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Total Synthesis of (–)-Pepluanol B: Conformational Control of the Eight-Membered Ring System

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Abstract: The first total synthesis of the *Euphorbia* diterpenoid pepluanol B is described in 20 steps from a known bicyclic diol in both racemic and asymmetric manners. This synthesis highlights an unprecedented bromo-epoxidation maneuver to control the eight-membered ring conformation. In addition, salient features for construction of the tetracyclic backbone include a sterically hindered aldol reaction to establish the quaternary center, a ring-closing metathesis (RCM) to forge the eight-membered ring and a diastereoselective cyclopropanation to assemble the embedded cyclopropane motif.

Owing to their wide distribution and medicinal value, many species of the *Euphorbia* genus have been used in traditional herbal medicines to treat a range of diseases with long history.[1] The plants of this genus have provided a large number of significant diterpenoids that have attracted widespread attention from both chemical and biological communities.[2] The *Euphorbia* diterpenoids generally possess diverse intricate polycyclic molecular archetectures,[2] and moreover, display a broad spectrum of bioactivities[3] closely associated with human health, such as antitumor, multidrug-resistance reversing (MDR), antiviral and anti-inflammatory properties, which render them intriguing and challenging targets for total synthesis, culminating in numerous elegant synthetic achievements.[4]

In 2016 and 2018, five novel biogenetically related diterpenoids have been successively discovered and named as pepluacetal (**1**) and pepluanols A-D (**2**-**5**) respectively by Qiu and co-workers from the plant of *E. peplus* (Figure 1).[5] Significantly, all the five compounds showed effectively inhibitory actions on the kv1.3 potassium channel which is responsible for autoimmune disorders, making them applicable for treatment of intractable diseases such as asthma, type-1 diabetes, multiple sclerosis, and psoriasis. Among them, pepluanol B (**3**) offered the best IC_{50} value of 9.50 μM. The unique fused polycyclic skeletons with a high oxidation pattern, incorporating 6-8 stereogenic centers, renders these natural products formidable synthetic targets. So far, only the total synthesis of (±)-pepluanol A (**2**) has been accomplished by Ding and coworkers via exploiting an elegant Ti(III)-catalyzed reductive annulation.[4o] Herein, we report the first total synthesis of pepluanol B in both racemic and asymmetric manners in 20 steps.

Structurally, pepluanol B (**3**) comprises a rare fused [5-5-8-3] tetracyclic framework and six stereogenic centers including

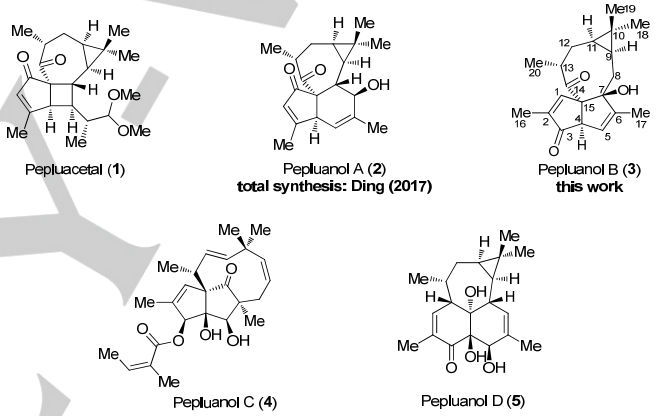
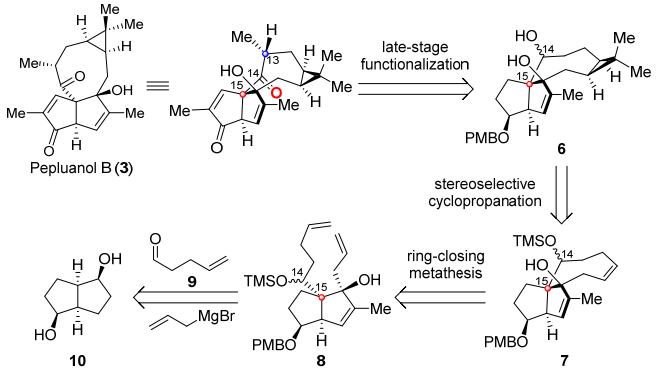
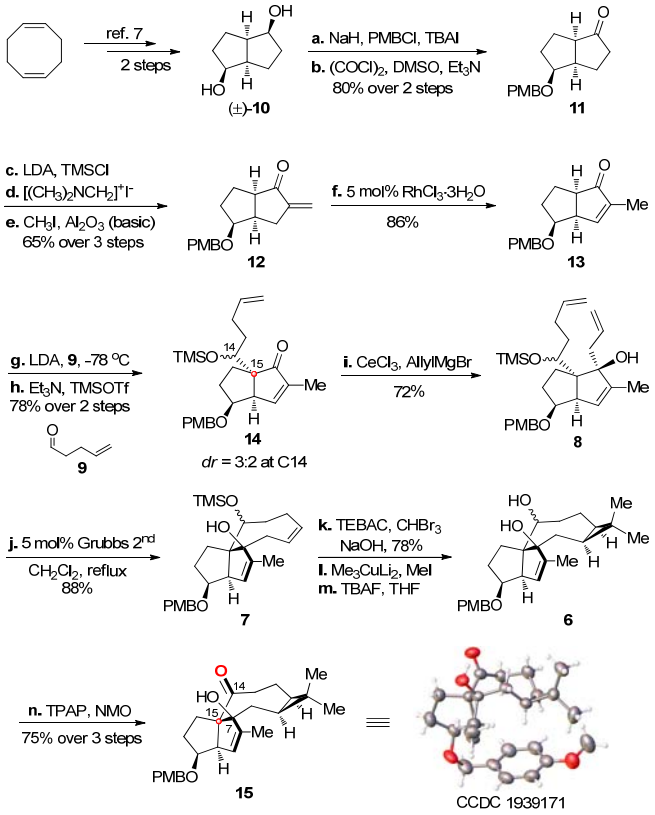


Figure 1. Structures and synthetic progress of *Euphorbia* diterpenoids **1**-**5**.

one bridge-head all-carbon quaternary center (Scheme 1). Notably, the C14 carbonyl adopts a downward orientation based on the single X-ray diffraction analysis. Furthermore, the situation that the C14 carbonyl locates between the C13 and C15 stereocenters is quite similar with the famous challenging "*in-out*" substructure in bridged cyclic systems like ingenol.[6] Thus, it was envisaged that the stereoselective construction of the eight-membered ring system with proper control of the cyclooctanone conformation and installation of the stereocenters would be the critical and formidable task of the synthesis. As for



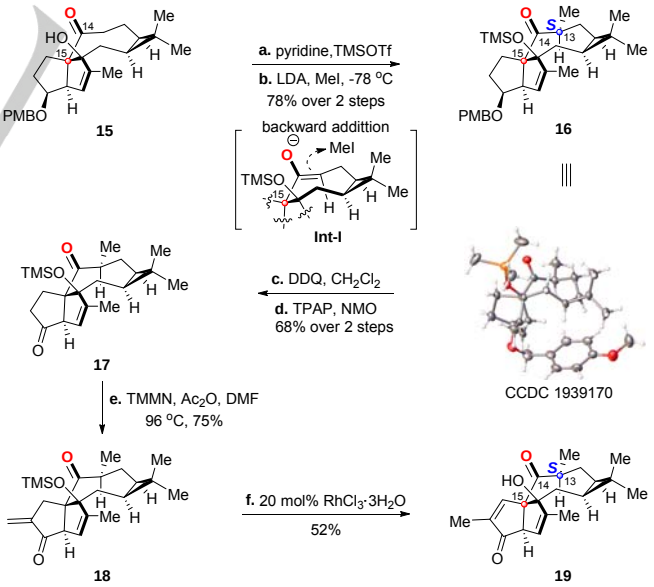
Scheme 1. Retrosynthetic analysis of pepluanol B.



Scheme 2. Construction of tetracyclic scaffold **15**. Reagents and conditions: a) NaH (1.0 equiv.), PMBCl (1.0 equiv.), TBAI (0.1 equiv.), THF, 0 °C → reflux, 3 h; b) $(COCl)_2$ (2.0 equiv.), DMSO (4.0 equiv.), Et_3N (6.0 equiv.), CH_2Cl_2, –78 °C → 25 °C, 1 h, 80% (2 steps); c) LDA (1.2 equiv.), TMSCl (2.0 equiv.), THF, –78 °C → 0 °C, 3 h; d) $[(CH_3)_2NCH_2]^+I^-$ (3.0 equiv.), CH_2Cl_2, 25 °C, 16 h; e) MeI (12.0 equiv.), Al_2O_3 (basic), CH_2Cl_2, 25 °C, overnight, 65% (3 steps); f) $RhCl_3$•H_2O (5 mol%), EtOH/pH 7 buffer (19:1), sealed tube, 110 °C, 25 min, 86%; g) LDA (1.3 equiv.), aldehyde **9** (1.5 equiv.), THF, –78 °C, 3 h; h) Et_3N (4.0 equiv.), TMSOTf (2.0 equiv.), CH_2Cl_2, 0 °C, 30 min, 78% (2 steps); i) $CeCl_3$ (3.0 equiv.), allylmagnesium bromide (3.0 equiv.), THF, –78 °C → 25 °C, 4 h, 72%; j) Grubbs catalyst 2nd generation (5 mol%), CH_2Cl_2, reflux, 3 h, 88%; k) TEBAC (0.1 equiv.), $CHBr_3$ (5.0 equiv.), NaOH (aq., 50 wt%), CH_2Cl_2, 0 °C → 25 °C, 1 h, 78%; l) CuI (4.0 equiv.), MeLi (12.0 equiv.), MeI (28.0 equiv.), Et_2O, –45 °C → 25 °C, 12 h; m) TBAF (1.5 equiv.), THF, 25 °C, 30 min; n) TPAP (10 mol%), NMO (1.5 equiv.), 4 Å MS (0.5 g/mmol), CH_2Cl_2, 25 °C, 30 min, 75% (3 steps). PMB = *p*-methoxybenzyl, TBAI = tetrabutylammonium iodide, DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, TEBAC = benzyltriethylammonium chloride, TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine oxide.

the [5-5] bicyclic system, we recognized that it exhibits a hidden C_2-symmetric character and could be arisen from the known bicyclic diol **10**[7] just by elaborating it to α-methylcyclopentenone. Thus, with the point in mind that the key solution for its synthesis lies in the stereoselective construction of the fused [8-3]-bicyclic framework containing a cyclooctanone and a *gem*-dimethyl cyclopropane motif, a general disconnection was devised as shown in Scheme 1. First, the target molecule **3** could be obtained via an array of late-stage transformations from its precursor **6** which could be traced back to a tricyclic alkene **7** through diastereoselective cyclopropanation. Next, an RCM reaction was chosen to forge the eight-membered ring from intermediate **8**,[8] and the two terminal olefin arms in **8** could be installed through elaboration of bicyclic diol **10** with aldehyde **9** and allylmagnesium bromide. Ultimately, the bicyclic diol **10** could be derived from cyclooctadiene in 2 steps according to the literature protocol.[7]

We commenced our synthesis with the decagram-scale preparation of bicyclic diol **10** in 2 steps from commercially available cyclooctadiene according to the modified literature procedures (Scheme 2).[7] To quickly examine our designed strategy, racemic **10** was initially utilized for route exploration. Mono-protection of **10** with PMB and subsequent oxidation of the other alcohol smoothly delivered ketone **11**, followed by Eschenmoser methylenation[9] giving enone **12**. Then, the *exo*-methylene was effectively converted to the more stable *endo* form enabled by Rh-catalyzed double bond isomerization,[10] which afforded the α-methylcyclopentenone product **13**. To construct the eight-membered ring, it next calls for two terminal olefin arms with different length. Therefore, aldol reaction of **13** with aldehyde **9** by using LDA as base formed the desired C15 all-carbon quaternary center along with 3:2 *dr* for the secondary alcohol, furnishing compound **14** after the ensuing TMS protection. Then, 1,2-nucleophilic addition of the enone moiety with allylmagnesium bromide in the presence of anhydrous $CeCl_3$[11] delivered **8** with exclusive facial selectivity. For the critical RCM reaction to forge the eight-membered ring, after several trials, Grubbs catalyst 2nd generation was gratifyingly found capable for this transformation with high efficiency to deliver cyclic Z-alkene intermediate **7**. Furthermore, dibromocyclopropanation of the Z-alkene **7** proceeded with exclusive regio- and diastereoselectivity followed by nucleophillic bismethylation with Me_3CuLi_2/MeI which successfully assembled the requisite *gem*-dimethyl cyclopropane subunit.[12] The stereospecificity of this cyclopropanation reaction is presumably because the alkene in **7** provided the less hindered convex face for dibromocarbene attacking. Subsequent desilylation with TBAF gave the diol intermediate **6** and Ley-Griffith oxidation of **6**



Scheme 3. Synthesis of compound **19**. Reagents and conditions: a) pyridine (4.0 equiv.), TMSOTf (2.0 equiv.), CH_2Cl_2, 0 °C, 30 min; b) LDA (10.0 equiv.), MeI (10.0 equiv.), THF, –78 °C, 30 min, 78% (2 steps); c) DDQ (3.0 equiv), CH_2Cl_2/pH 7 buffer (9:1), 25 °C, 1 h; d) TPAP (10 mol%), NMO (1.5 equiv.), 4Å MS (0.5 g/mmol), CH_2Cl_2, 25 °C, 30 min, 68% (2 steps); e) TMMN, Ac_2O, DMF, 96 °C, 1 h, 75%; f) $RhCl_3$•$3H_2O$ (20 mol%), EtOH/CH_2Cl_2 (6:1), sealed tube, 100 °C, 2 h, 52%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TMMN = tetramethylmethylenediamine.

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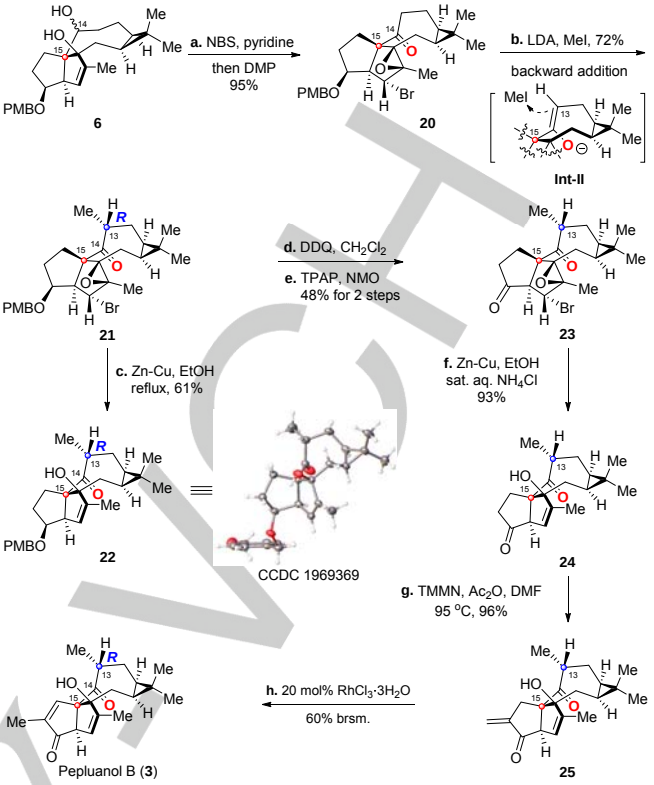
with TPAP produced the crucial compound **15** that contains the tetracyclic framework of pepluanol B.

After comparing the ^{13}C NMR spectra of **15** with natural pepluanol B, a considerable discrepancy of the chemical shifts for the C14 carbonyl signal (223.1 ppm and 209.2 ppm for **15** and **3** respectively) was observed. To further secure the specific structure of **15**, subsequent X-ray analysis of **15** (CCDC 1939171) was then carried out, and we surprisingly found that the C14 carbonyl in **15** adopted an upward orientation nearly parallel to the C7-OH group, which is opposite with natural pepluanol B (*vide supra*) although they share the similar cyclic backbones. To invert the cyclooctanone to the desired twist-boat conformation, **15** was subjected to thermally basic conditions. However, neither DBU in refluxing toluene nor NaOMe in refluxing MeOH was effective for this transformation. We initially anticipated that this conformational issue[13] might be *in situ* diminished in the following synthetic steps with basic conditions. Thus, compound **15** was directly utilized in the following synthetic attempts aiming for the target pepluanol B (Scheme 3). When **15** was treated with NaHMDS and methylation reagent (MeI or MeOTf), the free tertiary alcohol was methylated preferably. Therefore, TMS protection was performed prior to the C13 methylation, which successfully delivered intermediate **16** with excellent diastereoselectivity. X-Ray crystallographic analysis of **16** (CCDC 1939170) suggested that the expected inversion of the cyclooctanone conformation didn't occur while the newly formed C13 configuration was determined to be the undesired *S* rather than *R*. We speculated that the stereochemical outcome for the C13 methylation was because it might generate a stereospecific *Z*-enolate intermediate (**Int-I**) that only provides the backward direction for MeI approaching. To invert the C13 configuration, compound **16** was exposed to a series of basic conditions, but all failed even the strong base *t*BuLi was used. Further removal of the PMB protection with DDQ and oxidation of the corresponding secondary alcohol resulted in ketone **17**, which underwent similar process with **11** including α-methylenation with the *in situ* generated dimethyl iminium cation[14] to afford **18** and Rh-catalyzed double bond isomerization[10] with simultaneous TMS deprotection to introduce the left α-methylcyclopentenone moiety to furnish compound **19**. Even up to this stage, the NMR spectra of **19** were not identical with natural pepluanol B, signifying that the expected *in situ* inversion event of the cyclooctanone conformation as well as the C13 configuration still didn't happen. Disappointingly, DBU in refluxing DCE also failed to convert the stereoisomer **19** to pepluanol B.

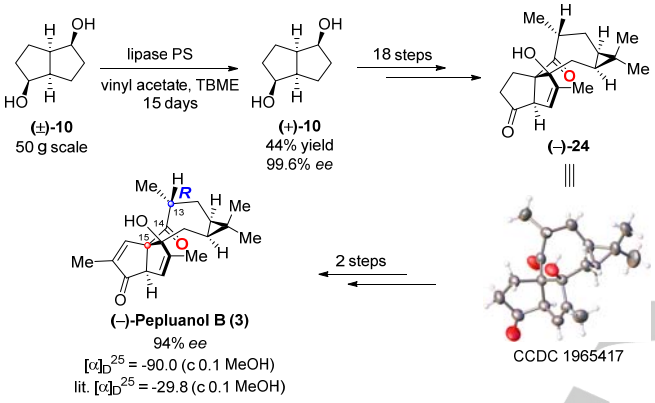
Faced with the failure on inversion of the C14 carbonyl orientation and the configuration at C13 stereogenic center, we supposed that the C13 methylation selectivity was dominated by the cyclooctanone conformation because it determines the spatial direction of the *Z*-enolate double bond. Thus, the key point to tackle the problem lies in the conformational control of the cyclooctanone, which drove us back to reinvestigate the TPAP oxidation step from **6** to **15** (Scheme 2). It was presumed that the C7 tertiary alcohol with an upward orientation might drag the C14 oxygen atom through intramolecular hydrogen bonding in the oxidation process, leading the C14 carbonyl to adopt a favored upward direction. Thereby, the allylic alcohol motif in intermediate **6** was supposed to be temporarily hidden prior to the oxidation of the C14 hydroxyl group. Hence, a bromo-epoxide[15] was chosen to unravel this task because it could



Scheme 4. Total synthesis of (±)-pepluanol B. Reagents and conditions: a) NBS (6.0 equiv.), pyridine (6.0 equiv.), CH_2Cl_2, 25 °C, 1 h, then DMP (3.0 equiv.), 0 °C → 25 °C, 2h, 95%; b) LDA (10.0 equiv.), MeI (10.0 equiv.), THF, −78 °C, 30 min, 72%; c) Zn-Cu couple (1-3% Cu, 45 equiv.), EtOH, reflux, 3 h, 61%; d) DDQ (3.0 equiv.), CH_2Cl_2/pH 7 buffer (9:1), 25 °C, 1 h; e) TPAP (10 mol%), NMO (1.5 equiv), 4 Å MS (0.5 g/mmol), CH_2Cl_2, 25 °C, 30 min, 48% (2 steps); f) Zn-Cu couple (1-3% Cu, 15 equiv.), EtOH/sat. aq. NH_4Cl (10 : 1), 25 °C, 15 min, 93%; g) TMMN, Ac_2O, DMF, 95 °C, 1 h, 96%; h) $RhCl_3$•$3H_2O$ (20 mol%), EtOH/pH 7 buffer (4:1), sealed tube, 95 °C, 40 min, 48%, 60% brsm. NBS = *N*-bromosuccinimide, DMP = Dess-Martin periodinane, brsm = based on recovered starting material.

release allylic alcohol at proper time and moreover, the strained epoxide could enhance the rigidity of the molecular backbone for better stereocontrol. Therefore, intermediate **6** was exposed to NBS/pyridine to convert the allylic alcohol into the bromo-epoxide and subsequently treated with Dess-Martin periodinane in one-pot to oxidize the secondary alcohol to ketone **20** as a sole isomer (Scheme 4). Then, the LDA-promoted methylation occurred smoothly to give compound **21** with the *R* configuration at the C13 stereocenter established exclusively, suggesting that, in one hand, the *Z*-enolate configuration provided the backward direction for MeI approaching, and on the other hand, the *Z*-enolate double bond was dominated by the cyclooctanone to adopt a vertical spatial orientation (**Int-II**). Gratifyingly, subsequent release of the tertiary allylic alcohol with Zn-Cu couple in refluxing EtOH[15a] yielded compound **22** as a white solid for single crystallographic X-ray analysis (CCDC 1969369) which unambitiously revealed that the C14 carbonyl adopted a downward orientation as expected, and the C13 methyl configuration was well-established as desired. Up to this stage, the obtained eight-membered ring conformation in compounds **20** and **21** could also be elucidated as the desired one.

With the conformational issue addressed successfully, and in order to further introduce the left α-methylcylcopentenone moiety for finishing the total synthesis, we initially tried to remove the PMB protecting group in **22**. However, a series of conditions failed to achieve this transformation, probably due to the instability of the allylic alcohol moiety. Pleasingly, it was found that the bromo-epoxide intermediate **21** could tolerate the oxidative condition with DDQ to cleave the PMB protecting group and the corresponding secondary alcohol was then oxidized to cylcopentanone **23** with TPAP. Subsequently, the bromo-epoxide mask in **23** was taken off to unveil the allylic alcohol **24** in excellent yield with Zn-Cu couple in the presence of saturated aqueous NH_4Cl.[15b] As the endgame, following similar protocol shown in Scheme 3, compound **24** underwent α-methylenation[14] to furnish enone **25** and Rh-catalyzed double bond isomerization[10] of **25** completed the first total synthesis of (±)-pepluanol B. Accordingly, the NMR data of the obtained sample were in good agreement with the isolated pepluanol B.



Scheme 5. Enantioselective synthesis of (–)-pepluanol B. Reagents and conditions for lipase resolution: lipase from *Pseudomonas cepacia (*15.0 g/50.0 g starting material), vinyl acetate/TBME = 1/2 (v/v), *c* = 0.70 M, 25 °C, 15 days, 44%. TBME = *tert*-butyl methyl ether.

Having established the stereoselective route toward (±)-pepluanol B, its enantioselective version was implemented starting from the chiral diol (+)-**10** (Scheme 5). Thus, efficient kinetic resolution of racemic **10** was carried out to supply chiral diol (+)-**10** in 99.6% *ee* when lipase from *pseudomonas cepecia* served as an acetylation enzyme.[7] Following the developed synthetic route, the first enantioselective total synthesis of (–)-pepluanol B was finally realized with 94% *ee*. Based on the X-ray crystallographic analysis of the chiral intermediate (–)-**24** (CCDC 1965417), and in association with the optical rotation data comparison of the synthetic and authentic samples ($[\alpha]_D^{25}$ = –90.0, c 0.10 MeOH; lit. $[\alpha]_D^{25}$ = –29.8, c 0.10 MeOH), the absolute configuration of naturally-occurring pepluanol B was unambitiously confirmed.

In conclusion, the first total synthesis of bioactive *Euphorbia* diterpenoid pepluanol B in both racemic and highly enantioselective manners was accomplished in 20 steps from the known bicyclic diol **10** (23 steps from commercially available feedstock) in 3.0% overall yield. The tetracyclic carbon backbone of the target molecule was constructed through a series of highly stereoselective C-C bond formation reactions including a sterically hindered aldol reaction, a nucleophilic Grignard reagent addition, an RCM reaction and a cyclopropanation reaction. Notably, the C14 carbonyl orientation was found to be critical to the C13 methylation stereochemical outcome, making the conformational control of the eight-membered ring a formidable problem for the synthesis. Finally, when a bromo-epoxide was significantly designed and exploited as the tertiary allylic alcohol mask, the challenging goal was successfully achieved with the C14 carbonyl to adopt a desired downward orientation and the C13 methylation stereochemistry to be solved accordingly. The enantioselective synthesis of pepluanol B was accomplished starting from chiral bicyclic diol (+)-**10** that was obtained with high optical purity by enzyme-promoted kinetic resolution. This described route allows sufficient supply of (–)-pepluanol B (7.7 mg) for further biological investigations. Synthetic efforts towards other members of this family is currently ongoing in our laboratory.

Acknowledgements

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Keywords: Euphorbia diterpenoid • pepluanol B• total synthesis • conformational control • bromo-epoxide

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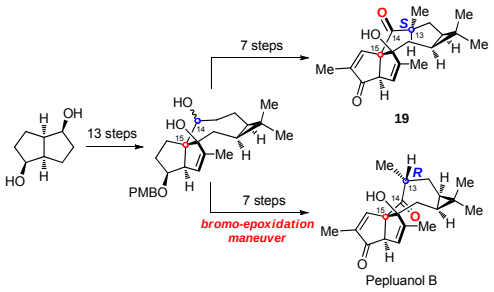

Make it downward. The first total synthesis of the *Euphorbia* diterpenoid pepluanol B is described in both racemic and asymmetric manners. This synthesis features an unprecedented bromo-epoxidation maneuver to dominate the C14 carbonyl to a downward orientation as naturally-occurred, with which the stereochemistry of C13 methylation can be established properly. In addition, an array of other stereocontrolled chemical transformations are exploited to construct the tetracyclic backbone, including a sterically hindered aldol reaction to establish the C15 quaternary center, a ring-closing metathesis (RCM) to forge the eight-membered ring and a diastereoselective cyclopropanation to assemble the embedded cyclopropane motif.