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A Concise Synthetic Route to the Stereotetrad Core of the Briarane Diterpenoids

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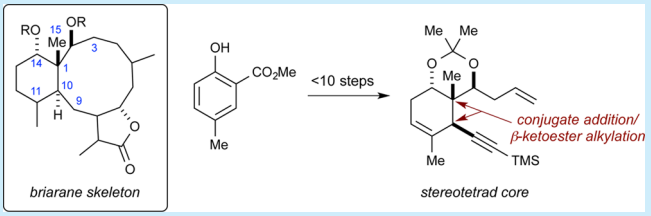
Supporting Information

ABSTRACT: A concise synthesis (under 10 steps) of the stereotetrad core of the briarane diterpenoids is reported. This approach harnesses the unique reactivity of salicylate ester derived 2,5-cyclohexadienones to quickly build complexity. In particular, a highly diastereoselective acetylide conjugate addition/β-ketoester alkylation sequence was used to set the relative configuration of the C1 (quaternary) and C10 (tertiary) vicinal stereocenters. The sterochemical outcome of the β-ketoester alkylation appears to be governed by torsional steering in the transition state.



The briaranes are a large family (>600 members) of diterpenoid natural products that have been isolated, primarily, from marine gorgonians[1] (coral) located around the world.[2] As illustrated in Figure 1, the family is characterized by

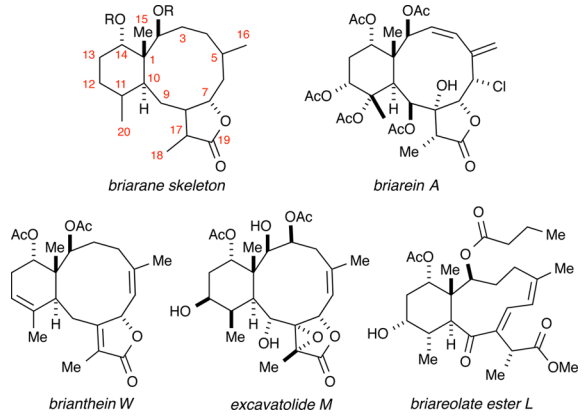


Figure 1. Briarane diterpenoid skeleton and representative family members.

a *trans*-fused bicyclo[8.4.0]tetradecane ring system. A majority of the family members also contain a γ-lactone comprising C7, C8, C17, and C19 and a stereotetrad that involves C1, C2, C10, and C14. Oxidative processing by the organism can install oxygenation or unsaturation at virtually all remaining C-atoms.

Given the size and structural diversity associated with the briarane family, it is not surprising that many family members have demonstrated activity in a number of areas, including anti-inflammatory, antiviral, antifungal, immunomodulatory, insect control, antifouling, and ichthyotoxicity.[2] Others, like brianthein W,[3] excavatolide M,[4] and briareolate ester L,[5] have promising activity against several cancer cell lines.[6] Further investigations into the bioactivity of these compounds have been hampered by the lack of material.

Surprisingly, there has been little synthetic work on the briarane family. In 1995, Procter et al. reported the use of a Nozaki–Hiyama–Kishi reaction to close the 10-membered ring in a greatly simplified system.[7] In 1997, Nantz et al. reported the synthesis of two fragments containing C1–C3, C10, and C7–C9.[8] Ito/Iguchi[9] and Bates[10] have reported approaches to what is arguably the most difficult portion of these molecules, namely, the aforementioned stereotetrad. Recently, Crimmins reported a dianionic Ireland–Claisen rearrangement, which furnished acyclic substrates containing three of the four stereocenters necessary for the briarane stereotetrad.[11] To date, no completed total synthesis of any member of the briarane family has been reported. Developing a versatile and efficient synthetic route to these molecules, and their unnatural analogues, would enable further studies into their mechanism of action and biological activity. Herein, we report our initial efforts toward this goal.

Our synthetic approach to the briarane skeleton is outlined in Scheme 1. Given sufficient functionality, we envisioned an intermediate similar to **1** could be used to close the 10-membered ring and install the butyrolactone moiety. It is well-known that the TMS alkyne in **2** can serve as a synthetic equivalent to the carboxylic acid present in **1**.[12] Meanwhile, Ito and Iguchi[10] have shown that the C2 stereocenter[13] can be installed through a diastereoselective addition of a Grignard reagent into a β-hydroxy aldehyde similar to **2**. We planned to generate the C11–C12 double bond by reductive cleavage of γ-methoxycyclohexenone **3**. The C10 and C1 stereocenters would be forged through conjugate addition of TMS acetylide

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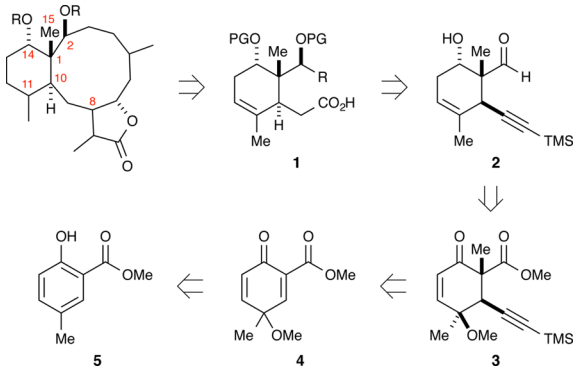
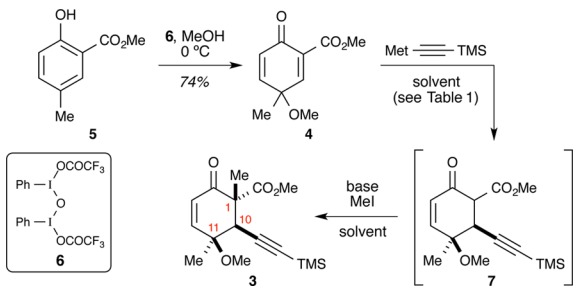
Scheme 1. Synthetic Plan to the Briarane Diterpenoids



into 2,5-cyclohexadienone **4**, followed by methylation of the resulting β-ketoester. In accord with recent computational results from our group,[14] the methyl group was expected to approach C2 from the same side as the acetylide in order to minimize torsional strain in the alkylation transition state.[15,16] Ultimately, dienone **4** would be available through oxidation of known[17] salicylate ester **5**.

Our synthesis began with the oxidative dearomatization of salicylate ester **5** (Scheme 2). When $PhI(OAc)_2$ was used as the

Scheme 2. Conjugate Addition/Alkylation Sequence



oxidant, the reaction gave complex mixtures and low conversions. Others have observed similar difficulties while attempting to oxidize salicylate esters.[18] Presumably, this is due to the strongly electron-withdrawing ester making the oxidation much more difficult. However, Kita has shown that μ-oxo-bridged diiodides, like **6**, demonstrate improved performance over $PhI(OAc)_2$ in certain oxidative dearomatization reactions.[19] We were pleased to find diiodide **6** performed very well in this case, and dienone **4** could be obtained in a much-improved 74% yield.

With an ample supply of dienone **4**, we then investigated the conjugate addition of appropriately metalated TMS-acetylene (Table 1). In all cases, the intermediate acetylide-addition product (**7**) was immediately methylated without purification out of concern that it would undergo facile rearomatization. A variety of acetylide counterions were screened including Zn, Mg, and Al.[20] Aluminum acetylides were found to give the cleanest intermediate products, as judged by ^{1}H NMR spectroscopy of the crude material. When Cs_2CO_3 was used as the base in the methylation step, substantial amounts of aromatized material were isolated along with ketoester **3**, which was obtained as a single diastereomer.[21] A screen of methylation conditions revealed that performing the methylation in toluene with K_2CO_3 and 18-crown-6 prevented the undesired rearomatization and afforded enone **3** in an acceptable yield over two steps. Though the yield of this sequence is lower than we would have liked, this is balanced by the significant increase in molecular complexity; a key carbon fragment, an all-carbon quaternary stereocenter, and the C1−C10 stereochemical relationship are set with almost perfect selectivity in only a few synthetic transformations.

Two factors contribute to the stereoselectivity of the acetylide addition into dienone **4**. It is possible that the C11 methoxy group coordinates to the metal and delivers the acetylide to the same face of the dienone. But, the same sense of diastereoselectivity can be achieved in the absence of a coordinated delivery if one invokes the *syn*-oxygen phenomenon identified by Wipf[22] and Paquette.[23] This is a Cieplak-type effect,[24] in which the σ^*-orbital of the developing C−C bond is stabilized by hyperconjugation with the *anti* C11−CH_3 bond.

Recent work from our group has revealed that Houk's torsional steering model[25] can be used to explain the stereochemical outcome of β-ketoester[26] and enolate[27] alkylation reactions. We suspected that these effects may be operating here, but the situation is complicated by uncertainty regarding the conformational preference of **8** (the enolate derived from **7**). DFT calculations[28] revealed that the preferred conformer (**8B**) contains an axial alkyne and equatorial OMe (Figure 2A). However, this leads to a problem when the transition states leading from **8** are considered (Figure 2B). Both **TS1** (from conformer **8A**) and **TS3** (from conformer **8B**) lead to the observed diastereomer (**3**). But, **TS3** should experience increased torsional strain, relative to **TS4**, due to developing eclipsing interactions. This transition state also requires the electrophile to approach next to the axial alkyne. Thus, **TS4** is expected to be the preferred transition state for the alkylation of conformer **8B**. In order to explain this dichotomy, we propose that the alkylation of **7** is under Curtin−Hammett-type control.[26]

Treating enone **3** with Zn effected the reductive elimination of the methoxy group[29] and established the C11−C12 double bond (Scheme 3). We then turned our attention to the reduction of the C14 ketone. We expected[30] the bulky reducing

Table 1. Optimization of Acetylide Addition to 4 Followed by in Situ Methylation

entry	met	solvent (temp)	methylation conditions	yield of **3** (%)[a]
1	MgBr	THF (−78 °C)	Cs_2CO_3, MeI, MeCN, rt	decomp
2	ZnOTf	MeCN (60 °C)	Cs_2CO_3, MeI, MeCN, rt	10
3	MgBr[b]	THF (−78 °C)	Cs_2CO_3, MeI, MeCN, rt	33
4	Et_2Al	Et_2O/PhMe/hexane (0 °C)	Cs_2CO_3, MeI, MeCN, rt	25
5	Et_2Al	Et_2O/PhMe/hexane (0 °C)	K_2CO_3, MeI, 18-c-6, toluene, rt	37
6	Et_2Al	Et_2O/PhMe/hexane (0 °C)	K_2CO_3, MeI, 18-c-6, toluene, rt	41[c]

[a]After methylation of **7** and chromatographic purification of **3**.. [b]With 0.1 equiv CuCl. [c]Reaction performed on a 1.44 mmol scale. 18-c-6 = 18-crown-6.

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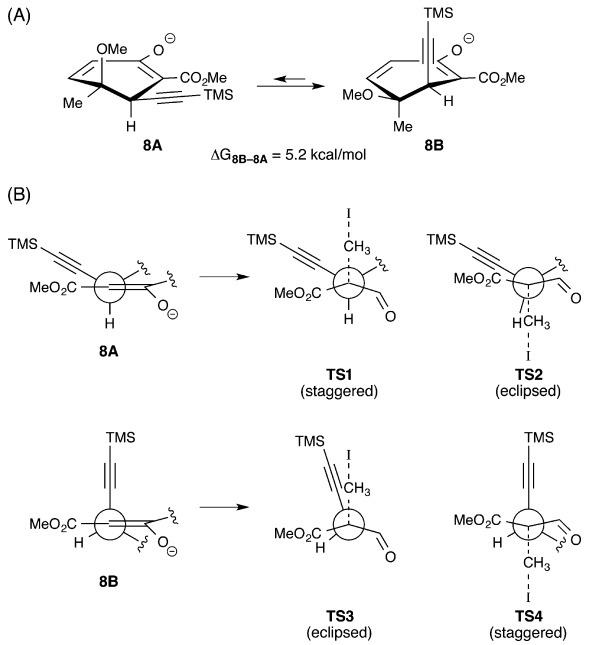
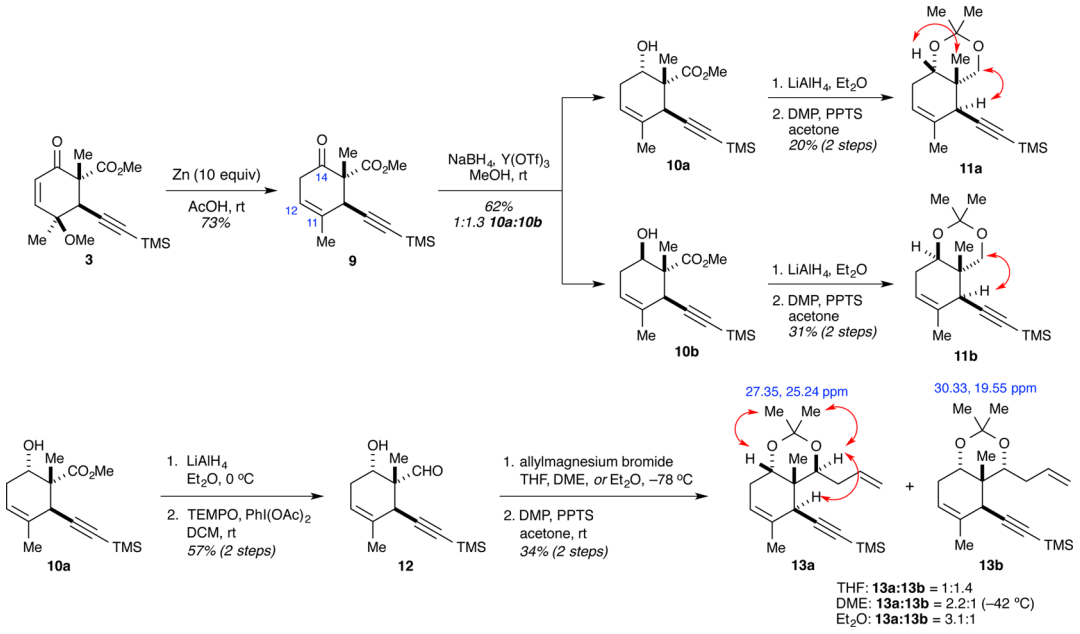


Figure 2. (a) Conformational analysis of enolate **8**. (b) Transition state analysis for the alkylation of **8A** and **8B**.

agent LiAl(O*t*-Bu)$_3$H would provide the axial hydroxyl group (i.e., **10a**). We were surprised, therefore, when initial attempts to reduce **9** with LiAl(O*t*-Bu)$_3$H gave undesired alcohol **10b** almost exclusively. Curiously, small reducing agents, such as $NaBH_4$, gave identical results. This trend is, perhaps, due to complexation of the B or Al with the ester, leading to preferential equatorial hydride delivery.[31] Also, an axial alkyne (*A* value: 0.41−0.52[32]) would be expected to block the approach of hydride reagents to the β face of ketone **9** and lead to the preferential formation of **10b**. We hypothesized that precomplexation of the ketoester with another Lewis acid might block the α face and improve the observed diastereoselectivity. After an extensive screen of Lewis acids,[27] we found that Y(OTf)$_3$ gave the best results, giving a 1:1.3 ratio of **10a:10b**. Fortunately, the two diastereomers could be separated by silica-gel chromatography. The stereochemical assignments were confirmed by examination of the NOESY spectra of acetonides **11a** and **11b**. Although these results are not fully optimized,[33] we decided to carry material forward to evaluate the remainder of the synthetic sequence.

Reduction of ester **10a** with $LiAlH_4$, followed by immediate oxidation of the primary alcohol, gave aldehyde **12** in an acceptable yield. We investigated the addition of a simple model Grignard reagent into the aldehyde. When the aldehyde was treated with allylmagnesium bromide in THF at −78 °C, diastereomeric diols were obtained in a 1:1.4 ratio. The relative stereochemistry was tentatively determined by converting the mixture into acetonides **13a** and **13b** and comparing the ^{13}C NMR chemical shifts of the acetonide methyl groups (assigned by HSQC of the mixture). For compound **13a**, the ^{13}C resonances were observed at 27.35 and 25.24 ppm, which is consistent with Rychnovsky's reported values for *anti* 1-3 diols.[34] The analogous chemical shift values for **13b** (30.33 and 19.55 ppm) were consistent with a *syn*-diol. Gratifyingly, the diastereomeric ratio could be improved to 3.1:1 **13a:13b**, when the Grignard reaction was performed in Et_2O. In this case, NOESY analysis of the separated major acetonide diastereomer further confirmed the stereochemical assignment of both the Grignard addition product and the relative configuration of C1 and C10. The use of DME led to reduced selectivity relative to Et_2O. The low diastereoselectivity during the Grignard addition step differs from that reported by Ito/Iguchi who observed complete stereoselectivity in a very similar system.[10] At this time, it is not clear what the root cause of this discrepancy is, but it may be related to the axial preference of the alkyne enforcing a conformational population that is much different from that experienced by Ito and Iguchi.

Scheme 3. Completing the Synthesis of the Briarane Stereotetrad[a]



[a]Red arrows indicate key NOESY correlations.

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In conclusion, we have developed a rapid synthesis of the stereotetrad core of the briarane diterpenoids. The densely substituted core structure was accessed in only eight steps from salicylate ester **5** and features a highly diastereoslective conjugate addition/β-ketoester alkylation sequence that establishes the C1 and C10 stereocenters. Work is ongoing to improve the C14 ketone reduction and C1 allyl addition, which will enable the total synthesis of brianthein W, briareolate ester L, and unnatural analogues. These results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, optimized geometries and energies of all computed species, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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