Total Synthesis

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An Enantioselective Total Synthesis of (+)-Peloruside A**

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Peloruside A (**1**), a potent microtubule stabilizer that acts in a manner synergistic to that of paclitaxel, was first isolated in 2000 by Northcote and co-workers from a marine sponge of the Pelorus Sound in New Zealand.[1a] The absolute stereochemistry of **1** was established in De Brabander and co-workers' initial total synthesis in 2003,[2] and since then three other total syntheses have been reported.[3–5]

Herein, we describe a convergent total synthesis of peloruside A in which three different enantioenriched epoxides (**8**, **9**, and **11**; Figure 1), obtained using asymmetric catalytic methodologies, serve as the key building blocks for the stereochemically complex macrocyclic framework. A second key strategic feature is a chiral-catalyst-controlled diastereoselective hetero-Diels–Alder reaction for the construction of intermediate **7**. The application of direct catalyst control is complementary to the previous synthetic approaches to peloruside A, which relied primarily on substrate- and auxiliary-based diastereocontrol to establish the relative and absolute stereochemical features of the natural product.[2–5]

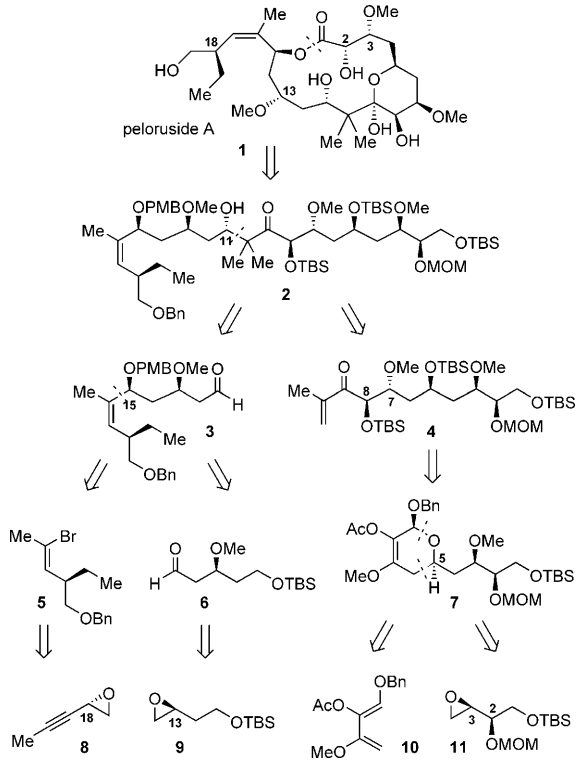
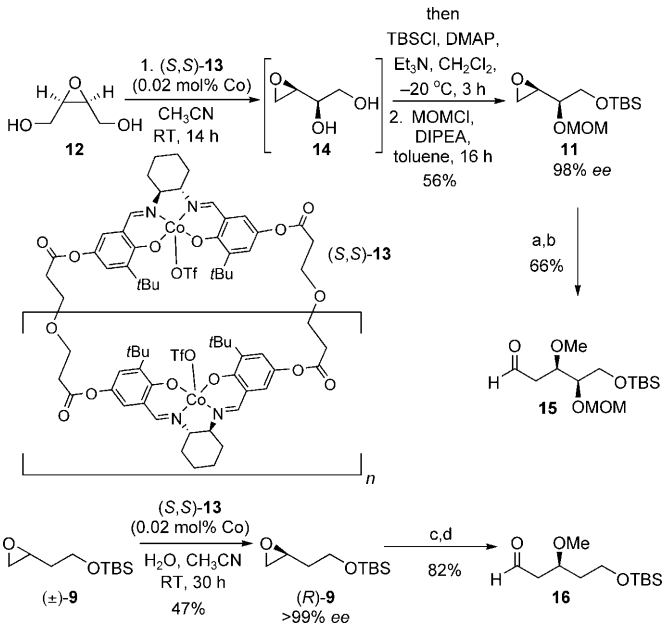


Figure 1. Retrosynthetic analysis of peloruside A.

Dissection of the seco ester form of peloruside A into fragments of roughly equal size and complexity suggested aldehyde **3** and enone **4** as potentially useful late-stage intermediates (Figure 1).[6] The synthesis of enone **4** began with a highly enantioselective Payne rearrangement of *meso*-epoxy diol **12**, available in one step from commercial *cis*-2,3-butenediol, into enantioenriched terminal epoxide **14** (Scheme 1).[7] This transformation was catalyzed by oligomeric cobalt salen catalyst **13**,[8] which established an equilibrium that favored terminal epoxide **14** over *meso* epoxide **12** in a 7:3 ratio. Epoxide **14** was unstable to purification, but protection as the primary silyl ether in situ and subsequent



Scheme 1. Asymmetric Payne rearrangement and elaboration. Reagents and conditions: a) CuBr (10 mol%), vinyl magnesium bromide, −40 °C, 2 h; then HMPA, Me_2SO_4, RT, 48 h; b) O_3, CH_2Cl_2, −78 °C; then PPh_3, RT, 3 h; c) CuBr (10 mol%), vinyl magnesium bromide, −40 °C, 2 h; then HMPA, Me_2SO_4, 4 °C, 48 h; d) O_3, CH_2Cl_2, −78 °C; then PPh_3, RT, 3 h. DIPEA = diisopropylethylamine, TBSCl = *tert*-butyldimethylsilyl chloride, MOMCl = methoxymethyl chloride, HMPA = hexamethylphosphoramidite, PPh_3 = triphenylphosphine.

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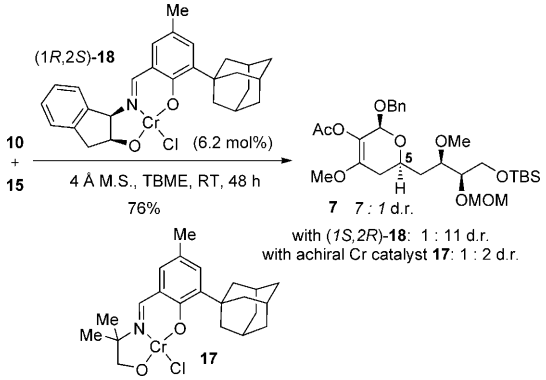
alkylation of the secondary alcohol provided the functionally rich bis-protected epoxide **11** in good overall yield.[9]

Epoxide **11** was subjected to a one-pot vinyl cuprate addition/methylation, followed by ozonolysis to provide aldehyde **15** in 66% overall yield. In an analogous manner, enantiopure aldehyde **16** was obtained from racemic epoxide **9** using a high-yielding hydrolytic kinetic resolution (HKR)/vinylation/alkyation/ozonolysis sequence.

Aldehyde **15** was then engaged in a hetero-Diels–Alder (HDA) reaction with trioxy-substituted diene **10**, available in two steps from methyl benzyloxyacetate (Scheme 2; for

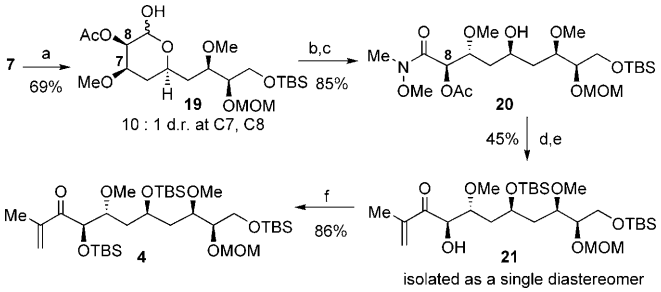


Scheme 2. Diastereoselective hetero-Diels–Alder Reaction. TBME = *tert*-butyl methyl ether.

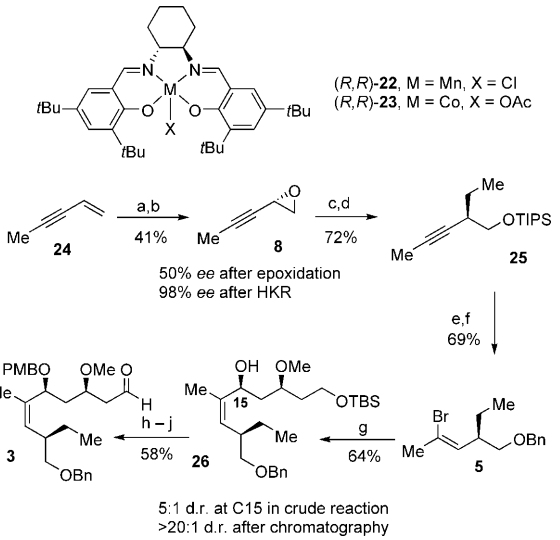
further details, see the Supporting Information). Diene **10** was highly sensitive to decomposition in the presence of strong Lewis acids, but cycloadditions catalyzed by (Schiff-base)chromium complexes were found to proceed cleanly. The degree of intrinsic substrate diastereocontrol was poor, as reaction with achiral chromium catalyst **17** afforded cycloadduct in a 1:2 diastereomeric ratio, favoring the undesired isomer. However, the chiral chromium–Schiff-base complex (1*R*,2*S*)-**18**[10] catalyzed the formation of the desired product **7** in good yield and 7:1 d.r., favoring the desired isomer. Conversely, the enantiomeric catalyst (1*S*,2*R*)-**18** provided the undesired diastereomer in high (1:11) selectivity. This result represents one of the most demanding applications reported to date of the use of catalyst **18** in a HDA reaction between stereochemically and functionally complex substrates.[11]

Hydrogenation of hetero-Diels–Alder adduct **7** took place diastereoselectively, and concomitant hydrogenolysis of the *O*-benzyl acetal provided **19** in 69% yield and in 10:1 d.r. (Scheme 3).[12] Oxidation of lactol **19** and opening of the resulting lactone with *N*,*O*-dimethylamine hydrochloride afforded Weinreb amide **20**, which was protected as a secondary TBS ether. Addition of isopropenylmagnesium bromide occurred with cleavage of the C8 acetate ester to provide hydroxyenone **21**, which was purified chromatographically to >20:1 d.r. The C8 hydroxy group was then reprotected as the TBS ether to provide aldol coupling partner **4**.

In the approach to aldehyde **3**, epoxide **8** was prepared in high *ee* from enyne **24**, available in two steps from commercial 3-pentyn-1-ol,[13] using a (salen)manganese-catalyzed epoxidation[14]/hydrolytic kinetic resolution (HKR) sequence.[15] Epoxide **8** was then opened stereospecifically and regioselectively at the propargylic position, and the resulting primary alcohol was protected as the triisopropylsilyl ether to provide alkyne **25** in 72% yield over two steps (Scheme 4). This strategy of opening a terminal epoxy-alkyne at the internal position with a simple Grignard reagent provides a concise and convenient method for the stereocontrolled synthesis of homopropargylic primary alcohols.



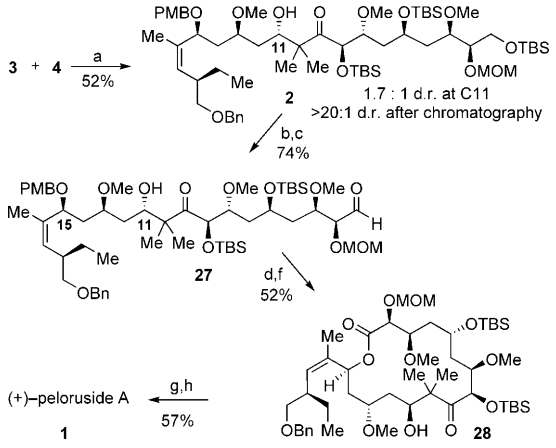
Scheme 3. Elaboration of the hetero-Diels–Alder adduct **7** to enone **4**. Reagents and conditions: a) Pd/C, *i*PrOH, pH 7 buffer, H_2 (200 psi), 48 h; b) KBr, TEMPO, NaOCl, pH 7 buffer, CH_2Cl_2, 0 °C, 90 min; c) *N*,*O*-dimethylamine hydrochloride, $AlMe_3$, toluene, −10 °C, 90 min; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; e) isopropenyl-magnesium bromide, THF, 5 h; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C, 4 h. TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxyl (free radical), THF = tetrahydrofuran, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.



Scheme 4. Synthesis of key aldehyde fragment **3**. Reagents and conditions: a) **22** (5.0 mol%), NaOCl, CH_2Cl_2, 0 °C, 6.5 h; b) **23** (0.50 mol%), H_2O, Et_2O, 0 °C to RT, 24 h; c) ethylmagnesium chloride, THF, −78 °C to rt, 4 h; d) TIPSCl, imidazole, DMF, RT, 16 h; e) catecholborane, 40 to 50 °C, 48 h; then bromine, CH_2Cl_2, −78 °C, 10 min.; then TBAF, THF, 40 °C, 2.5 h; f) 2-benzyloxy-1-methylpyridinium triflate, MgO, trifluorotoluene, 83 °C, 24 h; g) *sec*-butyllithium, THF, Et_2O, −78 °C; then **16**, THF, −78 °C to RT, 16 h; h) PMBBr, NaH, DMF, RT, 2 h; i) acetic acid, H_2O, THF, RT, 16 h; j) Dess–Martin periodinane, CH_2Cl_2, RT, 4 h. DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, TIPSCl = triisopropylsilyl chloride, PMBBr = *p*-methoxybenzyl bromide.

Silyl ether **25** was further elaborated to vinyl bromide **5** by a one-pot hydroboration/bromination/elimination/silyl-deprotection sequence (Scheme 4).[16] Protection of the resultant primary alcohol as the benzyl ether provided compound **5** in 69% overall yield from **25**.[17] This protecting group exchange on the C20 hydroxy group was advantageous because a large silyl protecting group was required for attaining high regioselectivity (9:1) in the hydroboration of compound **25**, whilst the presence of a benzyl protecting group led to improved diastereoselctivity in the addition of the vinyl lithium reagent (derived from **5**) to aldehyde **17**. In this manner, alcohol **26** was obtained in 5:1 d.r. and isolated in 64% yield following chromatographic purification. In contrast, analogous silyl-protected vinyl bromides (TIPS, TBDPS) led to their corresponding allylic alcohols in only 2:1 d.r. Alcohol **26** was then protected as the paramethoxybenzyl ether, and the primary alcohol was selectively unmasked and oxidized with the Dess–Martin periodinane to provide aldehyde **3** in 58% yield over the three steps.

Enone **4** and aldehyde **3** were coupled using a reductive aldol reaction, similar to that utilized in the Ghosh synthesis of peloruside A,[4] to afford **2** in 1.7:1 d.r. Despite the modest stereoselectivity in this step, **2** could be isolated in diastereomerically pure form in 52% yield following chromatographic purification (Scheme 5). The primary TBS ether was then removed selectively using buffered HF·pyridine and the resulting alcohol was oxidized into aldehyde **27** in 74% yield over the two steps. Aldehyde **27** was then oxidized into the corresponding acid, and the crude reaction mixture was subjected to pH 7-buffered DDQ to cleave the C15 PMB ether and afford the macrolaconization substrate. The seco acid was subjected without purification to Yamaguchi conditions to provide macrolactone **28** in 52% yield for the three steps from aldehyde **27**. This macrolactonization strategy drew direct inspiration from the Evans approach to peloruside A, employing a similarly protected seco acid,[5] wherein differentiation between free hydroxy groups at C11 and C15 was also observed. Finally, the benzyl protecting group at the C20 hydroxy group was removed under transfer hydrogenolysis conditions, and a subsequent global removal of the remaining protecting groups under strongly acidic conditions[18] afforded (+)-peloruside A (**1**), isolated in 57% yield, with characterization data matching those reported for the natural product.[1]



Scheme 5. Synthesis of (+)-peloruside A. Reagents and conditions: a) L-Selectride, THF, −78 °C, 2 h; then −40 °C, 2 h; b) HF·pyridine, pyridine, THF, 0 °C to RT, 2 h; c) bis-acetoxyiodobenzene, TEMPO, CH_2Cl_2, RT, 16 h; d) $NaClO_2$, NaH_2PO_4, isoamylene, H_2O, *t*BuOH; e) DDQ, pH 7 buffer, CH_2Cl_2, 5 h; f) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, RT, 16 h; then DMAP, toluene, 60 °C, 48 h; g) Pd/C, formic acid, EtOAc, MeOH, RT, 1 h; h) 1 N HCl, THF, RT, 16 h; then 4 N HCl, THF, RT, 3.5 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-bezoquinone, DMAP = 4-(dimethylamino)pyridine.

This convergent synthesis of (+)-peloruside A required 20 steps in the longest linear sequence from commercially available materials. This approach relies on the availability of both simple (e.g., **8** and **9**) and relatively complex (i.e., **11**) terminal epoxides from (salen)Co-catalyzed ring-opening reactions, and on chiral-catalyst-induced diastereocontrol in a key hetero-Diels–Alder cycloaddition reaction between advanced intermediates. This route provides a useful illustration of the applicability of modern asymmetric catalytic methods in the total synthesis of stereochemically complex polyketides.

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