature) was useless.[12] Several other types of catalysts were also fruitless, except for using the cationic Rh catalyst $[RhCO(dppp)_2]Cl$.[13] In fact, a solution of **10** in toluene was refluxed in the presence of 5 mol % of $[RhCO(dppp)_2]Cl$, prepared in situ from the reaction of 5 mol % of $[RhCl(cod)]_2$ and 25 mol % of dppp,[13] under an atmosphere of CO to produce exclusively the bicyclo-[4.3.0]nonenone derivative **13** with the proper stereochemistry in 74% yield.

The stereochemistry of **13** was established by an NOE experiment.[14,15] The mechanism for the highly stereoselective construction of **13** is uncertain yet, but it might be tentatively rationalized in terms of the stability of the plausible rhoda-

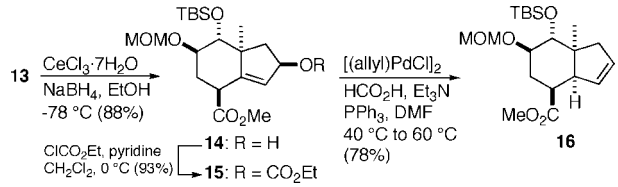
Scheme 4



cycle intermediates (Scheme 4). The rhodacycle **A**, collapsing to **13**, has a chairlike six-membered ring in which both oxygenated functionalities take equatorial positions. On the other hand, the rhodacycle **B**, leading to the C_6-epimer of **13**,[15] also has a chairlike six-membered ring with two axial oxygenated substituents, which might destabilize itself compared to the rhodacycle **A**. The ring-flipping would convert the conformer **B** into the conformer **B′**, where two oxygenated functionalities can take stabler equatorial positions. However, the rhodacycle **B′** no longer exists as a chairlike conformation but also a boat-like form. As a result, rhodacycle **A** seems to be stabler than rhodacycle **B** (**B′**). Therefore, the ring-closing reaction would exclusively proceed via rhodacycle **A** to give rise to **13** in a highly stereoselective manner.

The stereoselective transformation of the α,β-unsaturated carbonyl functionality of **13** into the *cis*-perhydroindane framework was realized as follows. The 1,2-reduction of **13** with $NaBH_4$ and $CeCl_3$ gave the allyl alcohol **14**[16] in 88% yield. The ethyl carbonate derivative **15**,[17] derived from **14** in 93% yield, was exposed to $[(allyl)PdCl]_2$, PPh_3, formic acid, and triethylamine resulting in the palladium-catalyzed dehydroxylation[18] of the allyl alcohol moiety with migration of the double bond to provide the *cis*-perhydroindane derivative **16**[19,20] in 78% yield in a highly stereoselective manner (Scheme 5).

Scheme 5



The next phase of this synthesis was confronting the construction of the three-membered ring. Exposure of **16** to some diazo derivatives such as diazoacetone[21] and ethyl diazoacetate,[22] for example, under typical cyclopropanation conditions, did not produce the desired product **17** at all. The reaction of **16** with diazoisobutane[23] or isopropylidene carbene[24] species was also shown to be fruitless. After screening various cyclopropanation reactions, we finally found that dibromocyclopropanation[25] was effective for our purpose. Thus, **16** was converted into **18**[26] by the conventional means and was then treated with bromoform in the presence of bases[25] to exclusively yield **19**[27] in 89% yield. The cyclopropanation proceeded from the convex face of **18** as expected. Introduction of an isopropyl group on the three-membered ring was realized as follows. According to Seebach's procedure,[28] upon exposure to ^{n}BuLi and acetone at −78 °C, **19** underwent consecutive halogen-metal exchange reaction and carbon−carbon bond formation reaction with acetone to furnish **20**[29] in 68% yield. Compound **20** was treated with ^{n}BuLi at −78 °C again,[28] and the reaction mixture was gradually warmed to room temperature to give **21**[27] in 86% yield. Alternatively, direct conversion of **19** into **21** without isolation of **20** could be achieved in 53% yield. Dehydration of **21** under mesylation conditions afforded **22**[27] (84%), which was hydrogenated in the presence of the Wilkinson catalyst to provide **23**[27] in 96% yield. Thus, construction of the isopropylcyclopropane ring onto **18** was accomplished in a completely stereocontrolled manner.

Elaboration of the required functionalities of the cyclohexane ring of **23** remained before completing the total synthesis of **1** and **2**. Selective desilylation of **23** with camphorsulfonic acid in MeOH afforded the hydroxymethyl derivative **24** (96%), which was then converted into the exomethylene derivative **25**[30] in 87% by Grieco's procedure.[31] Finally, both MOM and TBS groups on the vicinal diol moiety of **25** were removed under acidic conditions (10% HCl aq, MeOH, 40 °C) to provide **1** in 90% yield. Acetylation of **1** with acetic anhydride produced **2** in 96% yield. Both synthetic **1** and **2** were identical with the natural products by comparison with their spectra (Scheme 6).

In summary, we have completed the stereoselective total syntheses of two tricyclic sesquiterpenes **1** and **2**, isolated from *Jatropha neopauciflora*, from dimethyl D-tartrate. The noteworthy tactical feature of our method involves (i) stereoselective formation of the bicyclo[4.3.0]nonenone framework based on the newly developed Rh(I)-catalyzed Pauson−Khand-type reaction of the allenene and (ii) stereoselective construction of the isopropylcyclopropane ring, both of which enabled us to accomplish the first total

(8) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.

(9) Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731–734.

(10) Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217–1220.

(11) For example, see: (a) Bolton, G. L.; Hodges, J. C.; Rubin, J. R. *Tetrahedron* **1997**, *53*, 6611–6634. (b) Ishizaki, M.; Satoh, H.; Hoshino, O. *Chem. Lett.* **2002**, 1040–1041. (c) Ishizaki, M.; Satoh, H.; Hoshino, O.; Nishitani, K.; Hara, H. *Heterocycles* **2004**, *63*, 827–844.

(12) The allenenes possessing different kinds of protecting groups instead of those of **10** (MOM and TBS groups) were prepared and their Pauson−Khand-type reactions were examined, but no favorable results could be obtained.

(13) Sanger, A. R. *J. Chem. Soc., Dalton Trans.* **1977**, 120–129.

(14) An NOE experiment with **13** indicated both a 12.0% enhancement of the C_4−H and a 14.1% enhancement of the C_2−H when the angular methyl group (C_6−Me) was irradiated.

(15) Numbering for compound **12** was used for convenience.

(16) Obtained as a mixture of **14** and its epimer in the ratio of 10 to 1. An NOE experiment with the major product **14** revealed a 2.3% enhancement between the angular methyl group and the C_8−H.

(17) Used as a mixture of **14** and its epimer in a ratio of 10 to 1.

(18) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623–627. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326–1327. (c) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24.

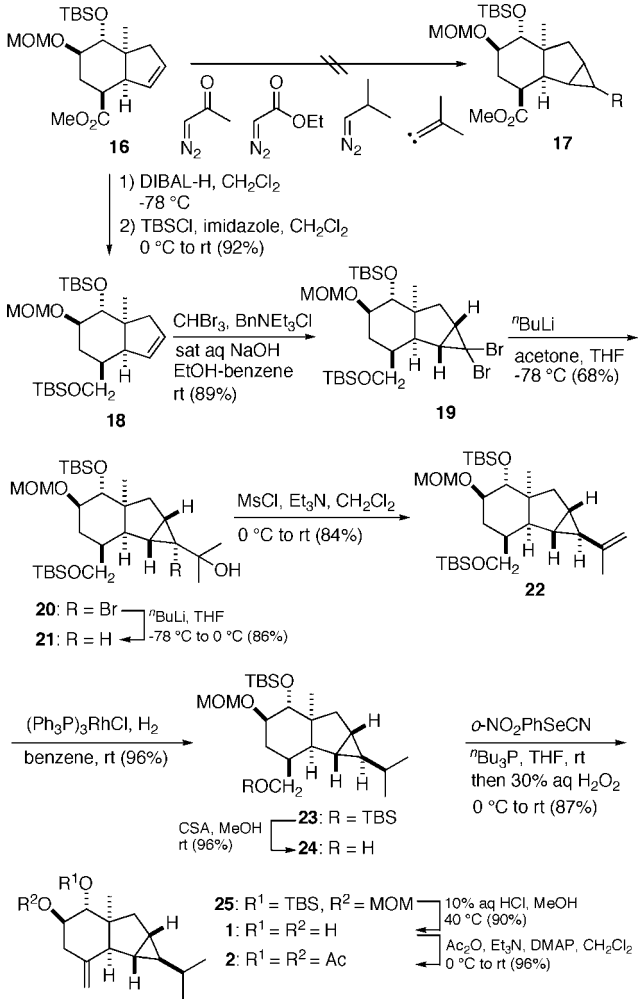
(19) An NOE experiment with **16** revealed a 3.9% enhancement between the angular methyl group and the C_1−H,[15] thereby confirming its *cis*-perhydroindane skeleton.

(20) The corresponding *trans*-perhydroindane product, which should be derived from the epimer of **14**, could not be detected.

(21) (a) Hendrickson, J. B.; Walf, W. A. *J. Org. Chem.* **1968**, *33*, 3610–3618. (b) Wenkert, E.; Greenberg, R. S.; Raju, M. S. *J. Org. Chem.* **1985**, *50*, 4681–4685.

(22) (a) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44–52. (b) Womack, E. B.; Nelson, A. B. *Org. Synth.* **1955**, *3*, 392–393. (c) Kurek-Tyrlik, A.; Michalak, K.; Wicha, J. *J. Org. Chem.* **2005**, *70*, 8513–8521.

Scheme 6



syntheses of these natural products in a stereoselective manner.

Acknowledgment. We are very grateful to Dr. Guillermo Delgado, Ciudad Universitaria, Mexico, for generous supply of NMR spectra of natural products. This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are grateful.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all new compounds **1**, **2**, **6**−**10**, **13**−**16**, and **18**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800633A

(23) (a) Werner, E. A. *J. Chem. Soc.* **1919**, *115*, 1093–1102. (b) Girberto, S.; Cesare, G.; Annalida, B. *Farmaco* **1993**, *48*, 1663–1674.

(24) Seyferth, D.; Dagani, D. *J. Organomet. Chem.* **1976**, *104*, 145–151.

(25) Banwell, M.; Edwards, A.; Harvey, J.; Hocklass, D.; Willis, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2175–2178.

(26) By taking into account the chemical elaboration at the latter stage, a methoxycarbonyl group **16** was converted into a siloxymethyl group.

(27) The stereochemistry of the newly generated chiral carbon centers was uncertain at this stage. The stereochemical assignment was unambiguously made on the basis of compound **25** whose stereochemistry was established by spectral evidence.

(28) (a) Braun, M.; Dammann, R.; Seebach, D. *Chem. Ber.* **1975**, *108*, 2368–2390. (b) Seebach, D.; Stucky, G.; Pfammatter, E. *Chem. Ber.* **1989**, *122*, 2377–2389.

(29) The stereogenic center of C_4 was not determined, although **20** was obtained as a single isomer judging from its ^{1}H NMR spectrum.

(30) The stereochemical assignment of three stereogenic centers (C_3, C_4, and C_5) of **25** was confirmed by an NOE experiment. The fact that irradiation of H-4 resulted in a 10.4% enhancement of H-6, whereas a 14.9% enhancement of H-4 was observed upon irradiation of H-6, could completely rule out the possibilities of **25** to be (3*R*,4*S*,5*R*)-, (3*S*,4*R*,5*S*)-, and (3*S*,4*S*,5*S*)-isomers.

(31) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.