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Total Syntheses of Aromatic Abietane Diterpenoids Utilizing Advances in the Pummerer Rearrangement

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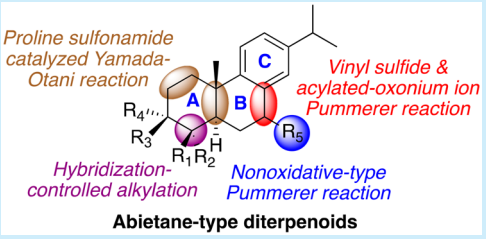
Supporting Information

ABSTRACT: The first total syntheses of triptobenzene T, vitexifolin C, 4-*epi*-triptobenzene L, triptobenzene L, and nepetaefolin F have been accomplished through an enantioselective, common intermediate approach and have enabled the confirmation and/or establishment of the absolute stereochemistry of each natural product synthesized. Application of three new and/or underutilized Pummerer reaction pathways proved critical to the synthetic work. A proline sulfonamide-catalyzed Yamada−Otani reaction was used to access the highly functionalized cyclohexane A ring core, including the C_{10} all-carbon quaternary stereocenter. Additionally, the importance of the A ring unsaturation for controlling the stereoselectivity during the C_4 alkylation is showcased.



The abietane diterpenoid family of natural products represents a sizable collection of compounds that possess both an interesting tricyclic core and intriguing biological activity (Figure 1).[1,2] Despite this appealing combination of attributes, significant cross sections of the family have not been previously synthesized.[3] We became intrigued by the possibility of utilizing our proline sulfonamide-catalyzed Yamada−Otani chemistry[4] to provide rapid access to the core carbon backbone, including the challenging all-carbon quaternary stereocenter at C_{10}. Herein, we describe the first total syntheses of five separate members of this natural product family through the efficient use of an enantioenriched common intermediate.

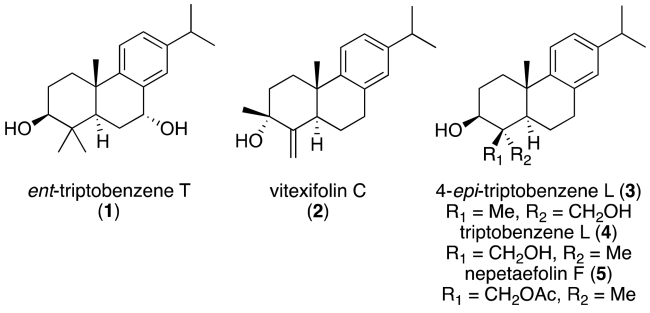
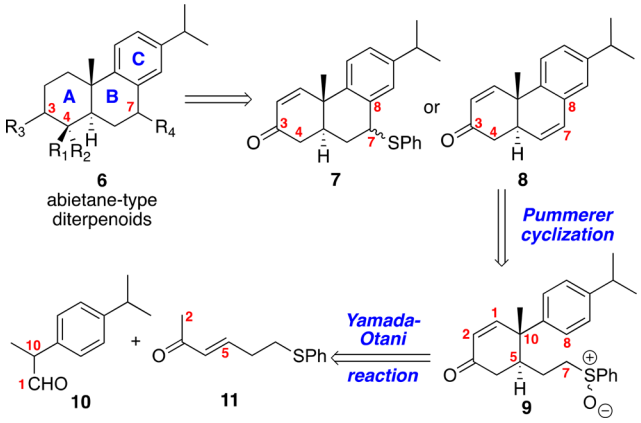


Figure 1. Abietane-type diterpenoid natural products.

Our overarching synthetic approach is outlined in Scheme 1. The pioneering work using the polyene cyclization[5] to access the abietane diterpenoids[6] laid an important foundation for how to construct these ring systems. While powerful, these approaches do limit the wealth of functionality that can be built into the cyclization precursor(s). In contrast, we envisioned exploiting our recently discovered advances in the Pummerer cyclization[7] of a prerequisite sulfoxide **9** to access the tricyclic cyclohexenones **7** or **8**. This approach allows for the early and efficient incorporation of more functionality in both the A and B rings. In turn, this sulfoxide **9** could be readily accessed through our enantioselective proline sulfonamide-catalyzed Yamada−Otani reaction[4] from the benzylic aldehyde **10** and the enone **11**.

Scheme 1. Retrosynthetic Analysis



Our successful construction of the common intermediate **9** and its utilization in divergent Pummerer cyclization pathways is showcased in Scheme 2. Starting from aldehyde **10** (two steps from 4-isopropylacetophenone), proline sulfonamide-catalyzed Yamada−Otani reaction with known enone **11**[8] using our improved DMSO conditions[8] gave the desired sulfide **13** in high diastereo- and enantioselectivity. The stereoselectivity of this process could be further enhanced from a single recrystallization to >20:1 dr and >99:1 er. Subsequent oxidation using H_2O_2 with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[9] smoothly provided the Pummerer cyclization precursor **9**. In accord with our

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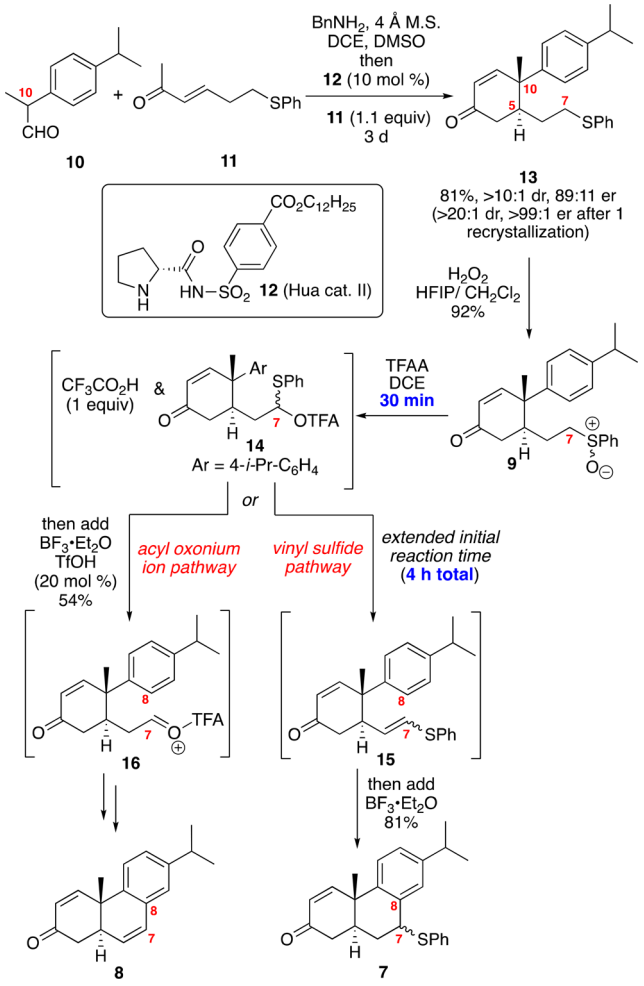
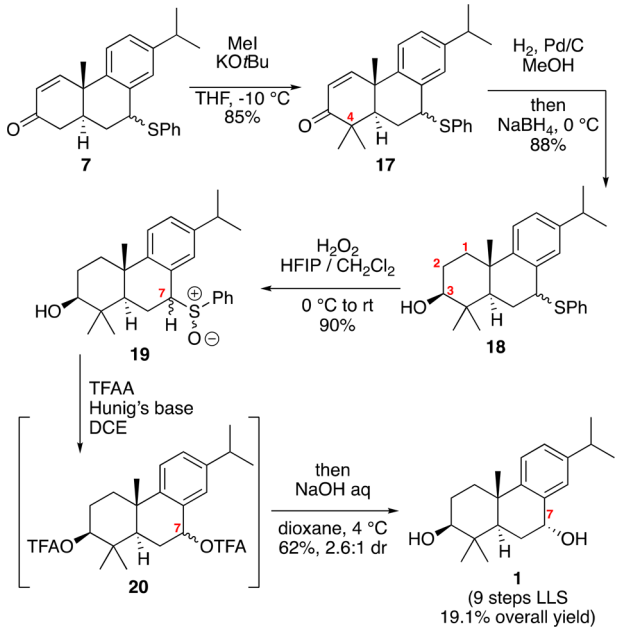
Scheme 2. Synthesis of Key Intermediates via Pummerer Cyclizations



methodological work,[7] Pummerer cyclization under short initial reaction time (30 min) proceeded through our novel acyl oxonium ion pathway (compound **16**) to yield the eliminated tricycle **8** in 54% yield. In contrast, the tricyclic sulfide can be accessed via the vinyl sulfide pathway (compound **15**) in high yield (81%) through extended initial reaction time prior to addition of the $BF_3{\cdot}Et_2O$.[7]

With rapid routes established for accessing the prefunctionalized tricyclic core, our efforts shifted to the synthesis of the abietane diterpenoid natural products. Our first target was triptobenzene T[10] (**1**) (Scheme 3). Dimethylation of the tricyclic enone **7** provided the adduct **17**. Selective hydrogenation of the enone alkene in the presence of the benzylic sulfide was smoothly accomplished with Pd/C and H_2 in methanol. Subsequent reduction produced the alcohol **18** as a single observed stereoisomer. Sulfide oxidation using H_2O_2/HFIP oxidation[9] cleanly provided the sulfoxide **19** as a mixture of stereoisomers on sulfur. While we had planned to conduct a traditional Pummerer rearrangement of sulfoxide **19**, we were pleased to find that a nonoxidative-type Pummerer rearrangement[11] had, in fact, occurred to provide the *ent*-triptobenzene T (**1**) directly in 2.6:1 dr favoring the desired stereochemistry (62% isolated yield of the pure diastereomer). To our knowledge, this is the first example of nonoxidative-type Pummerer rearrangement that has occurred without neighboring group participation. We have observed the key bis-

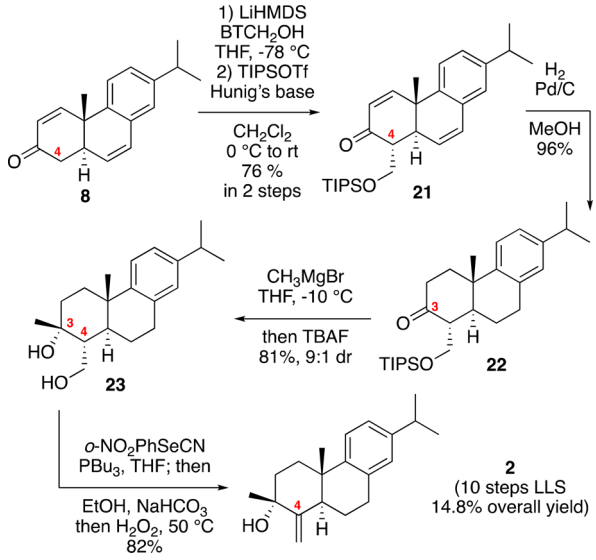
Scheme 3. Total Synthesis of 3α,7β-Dihydroxyabieta-8,11,13-triene (*ent*-Triptobenzene T)



trifluoroacetate ester **20** derivative as an intermediate through in situ analysis (^{1}H NMR, ^{19}F NMR) of the reaction prior to NaOH (aq) treatment as well as through HRMS. This reaction likely proceeds through formation of a benzylic carbocation after acylation of the sulfoxide by TFAA, which is in turn trapped by the trifluoroacetate counterion. Compound **1** was in agreement (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$) with the literature values[10,12] for the *ent*-triptobenzene T (**1**). This synthesis enabled the definitive assignment of the absolute configuration of this natural product where some confusion previously existed.[13]

Our next synthetic target was vitexifolin C (Scheme 4). Starting from tricycle **8**, enolization and formylation at C_4 generated the desired aldol product in excellent dr (>20:1). Subsequent silylation with TIPSOTf generated the silyl ether **21**. Standard hydrogenation of both alkenes produced the

Scheme 4. Total Synthesis of Vitexifolin C



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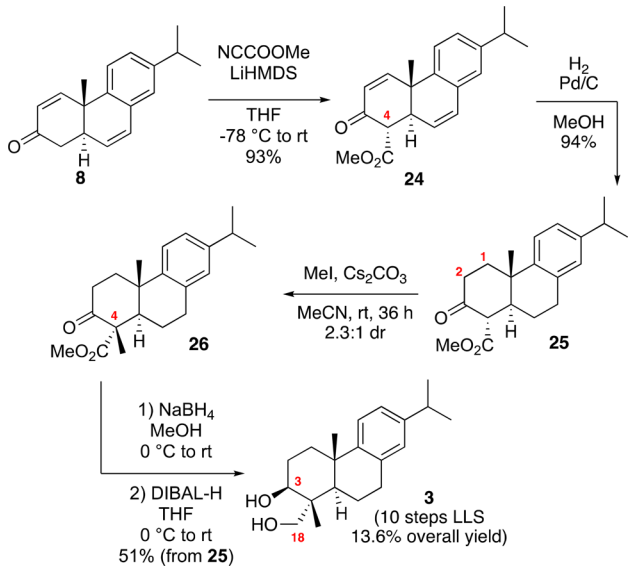
saturated ketone **22**. Stereoselective addition of MeMgBr to the C_3 ketone provided the desired isomer in 9:1 dr. The selectivity in this process was likely governed by the steric bulk of the neighboring and nonchelating CH_2OTIPS moiety. Removal of the silyl ether produced the diol **23**. Finally, Grieco–Nishizawa elimination provided vitexifolin C (**2**) in good yield and excellent agreement with the isolation data[14] (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$).

We next set out to access C_{19}-oxygenated triptobenzene L and nepetaefolin F from the same eliminated tricycle **8** (Scheme 5).

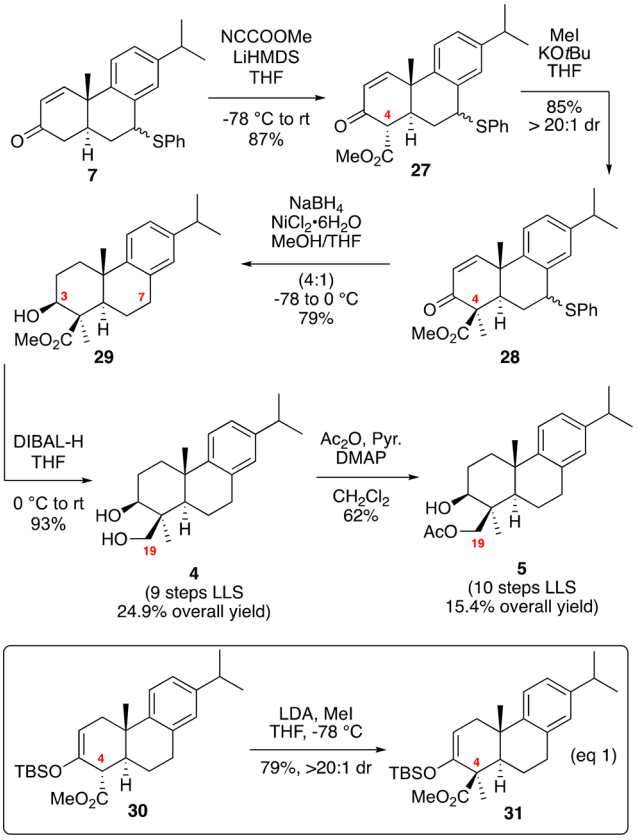
Scheme 5. Total Synthesis of 4-*epi*-Triptobenzene L



Use of Mander's reagent cleanly incorporated the methyl ester moiety as the equatorial isomer **24**, likely through an epimerization process due to the acidity of the C_4 methine proton. We were concerned about the stereoselectivity in the subsequent alkylation of **24** based on the literature examples of related structures which showed a strong preference for the β-epimer of the methyl moiety, particularly for a $C_{1,2}$-unsaturated enone ester system.[15] Based on work by Mander and Deslongchamps,[16] we hypothesized that removal of the unsaturation might reduce the preference for the β-epimer in this transformation. Unfortunately, the alkylation of this hydrogenated β-ketoester **25** provided the undesired stereochemistry (2.3:1 dr) at C_4, in alignment with prior reports on related scaffolds.[16] We attribute this modest stereoselectivity to the conflicting preferences between stereoelectronic factors of half-chair alkylations[17] and the C_{10} methyl moiety. Subsequent conversion further confirmed this assignment as natural product 4-*epi*-triptobenzene L (**3**) based on comparison with the literature values.[18]

The completion of the total syntheses of both triptobenzene L and nepetaefolin F is shown in Scheme 6. As noted in Scheme 5, alkylation of saturated β-ketoester **25** with methyl iodide provided poor selectivity. Interestingly, alkylation of enone ester **27** using KO*t*Bu and MeI smoothly gave the desired α stereoselectivity (>20:1 dr) in excellent yield. Similarly, methylation of the TBS-enol ether **30** (derived from β-ketoester **25**) also exclusively provided the desired stereoisomer **31** (eq 1). These results are in stark contrast to the work by Wenkert and co-workers on a similar tricyclic system.[15] Next, stereoselective reduction of enone **28** using $NiCl_2/NaBH_4$ produced the C_3

Scheme 6. Total Syntheses of Triptobenzene L and Nepetaefolin F



alcohol with concomitant removal of the C_7 sulfide. Finally, DIBAL-H reduction of the ester **29** produced triptobenzene L (**4**). Selective acylation of **4** completed a protecting-group free total synthesis nepetaefolin F (**5**). In both cases, synthetic **4** and **5** were in excellent agreement (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$) with the literature values[19,20] for the isolated natural products.

The unexpected selectivity in the C_4 alkylation of compounds **27** and **30** is worthy of further comment (Figure 2). We hypothesized that further flattening of the A ring (**32** and **33**) should maximize the steric hindrance on the top face (due to the

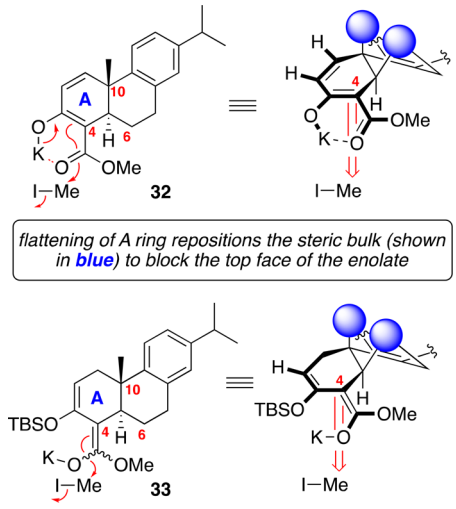


Figure 2. Possible explanation for stereoselective in alkylations.

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C_{10} methyl and the C_6 methylene moieties) while diminishing the stereoelectronic factors (half chair product vs chair product) that guide enolate alkylations in more conformationally flexible six-membered rings (e.g., substituted cyclohexanones).[21] This strategy should provide synthetic chemists with a valuable method for accessing high levels of α facial selectivity in related tricyclic systems.

In summary, the enantioselective total syntheses of multiple abietane diterpenoids (specifically *ent*-triptobenzene T, vitexifolin C, 4-*epi*-triptobenzene L, triptobenzene L, and nepetaefolin F) have been accomplished using a unified, common intermediate approach and have enabled the confirmation and/or establishment of the absolute stereochemistry of each natural product. In each case, these natural products had not been previously prepared synthetically. Key to these syntheses was the discovery of new insights for the Pummerer reaction—including the utilization of three separate mechanisms (vinyl sulfide, acylated oxonium ion and nonoxidative pathways). Additionally, the importance of A ring unsaturation for the stereoselective alkylation[16b,22] has been unearthed during the syntheses of triptobenzene L (**4**) and nepetaefolin F (**5**). Our highly efficient approaches open the door for biological evaluation of these natural products as well as related analogues. Further application of this work will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02060.

Complete experimental details (PDF)
^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) 3α,7β-Dihydroxyabieta-8,11,13-triene (**1**) has not previously been assigned a name; however, its structure is consistent with the triptobenzene family of natural products. Consequently, we have assigned the name *ent*-triptobenzene T to compound **1**. Tanaka, C. M. A.; Radke, V. S. C. O.; Silva, C. C. da; Nakamura, C. V.; de Oliveira, P. L.; Kato, L.; de Oliveira, C. M. A. *Quim. Nova* **2010**, *33*, 30−32.

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(13) In the original isolation paper by de Oliveira and co-workers (ref 10) for natural 3α,7β-dihydroxyabieta-8,11,13-triene, the observed optical rotation is below the level of quantification due to the low (c = 0.011) concentration ($[\alpha]_D$ = +17, c = 0.011, MeOH). Subsequently, Hu and co-workers (ref 12) reported a more concentrated sample of natural 3α,7β-dihydroxyabieta-8, 11, 13-triene ($[\alpha]_D$ = +7.0, c = 0.23, MeOH). It is critical to note that Hu and co-workers draw the *enantiomeric* configuration of the natural product to de Oliveira's originally proposed structure. Our synthesized material confirmed Hu's assignment of 3α,7β-dihydroxyabieta-8,11,13-triene is correct. Synthetic **1** is consistent with the enantiomer of the natural product ($[\alpha]_D$ = −1.7, c = 0.41, MeOH). We attempted to make a more concentrated sample of this synthetic material in methanol; however, a c = 0.41 appears to represent a saturated solution of **1**. We also collected the optical rotation of synthetic **1** in an alternate solvent with better solubility properties ($[\alpha]_D$ = −3.8, c = 0.82, $CHCl_3$). Unfortunately, neither ref 10 nor 12 reported the optical rotations in any solvent other than MeOH. Furthermore, the absolute stereochemistry of synthetic **1** is independently consistent with both of the other synthesized natural products in this manuscript and the known stereochemical model for the Yamada−Otani reaction (ref 4).

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