Natural Product Synthesis

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Total Synthesis of (±)-Pentalenolactone A Methyl Ester**

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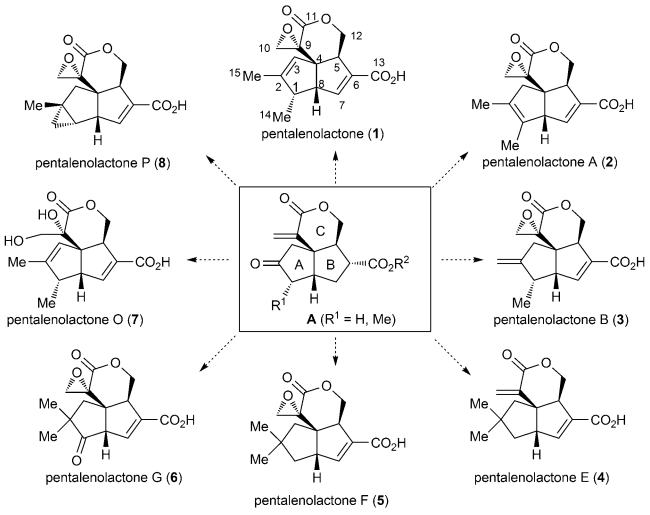
Pentalenolactone A (**2**) is a prominent member of a group of naturally occurring antibiotics (**1**–**8** in Scheme 1) produced by prokaryotic organisms.[1] These compounds exhibit a broad spectrum of activities against bacteria, fungi, viruses, and tumors.[2] Biological evaluation of the pentalenolactones has demonstrated that they can specifically inhibit glyceraldehyde-3-phosphate dehydrogenase in *Trypanosoma brucei*,[3] thus indicating that these compounds could be potential candidates for the development of new antibiotic agents.

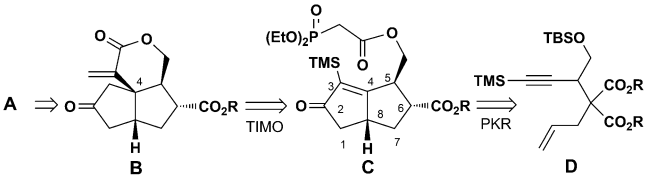
The structure of **2** was determined by NMR analysis of its methyl ester derivative.[1d] the analysis revealed that the structure consisted of a highly compact carbon skeleton, with a rare, angularly fused tricyclic pentanoid lactone with different oxidation states in each of the rings. Efforts have been focused on exploring feasible strategies for the chemical synthesis of these pharmacologically significant natural substances, leading to the first total synthesis of pentalenolactone (**1**) in 1978, as well as the more recent synthesis of pentalenolactones E, F, G, H, and P.[4]

In our laboratories, we have endeavored to identify an approach that would allow for rapid access to the compact carbon skeleton **A** (Scheme 1). It was envisaged that this structure would provide a platform for the total synthesis of the entire family of pentalenolactones, and the modular construction of a library of analogues for further medicinal chemistry studies.

Previous investigations have demonstrated that the Pauson–Khand reaction[5] (PKR) is an efficient method for the construction of cyclopentenone frameworks in the total synthesis of natural products.[6] Our interest in expanding the scope of the PKR in the synthesis of cyclopentenones led us to explore the viability of PKR in the synthesis of intermediate **C** from TMS-substituted enyne **D** (TMS = trimethylsilyl; Scheme 2). We were also interested in investigating the



Scheme 1. Pentalenolactones and their synthetic relationship.



Scheme 2. Retrosynthetic analysis.

construction of the tricyclic pentalenolactone core **B** from **C** through the telescoped intramolecular Michael/olefination (TIMO), which was developed by Taylor et al. in 2007.[7] Herein, we report a novel strategy for the stereoselective total synthesis of the stable methyl ester of pentalenolactone A (**23**). The key steps in the synthesis include an intramolecular PKR for the formation of the cyclopentenone and a TMS-mediated TIMO reaction for the construction of the quaternary carbon-based and highly strained tricyclic pentanolactone core (Scheme 2).

Because the reactivity and stereoselectivity of intramolecular PKRs are often substrate-dependent,[8] particularly when there is a substituent at the C5 position,[9] we initially began to profile substrates and identified enyne **11** as an ideal substrate for the PKR, because it provided exclusive formation of cyclopetenone **12** (Scheme 3). To begin the synthesis of

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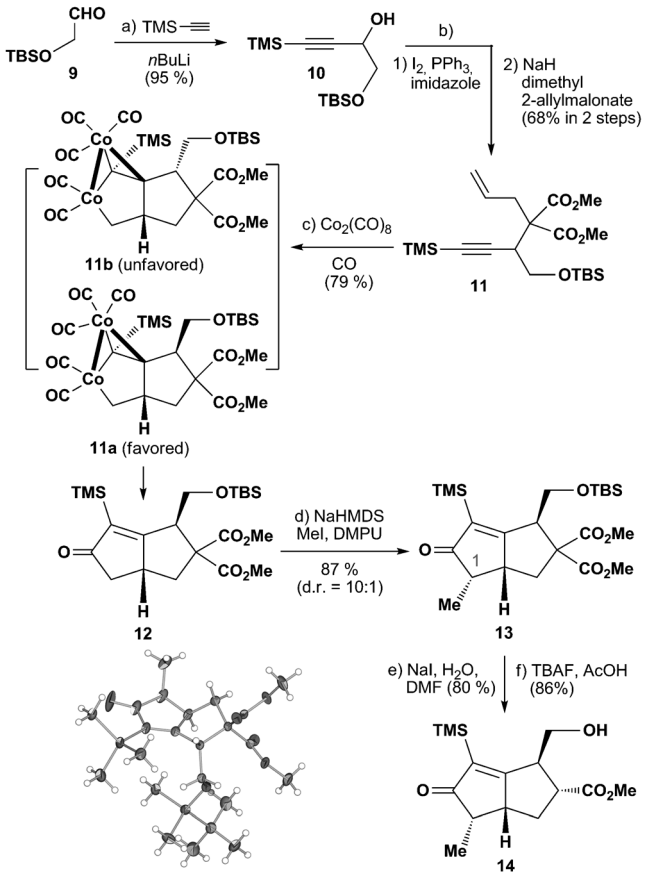


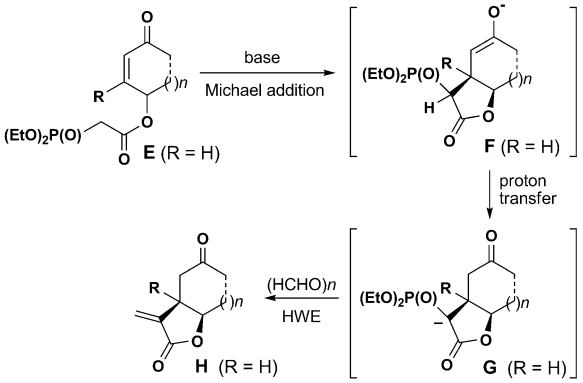
Scheme 3. Synthesis of compound **14**. a) *n*BuLi (1.5 equiv), TMSC≡CH (1.5 equiv), THF, −7 8 °C, 95 %. b) 1) I_2 (1.5 equiv), PPh_3 (1.5 equiv), imidazole (2.5 equiv), THF, 0 °C; 2) dimethyl 2-allylmalonate **12** (1.1 equiv), THF, reflux, 68 % (2 steps). c) $Co_2(CO)_8$ (1.0 equiv), CO, benzene, 70 °C, 8d, 79 %. d) NaHMDS (1.6 equiv), MeI (5.0 equiv), DMPU (3.0 equiv), THF, −78 °C, 9 h, 87 % (d.r. = 10:1). e) NaI (2.0 equiv), H_2O, DMF, 140 °C, 10.5 h, 80 %. f) TBAF/AcOH = 1:1.05, THF, 0 °C to RT, 12 h, 86 %. DMF = dimethylformamide, DMPU = dimethyltetrahydropyrimidin-2(1*H*)-one, NaHMDS = sodium bis(trimethylsilyl)amide, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

12, aldehyde **9** was first reacted with lithium ethynylate at −78 °C to give proparyl alcohol **10** in 95 % yield. The newly generated hydroxy group in **10** was converted into the corresponding iodo species by treatment with I_2/imidazole in the presence of Ph_3P. The resulting iodo species was then reacted with sodium dimethyl 2-allylmalonate to afford **11** in 68 % yield over two steps. With **11** in hand, we proceeded to evaluate its performance in the PKR. Pleasingly, under the optimized conditions, enyne **11** reacted to give **12** as a single diastereoisomer, although the reaction did require eight days to achieve a satisfactory level of conversion. The exclusive formation of **12** was attributed to the minimization of steric interaction between the TMS and CH_2OTBS (TBS = *tert*-butyldimethylsilyl) groups in complex **11a**[10] relative to complex **11b**, which subsequently led to the exclusive formation of the desired annulated product **12**.

To install the methyl group at the C1 position, **12** was initially treated with sodium hexamethyldisilazide (NaHMDS) in THF at −78 °C in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), followed by reaction with MeI to give the desired product **13** in 87 % yield, together with its diastereoisomer in 8 % yield. The stereochemistry of **13** was unequivocally confirmed by X-ray analysis.[11] **13** was then treated with NaI in a DMF and H_2O at 140 °C for 10.5 h to afford the corresponding mono-ester, which was subsequently desilylated to give alcohol **14** in 69 % yield over two steps.

We then turned our attention to the construction of the tricyclic α-methylidene-δ-pentyrolactone fragment, which represents a rare scaffold found in natural products. Previously reported strategies for the construction of this fragment are invariably low yielding[4m] and involved the construction of the lactone ring first, followed by reaction with Bredereck's reagent,[12] Stiles' reagent,[13] and Eschenmoser salt,[14] as well as hydroxylmethylation/dehydration[4a,4] as key steps.

The TIMO reaction has been reported as a concise method for the construction of α-methylidene-γ-butyrolactones,[7] and it has been suggested that the reaction occurs according to the process shown in Scheme 4. Unfortunately,

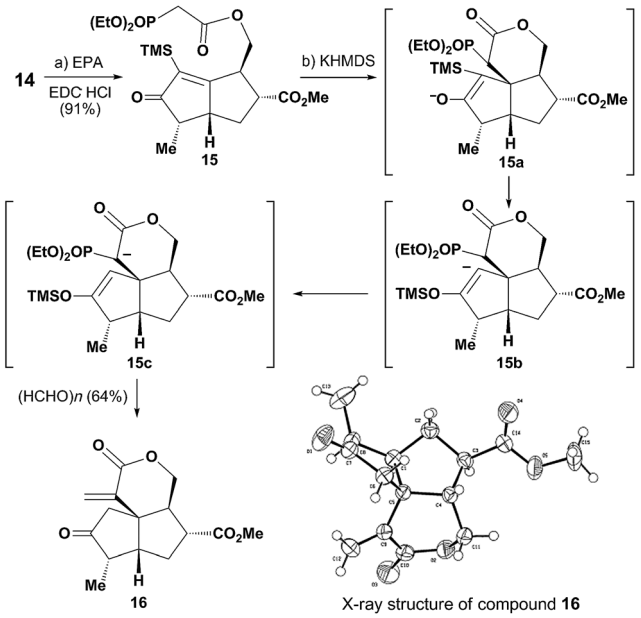


Scheme 4. Synthesis of α-methylidene-γ-butyrolactones **H**. HWE = Horner–Wadsworth–Emmons reaction.

however, this method could not be applied to the synthesis of α-methylene-δ-pentyrolactone, because the R group of substrate **E** would be an alkyl group, and this would result in a negative steric effect that would prevent the occurrence of the Michael addition and the formation of a quaternary carbon center.[7b,15]

It was envisaged that the incorporation of a TMS group into **15** (Scheme 5) through the formation of **15a** would provide the necessary additional driving force to promote the initial step of the Michael addition.[16] Furthermore, it was anticipated that the TMS enolate **15a** would undergo a Brook rearrangement[17] followed by a proton transfer to give stable phosphonate anion **15c**, which could react with formaldehyde to give the annulated product **16** through a Horner–Wadsworth–Emmons (HWE) reaction.

To achieve the proposed chemistry, alcohol **14** was coupled with diethyl phosphonoacetic acid (EPA) in the presence of 1-ethyl-3-(3-dimetylaminopropyl) carbodiimide



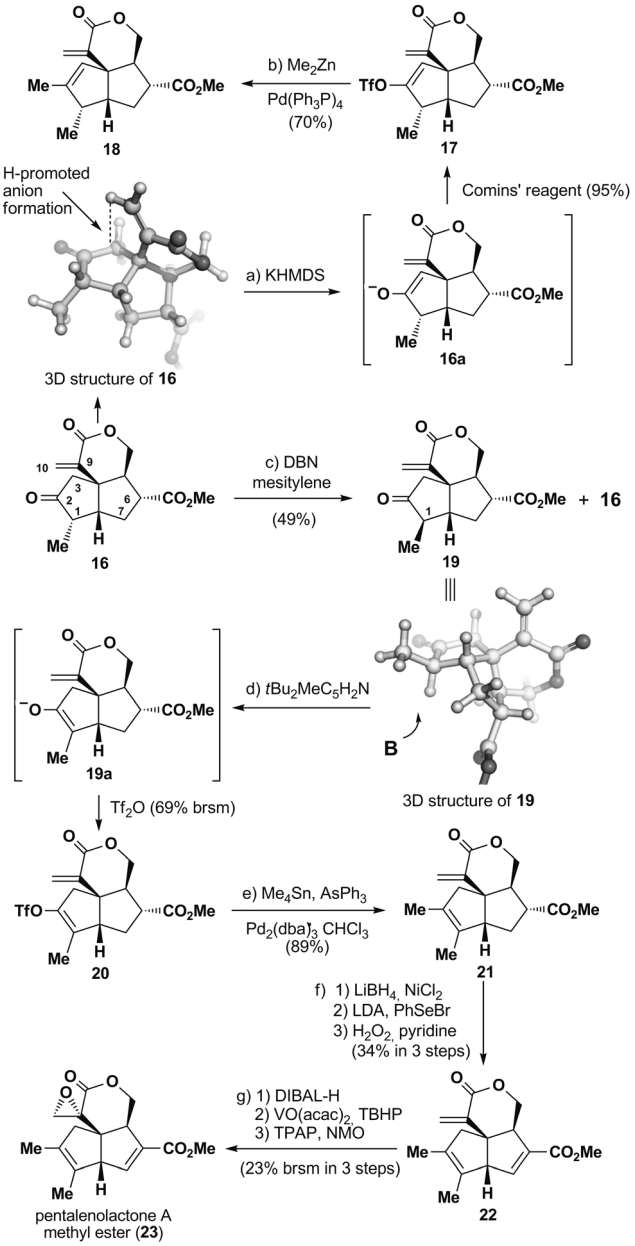
Scheme 5. Synthesis of key intermediate **16**. a) EPA (2.0 equiv), EDC·HCl (2.0 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 0 °C to RT, 3 h, 91 %. b) KHMDS (1.0 equiv), THF, −78 °C to RT, then $(HCHO)n$ (5.0 equiv), −78 °C to RT, 120 h, 64 %. 4-DMAP = 4-dimethylaminopyridine, EPA = diethyl phosphonoacetic acid, EDC·HCl = 1-ethyl-3-(3-dimethylaminopropyl)carboiimide hydrochloride, KHMDS = potassium bis(trimethylsilyl)amide.

hydrochloride (EDC·HCl) and 4-dimethylaminopyridine (4-DMAP) in CH_2Cl_2 to give keto-phosphonate **15** in 91 % yield.

Following a period of extensive experimentation, we found that substrate **15** could be converted into the corresponding α-methylidene-δ-pentyrolactone **16** in 64 % yield when **15** was treated with KHMDS in THF −78 °C, followed by reaction with paraformaldehyde. The structure of **16** was unequivocally confirmed by its X-ray crystallographic analysis.[18]

With key intermediate **16** in hand, we proceeded with the construction of advanced intermediate **21** (Scheme 6) and the total synthesis of pentalenolactone A methyl ester (**23**). Unfortunately, however, the regioselective installation of the C1=C2 bond proved to be problematic, as a consequence of difficulties associated with the formation of enol triflate **20**. Initially, we attempted to generate enol triflate **20** by the treatment of ketone **16** with strong bases (such as lithium diisopropylamide (LDA), LiHMDS, NaHMDS, and KHMDS). Unfortunately, in all cases enol triflate **17** was formed as the major product, and 95 % yield of **17** could be obtained when substrate **16** was treated with KHMDS in THF at −78 °C, followed by reaction with Comins' reagent.[19] The formation of enolate **16a** was ascribed to both the steric hindrance of the deprotonation of C1 and the stabilizing influence of the terminal methylene proton[20] on the formation of enolate **16b** through an electrostatic interaction[21] (see the 3D structure of **16** in Scheme 6).

The decision was made to synthesize compound **18** using the Negishi cross-coupling reaction[22] because this compound was a key intermediate in the total synthesis of pentaleno-



Scheme 6. Completion of the total synthesis. a) KHMDS (1.1 equiv), Comins' reagent (1.5 equiv), THF, −78 °C, 2 h, 95 %; b) Me_2Zn (3.0 equiv), $Pd(PPh_3)_4$ (0.2 equiv), THF, 0 °C to RT, 14 h, 70 %. c) DBN (0.02 equiv), mesitylene, 150 °C, 1 h, 49 %. d) Tf_2O (2.0 equiv), $tBu_2MeC_5H_2N$ (2.0 equiv), DCE, 90 °C, 19 h, 59 % (brsm 69 %). e) Me_4Sn (1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 % mol), $AsPh_3$ (0.2 equiv), NMP, 60 °C, 24 h, 89 %. f) 1) $LiBH_4$, $NiCl_2$ (2.0 equiv); MeOH, 0 °C, 80 min; 2) LDA (6 equiv), PhSeBr (7.0 equiv), −78 °C to RT, 8 h; 3) H_2O_2, pyridine, CH_2Cl_2, 0 °C, 0.5 h, 34 % (3 steps). g) 1) DIBAL-H (1.05 equiv), CH_2Cl_2, −78 °C, 1 h; 2) $VO(acac)_2$, TBHP (2.2 equiv), benzene, 60 °C, 20 min; 3) TPAP, NMO (2.0 equiv), 4 Å MS, CH_2Cl_2, 40 min, 23 % (brsm in 3 steps). acac = acetylacetonate, brsm = based on recovered starting material, $tBu_2MeC_5H_2N$ = 2,6-di-*tert*-butyl-4-methylpyridine, dba = dibenzylideneacetone, DBN = 1,5-diazabicyclo-[4,3,0]non-5-ene, DCE = 1,2-dichloroethane, DIBAL-H = diisobutylaluminum hydride, KHMDS = potassium bis(trimethylsilyl)-amide, LDA = lithium diisopropylamide, NMO = *N*-methyl morpholine-*N*-oxide, NMP = *N*-methyl-2-pyrrolidinone, TBHP = *tert*-butyl hydroperoxide, Tf = trifluoromethanesulfonyl, TPAP = tetrapropylammonium perruthenate.

lactone (**1** in Scheme 1), as reported by Danishefsky et al.[4a] Thus, triflate **17** was coupled with Me_2Zn using $Pd(PPh_3)_4$ as catalyst to give product **18** in 70% yield, which constitutes a formal total synthesis of pentalenolactone (**1**).

We envisioned that by inverting the stereochemistry at C1 of ketone **16**, the hypothetical precursor **19** formed (Scheme 6) might adopt a conformation that would favor the formation of enolate **19a**. To test this, ketone **16** was treated with 1,5-diazabicycle-[4,3,0]-non-5-ene (DBN) in mesitylene at 150°C for 1 h, resulting in the formation of a 1:1 mixture of compounds **19** and **16** in 49% yield. The ratio of **19**/**16** was increased to 4:1 when the mixture was recrystallized from ethyl acetate/*n*-hexane. Pleasingly, we discovered that ketone **19** could be converted into the corresponding enol triflate **20** in 69% yield by reaction with Tf_2O as a triflating agent in the presence of $tBu_2MeC_5H_2N$.[23] The regioselective formation of compound **20** observed in this reaction can presumably be attributed to the lower steric hindrance on the bottom face in substrate **19**, which might direct the attack of the base on the proton (see the 3D structure of **19** in Scheme 6).[24] The coupling reaction between the enol triflate **20** and Me_4Sn was then completed using a modified Stille protocol[25] with $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone) as the catalyst in the presence of $AsPh_3$, to provide the desired product **21** in 89% yield.

To complete the total synthesis of our target molecule, the installation of a double bond was required at the C6 and C7 positions, and this was achieved using a selenation–oxidation–elimination method.[26] Thus, the α,β-unsaturated double bond in **21** was reduced with $LiBH_4$ to give the saturated lactone. The resulting bis(ester) was initially treated with LDA in THF at −78°C followed by PhSeBr to afford the α-bis-arylseleno-diester, which was not isolated but instead exposed to hydrogen peroxide in the presence of pyridine at 0°C to afford the desired product **22** in an overall yield of 34%. The total synthesis of the methyl ester of pentalenolactone A was completed according to the known procedure developed by Danishefsky et al.[4a] through a sequence of reduction–epoxidation–oxidation to give the target molecule pentalenolactone A methyl ester (**23**). The synthetic material was fully characterized and its ^1H NMR and ^{13}C NMR spectra were found to be identical to those of the natural product.[27]

In conclusion, we have a successfully developed a novel strategy for the stereoselective synthesis of pentalenolactones. The critical steps in this strategy were a Co-mediated intramolecular PKR of a TMS-substituted enyne **11** for the stereoselective synthesis of the bicyclic cyclopentenone **12** and a TMS-promoted TIMO reaction of keto-phosphonate **15** for the stereoselective synthesis of α-methylidene-δ-pentyrolactone **16**, with a striking increase in molecular complexity in a single step. The implementation of this novel strategy allowed for the first reported stereoselective total synthesis of the methyl ester of pentalenolactone A (**23**). The asymmetric total synthesis of pentalenolactones is currently underway in our laboratories, and will be reported in due course.

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[11] CCDC 888783 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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