JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Asymmetric Total Synthesis of Propindilactone G

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Supporting Information

ABSTRACT: A concise total synthesis of (+)-propindilactone G, a nortriterpenoid isolated from the stems of *Schisandra propinqua* var. *propinqua*, has been achieved for the first time. The key steps of the synthesis include an asymmetric Diels–Alder reaction, a Pauson–Khand reaction, a Pd-catalyzed reductive hydrogenolysis reaction, and an oxidative heterocoupling reaction. These reactions enabled the synthesis of (+)-propindilactone G in only 20 steps. As a consequence of our synthetic studies, the structure of (+)-propindilactone G has been revised.

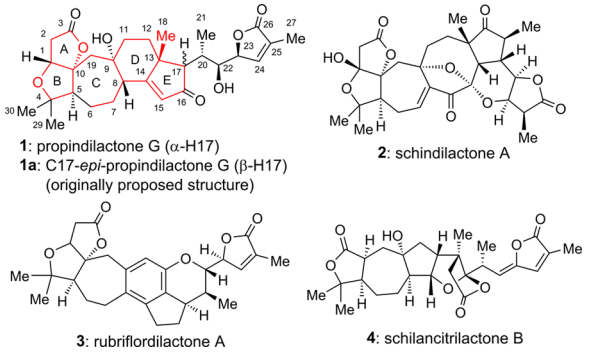
Propindilactone G (**1**)[1] and compounds **2**–**4** (Chart 1) represent a novel group of nortriterpenoids[2] isolated from various species of *Schisandracea* family by Sun et al. The species are widely distributed throughout Southeast Asia and North America and used as traditional Chinese herb medicines in China for liver protection and immune regulation.[2]

The intriguing chemical structures and potential biological activity of the nortriterpenoids, in combination with their scarcity in nature, which limits their further biological investigation, have spurred considerable interest among the chemistry community,[3] resulting in the total syntheses of schindilactone A (**2**) in 2011 by Yang et al.,[4] the total syntheses of rubriflordilactone A (**3**) in 2014 by Li et al.,[5] and the total syntheses of schilancitrilactone B (**4**) in 2015 by Tang et al.[6]

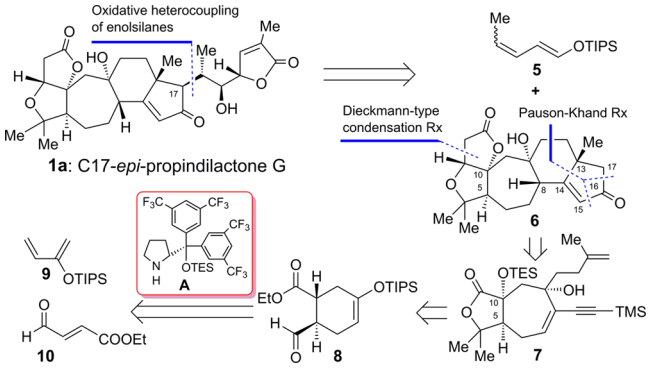
From a structural perspective, **1**, distinct from the other nortriterpenoids **2**–**4**, possesses a unique 5/5/7/6/5 pentacyclic core bearing seven stereocenters, three of which are quaternary centers[7] (C9, C10, and C13). The originally proposed structure of propindilactone G (**1a** in Chart 1) was established by NMR analysis.[1] Preliminary biological assays indicated that these types of nortriterpenoids exhibit promising anti-HIV activity,[8] which inspired us to develop synthetic methods and a strategy centered on the construction of the scaffold of propindilactone G, with the hope of providing a general approach for the total synthesis of other family members of propindilactone G. Here we report our efforts on the development of a concise strategy that allowed the first total synthesis of **1** in 20 steps.

Inspired by recent advances in the oxidative heterocoupling of enolsilanes for the formation of C–C bond,[9] we postulated our total synthesis of **1a** to involve the late-stage coupling of the

Chart 1. Naturally Occurring Nortriterpenoids



Scheme 1. Retrosynthetic Analysis of Propindilactone G

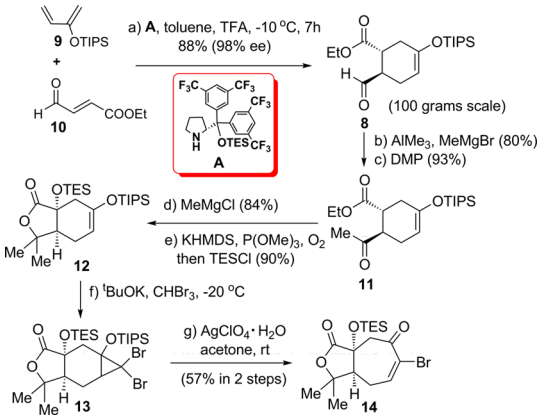


conjugated enolsilane **5** with the in situ generated enolsilane of ketolactone **6** to form the C17–C20 linkage (Scheme 1). This retrosynthetic analysis required the development of an efficient synthetic approach for the stereoselective synthesis of **6** bearing a quaternary carbon atom at C13. Encouraged by our recent application of the Pauson–Khand (PK) reaction as a key step in the total synthesis of (+)-fusarisetin A,[10] we envisaged that the PK reaction could be used for the synthesis of the cyclopentenone **6** from enyne **7**. **7** in turn could be made from ester **8** by using the chemistry developed in our total synthesis of **2**.[4] Because we

Received: June 22, 2015
Published: July 16, 2015

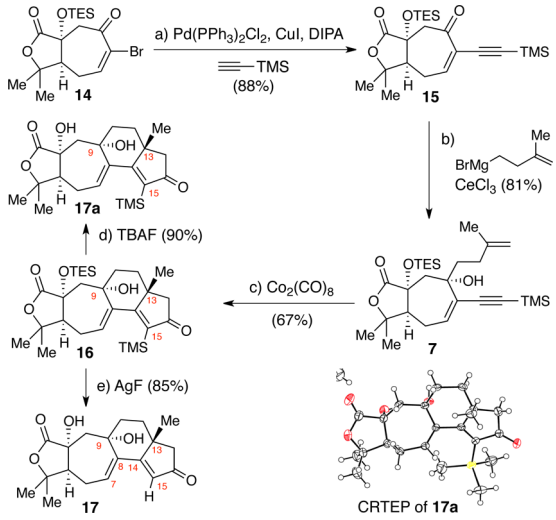
DOI: 10.1021/jacs.5b06480
J. Am. Chem. Soc. 2015, 137, 10120–10123

Scheme 2. Synthesis of the Bromoenone 14[a]



[a]Reagents and conditions: (a) **9** (1.2 equiv), **10** (1.0 equiv), Hayashi ligand (0.1 equiv), TFA (20 mol%), toluene, −10 °C, 7 h, 88% (98% ee); (b) $AlMe_3$ (2.3 equiv), MeMgBr (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, 80%; (c) DMP (1.1 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, rt, 93%; (d) MeMgCl, THF, −78 to −25 °C, 84%; (e) KHMDS (2.0 equiv), THF, −78 to 0 °C followed by addition of $P(OMe)_3$ (2.0 equiv), O_2, 0 °C, 1 h, 90%; then TESCl (1.2 equiv), THF, rt, 90%; (f) KO^{t}Bu (10.0 equiv), $CHBr_3$ (7.5 equiv), petroleum ether, −20 °C; (g) $AgClO_4 \cdot H_2O$ (2.5 equiv), acetone, rt, 57% for two steps.

Scheme 3. Synthesis of the Tetracyclic Ring Fragment 17[a]



[a]Reagents and conditions: (a) ethynyltrimethylsilane (1.25 equiv), DIPA (3.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.06 equiv), CuI (20 mol%), THF, rt, 88%; (b) (3-methylbut-3-en-1-yl)magnesium bromide (1.8 equiv), $CeCl_3$ (3.0 equiv), THF, 0 °C, 81%; (c) $Co_2(CO)_8$ (0.5 equiv), Celite (10 wt), toluene, reflux, 67%; (d) TBAF (1.5 equiv), THF, rt, 90%; (e) AgF (10.0 equiv), THF, MeOH, H_2O, 80 °C, 85%.

wanted to achieve an asymmetric total synthesis, we explored the use of an asymmetric Diels−Alder (DA) reaction of diene **9** and dienophile **10** in the presence of a chiral ligand[11] for the synthesis of the chiral building block **8**. In addition, we wanted our strategy to be in an agreement with the notion of concise synthesis by limiting the use of protecting group.[12]

The concise enantioselective synthesis of the key vinyl bromide (+)-**14** is shown in Scheme 2. We profiled a variety of asymmetric variations of DA reaction[11] for the synthesis of **8** from **9** and **10**. The desired DA reaction could be effectively achieved in the presence of Hayashi's ligand,[11e] leading to the formation of (−)-ester **8** in 88% yield with excellent ee (98%). This reaction worked well on a 100 g scale, providing a good foundation to pursue the asymmetric total synthesis.

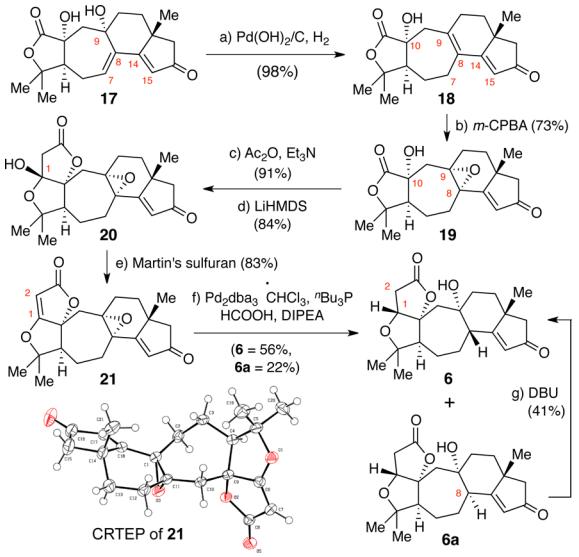
As illustrated in Scheme 2, further treatment of aldehyde **8** with MeMgBr in the presence of $AlMe_3$[13] afforded an alcohol, which was then oxidized with DMP in the presence $NaHCO_3$ in CH_2Cl_2 to give ketoester **11** in 74% yield over two steps. Grignard reaction of **11** with MeMgCl afforded a lactone, which underwent oxidation by reaction with KHMDS in the presence of O_2 and $P(OMe)_3$[14] in THF followed by the treatment with TESCl to give **12** in 76% overall yield. Further treatment of **12** with dibromocarbene[15] derived from $CHBr_3$/^{t}BuOK resulted in the formation of dibromide **13** as a pair of diastereoisomers in a ratio of 1:1, which then reacted with $AgClO_4 \cdot H_2O$[16] in acetone to give the cycloheptenone-based vinyl bromide **14** in 57% yield over two steps.

Scheme 3 depicts the synthesis of the tetracyclic fragment **17**. Although stereoselective synthesis of the cyclopentenone subunit containing an all-carbon quaternary stereocenter at C13 of propindilactone G is challenging, the recent applications of the PK reaction to the synthesis of such scaffolds in complex natural product total synthesis[17] encouraged us to use this reaction as a key step for the synthesis of intermediate **17**. To this end, **14** was coupled with TMS-acetylene in the presence of a catalytic amount of $Pd(PPh_2)Cl_2$/CuI and ^{i}Pr$_2$NH (DIPA)[18] to give enone **15** in 88% yield. Further reaction of **15** with (3-methylbut-3-en-1-yl)magnesium bromide in the presence of $CeCl_3$[19] resulted in enyne **7** in 81% yield as a single isomer. To prepare the cyclopentenone subunit bearing an all-carbon quaternary stereocenter, **7** was treated with $Co_2(CO)_8$ (0.5 equiv) in the presence of Celite[20] in toluene under reflux. The expected product **16** was indeed obtained in 67% yield, together with a 24% yield of its C13 diastereoisomer. Notably, the TMS group substituted at the terminal of the acetylene[21] in **7** played a critical role in the PK reaction, since the substrates without TMS did not afford any desired annulated products. Further treatment of **16** with TBAF afforded **17a** in 90% yield with retention of the TMS group, and the structure was confirmed by X-ray crystallographic analysis. However, when **16** was reacted with AgF,[22] dienone **17** was obtained in 85% yield with removal of its both silyl groups.

We then explored the pathway for stereoselective synthesis of the key intermediate **6** (Scheme 4). Initially, we expected that the C7−C8 double bond in **17** could be saturated by Pd-catalyzed hydrogenation. However, attempts with various Pd catalysts could not regioselectively remove this double bond. On the other hand, treatment of **17** with $Pd(OH)_2/C$[23] in the presence of Et_3N[24] under a balloon pressure of H_2 initiated a reductive isomerization to afford dienone **18** in 98% yield. Further treatment of **18** with *m*-CPBA in CH_2Cl_2 afforded epoxide **19** in 73% yield as a single isomer. The observed regio- and stereoselective epoxidation of dienone **18** could be the result of the free hydroxyl group at C10, which might direct the *m*-CPBA to approach the double bond from the bottom face. To install the lactone in **20**, **19** was first reacted with acetic anhydride in the presence of Et_3N, and the resulting acetate was treated with LiHMDS to initiate a Dieckmann-type condensation[4] to afford lactone **20** in 76% overall yield. To achieve the chemo- and stereoselective synthesis of **6**, **20** was first subjected to a dehydration with Martin's sulfuran,[25] and the resulting unsaturated lactone **21** underwent both a Pd-catalyzed hydrogenation to saturate its C1−C2 double bond and hydrogenolysis[26] to open the epoxide to give **6** in 56% yield, together with its C8-epimer **6a**, which could be converted to **6** in 41% yield

DOI: 10.1021/jacs.5b06480
J. Am. Chem. Soc. 2015, 137, 10120−10123

Scheme 4. Synthesis of Ketolactone 6[a]

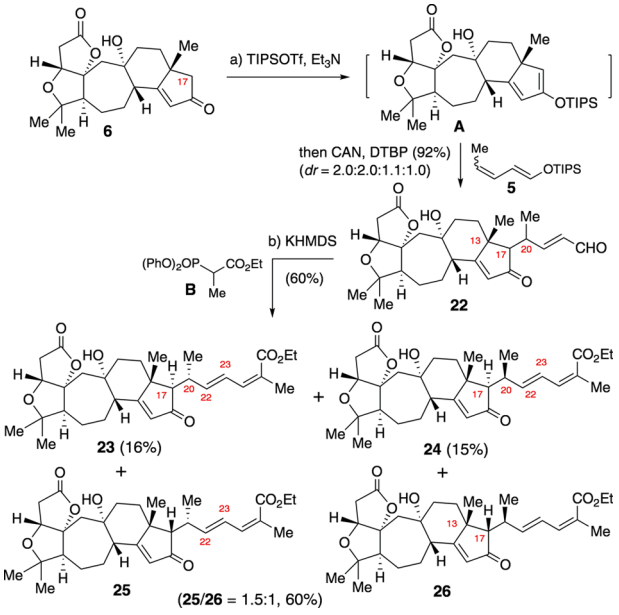


[a]Reagents and conditions: (a) $Pd(OH)_2/C$ (0.7 wt), CH_2Cl_2, rt, 98%; (b) *m*-CPBA (2.5 equiv), CH_2Cl_2, rt, 73% (brsm); (c) Ac_2O (3.0 equiv), Et_3N (10.0 equiv), CH_2Cl_2, 0 °C, 91%; (d) LiHMDS (2.5 equiv), THF, −78 to −40 °C, 84% (brsm); (e) Martin's sulfuran (1.8 equiv), CH_2Cl_2, rt, 83%; (f) $Pd_2dba_3{\cdot}CHCl_3$ (0.1 equiv), $^nBu_3P$ (0.2 equiv), HCOOH (5.0 equiv), DIPEA (2.0 equiv), dioxane, 45 °C, 56%; g) DBU (10.0 equiv), toluene, reflux, 41%.

by treatment with DBU in refluxing toluene. The structure of **21** was established by X-ray crystallographic analysis.

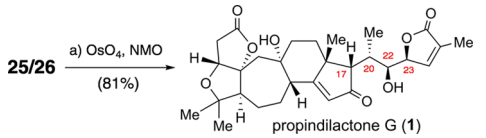
With ketolactone **6** in hand, we entered the final stage of the total synthesis as shown in Scheme 5. We anticipated that an intermolecular oxidative coupling of the conjugated enolsilane[27] **5** with enolsilane **A** could be applied to the synthesis of **22**. Realizing that the intermolecular oxidative heterocoupling of enolsilanes was a daunting task,[28] we systematically profiled this important coupling reaction by using **A** to react with **5**. After a systematic investigation, we found that when ceric (IV) ammonium nitrate[29] (CAN) was utilized as an oxidant, this coupling reaction could proceed smoothly to afford **22** as two pairs of diastereoisomers (corresponding to the two newly generated chiral centers C17 and C20) in 92% overall yield. This reaction was carried out in the presence of 2,6-di-*tert*-butylpyridine (DTBP) at −50 to −30 °C in acetonitrile, and the ratio for the four diastereoisomers was 2.0:2.0:1.1:1 according to ^1H NMR analysis. This mixture without separation then underwent a Horner−Wadsworth−Emmons (HWE) reaction by treatment with ethyl 2-(diphenoxyphosphoryl)propanoate **B** in the presence of KHMDS as a base in THF at −78 °C to give **23**, **24**, and inseparable products **25** and **26** in 16%, 15%, and 60% yields, respectively (see SI for details).

Scheme 5. Synthesis of Compounds 23, 24, and 25/26[a]



[a]Reagents and conditions: (a) **6** (1.0 equiv), TIPOTf (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C to rt, 1 h; then enolsilane **5** (3.0 equiv), CAN (4.5 equiv), DTBP (10 equiv), CH_3CN, −50 to −30 °C, rt, 1.5 h, 92%; (b) **22** (1.0 equiv), 18-crown-6 (15.0 equiv), KHMDS (5.0 equiv), HWE reagent **B** (5.0 equiv), THF, −78 °C, 1.5 h, **23** (16%), **24** (15%), and a mixture of **25**/**26** (60%).

Scheme 6. Total Synthesis of (+)-Propindilactone G (1)[a]



[a]Reagents and conditions: (a) **25**/**26** (1.0 equiv), OsO_4 (0.07 equiv), NMO (2.0 equiv), THF/H_2O (1:1), 4 °C, 72 h, 81% yield of **1** based on the amount of **25** in the mixture of **25**/**26**.

To complete the total synthesis, we expected that one of the four isomers mentioned above could undergo an OsO_4-mediated regio- and stereoselective dihydroxylation, and the resulting intermediate might undergo an intramolecular lactonization to afford the natural product.

To this end, **23**, **24**, and **25**/**26** were treated with OsO_4 in the presence of NMO[30] as a co-oxidant, respectively, to our delight, propindilactone G (**1**) could be made from substrate **25** in 81% yield (based on the amount of **25** in the mixture of **25**/**26**, Scheme 6). The ^1H and ^{13}C NMR spectra and specific rotation of the synthesized propindilactone G were in agreement with those reported in the literature ($[\alpha]_{25}^{D}$ = +39.0, *c* = 0.15 in MeOH; lit.[1] $[\alpha]_{D}^{25.6}$ = +41.1, *c* = 0.15 in MeOH), and its structure has been confirmed by X-ray crystallographic analysis.[31] Thus, as a consequence of our synthetic studies, the structure of (+)-propindilactone G has been revised as compound **1**, and the originally proposed structure of propindilactone G has been reassigned as **1a** (C17-*epi*-(+)-propindilactone G; see Chart 1).

Notably, substrate **26** in the mixture of **25**/**26** was converted to some unidentified products under the reaction conditions. To account for this observation, we carried out a DFT calculation (M11-L//B3LYP),[32], and our preliminary calculation showed that the oxidation of **25** to form intermediate **25**-Os is 1.5 kcal/mol more exothermic than that of **26**. The energy difference can be attributed to the repulsion between the oxygen atom on Os and the labeled carbon in the scaffold of **26**-Os (see SI for details). As a result, the selectivity for the dihydroxylation of **26** would be decreased, leading to the formation of multi-dihydroxylative products.

In conclusion, the total synthesis of (+)-propindilactone G (**1**) was accomplished for the first time in 20 steps (longest linear sequence) starting from (buta-1,3-dien-2-yloxy)triisopropylsilane **9** and (*E*)-methyl 4-oxobut-2-enoate **10**. The key steps in

DOI: 10.1021/jacs.5b06480
J. Am. Chem. Soc. 2015, 137, 10120−10123

this synthesis were an asymmetric DA reaction, a Co-mediated PK reaction, a Pd-catalyzed reductive hydrogenolysis reaction, an oxidative heterocoupling reaction of enolsilanes, and an OsO_4-mediated dihydroxylation. This work demonstrates the power of the PK reaction for the stereoselective construction of cyclopentenone bearing an all-carbon quaternary chiral center, and the oxidative heterocoupling reaction of enolsilanes for the concise ligation of cyclopentenone core **6** with its side chain. The true structure of **1** was revised in accord with our finding, and the originally proposed structure has been reassigned as C17-*epi*-(+)-propindilactone G (**1a**). The application of the synthetic propindilactone G and its analogues as probes to study their biology is currently underway in our laboratories, and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization (cif, pdf). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06480.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. Handong Sun on the occasion of his 75th birthday. We thank Prof. Yu Lan of Chong Qing University for the DFT calculation, and Prof. Wen-Xiong Zhang and Dr. Neng-dong Wang for the X-ray crystallographic analysis. This work is supported by the National 863 Program (Grant No. 2013AA092903, NSFC-Shandong Joint Fund for Marine Science Research Centers (U1406402), and Natural Science Foundation of China (Grant No. 21272015, 21372016, 21472006).

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■ NOTE ADDED AFTER ASAP PUBLICATION

Schemes 3 and 4 were corrected August 19, 2015.

DOI: 10.1021/jacs.5b06480
J. Am. Chem. Soc. 2015, 137, 10120−10123