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Enantioselective Synthesis of an Advanced Intermediate to Quassinoids.

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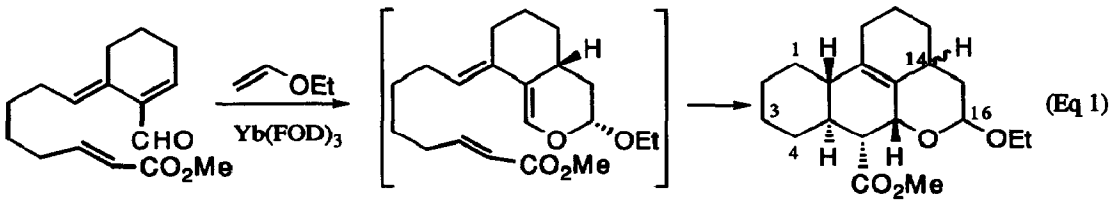
Abstract: An optically pure advanced intermediate to the quassinoids was prepared via the diene-transmissive Diels-Alder cycloaddition strategy. The absolute stereochemistry of the intramolecular cycloaddition was controlled by a methyl and a *t*-butyldimethylsilyloxy group via a chair-like endo transition state.

We have recently communicated our results on a novel strategy to efficiently and stereoselectively construct the quassinoid framework via a Diene-Transmissive Diels-Alder strategy (Eq 1).[1] Although both the hetero- and intramolecular Diels-Alders proceeded with complete endo-selectivity, the stereochemistry at $C_{14,16}$ directed the intramolecular cycloaddition mostly to the undesired face of the molecule. We now have prepared an enantiomerically pure tetracyclic intermediate demonstrating the ability of a methyl group at C_4 and a *t*-butyldimethylsilyloxy group at C_3 (steroid numbering) to control the absolute configuration at C_5, C_6, C_7, and C_{10} in the intramolecular cycloaddition,[2] and in fact reverse the effect of the $C_{14,16}$ stereocenters. Since we have described earlier a method to control the absolute stereochemistry at $C_{14,16}$,[1] we can now formally obtain the desired absolute stereochemistry at all newly created chiral centers in these sequential cycloadditions.

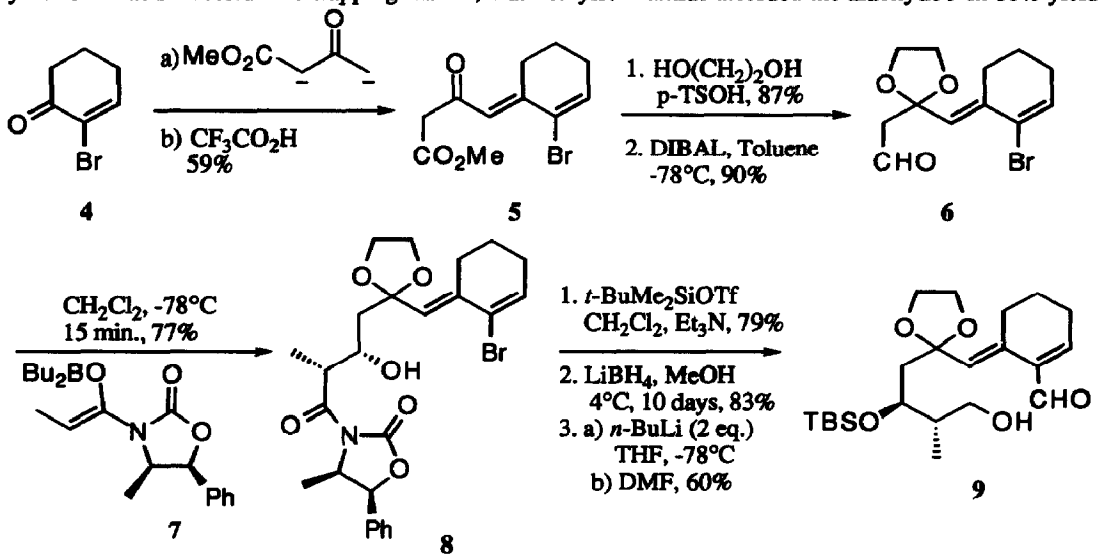


(Eq 1)

1 **2**, racemic **3**, racemic

The synthesis started with the addition of the dianion of methyl acetoacetate[3] to 2-bromo-2-cyclohexen-1-one[4] **4** to give, after elimination of water with neat trifluoroacetic acid followed by triethylamine, the dienone **5** (Scheme 1).[5] Protection of the ketone into the cyclic ketal was followed by the reduction of the methyl ester with diisobutylaluminium hydride in toluene at -78°C to yield 70% of the aldehyde **6** along with 25% of the primary alcohol resulting from over-reduction. The latter could be separated and oxidized for a total yield of 90% of the desired aldehyde **6**. Compound **6** was then subjected to the Evans Asymmetric Aldol methodology[6] to furnish the optically pure oxazolidinone **8** (>99% by GC analysis). Protection of the secondary alcohol was achieved using *t*-butyldimethylsilyl triflate and triethylamine in dichloromethane and

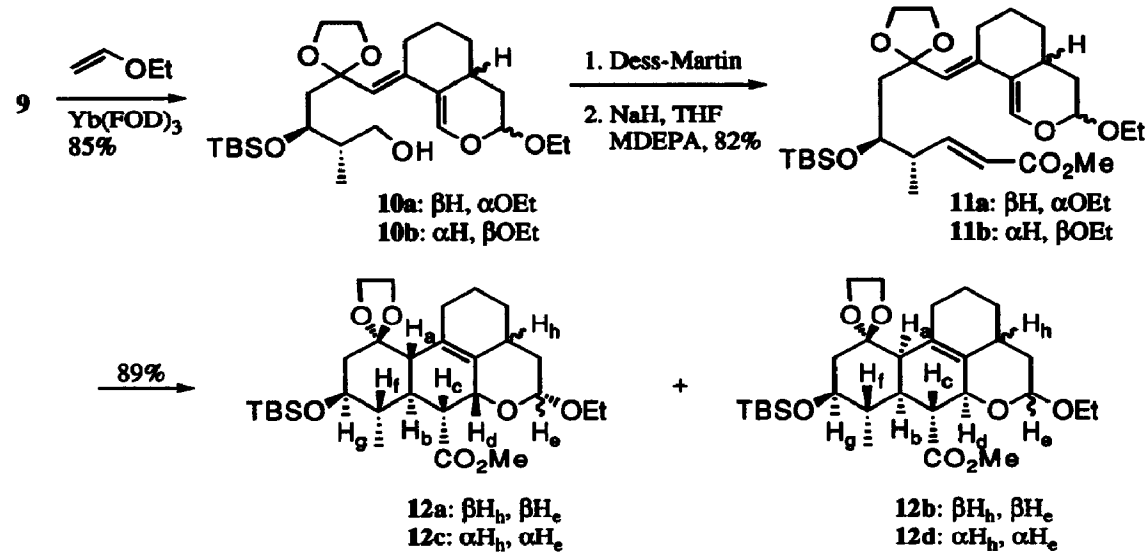
the oxazolidinone auxiliary was removed by careful reduction with lithium borohydride over a 10 day period. Other reducing agents such as lithium aluminium hydride and diisobutylaluminium hydride gave unsatisfactory yields of the alcohol. The α-methyl substitution in **8** may sterically hinder attack at the desired amide carbonyl. Metal-halogen exchange on the resulting unprotected primary alcohol using two equivalents of *n*-butyllithium was successful and trapping with N,N-dimethylformamide afforded the aldehyde **9** in 80% yield.



Scheme 1

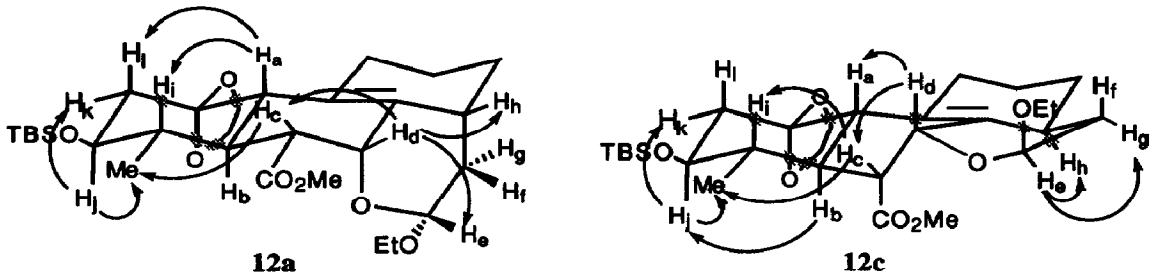
The oxidation of the primary alcohol in **9** to the corresponding dialdehyde could be achieved using PDC in dichloromethane. However, all subsequent attempts to react the saturated aldehyde chemoselectively failed.[7] It seems that the α,β-unsaturated aldehyde possesses a higher reactivity than the saturated one, probably due to steric encumbrance of the latter by the α-methyl group.

We therefore carried out the ytterbium-catalyzed hetero-Diels-Alder cycloaddition on hydroxy-aldehyde **9** and obtained a good yield of the inseparable diastereomeric cycloadducts **10a** and **b** with complete endo-selectivity (Scheme 2).[1,8] The two diastereomers were formed in a 1:1 ratio. The primary alcohol was then oxidized to the aldehyde using the Dess-Martin periodinane[9] followed by a standard Wadsworth-Emmons reaction with methyl diethylphosphonoacetate (MDEPA) to give the *E*-α,β-unsaturated esters **11a** and **b** in quantitative yield. These two inseparable diastereomeric esters could be isolated but slowly underwent a stereoselective cycloaddition reaction at rt over 72h (or 24h at 40°C) to give 89% of essentially three separable tetracyclic compounds **12a-c** in a 1.5:1:2.4 ratio as determined by ^{1}H NMR integration of the C_6-protons in the crude reaction mixture. The proton NMR spectrum of **12c**, before recrystallization, displayed small peaks which may belong to a fourth tetracyclic compound (~5%). The identity of the fourth isomer could not be ascertained but we believe it could be **12d** based on some of its ^{1}H NMR signals and from examination of the possible transition states.



Scheme 2

The two major tetracycles **12a** and **12c** had the desired absolute stereochemistry at C_5, C_6, C_7, and C_{10} as proved by 2D NOESY experiments (Figure 1). The main nOe enhancements in **12a** between H_c-H_d, H_d-H_e, and H_a-H_l were proof of the proposed structure since H_a-H_d and H_e-H_h must be *cis*, and H_b-H_c must be *trans*. Other nOe enhancements are shown in Figure 1. In the case of **12c**, enhancements between H_a-H_d, H_b-H_j, H_c-Me, H_c-H_d, H_e-H_h were evidence of the proposed structure. The minor compound is thought to have structure **12b** from a thorough analysis of its NMR spectra[10] and from careful consideration of the possible transition states (vide infra). Importantly, the ratio of **12c** is nearly equal to the sum of the ratios of **12a** and **12b** which reflects the near 1:1 diastereomeric mixture of the starting material **11a** and **11b**.[11]



12a **12c**

Figure 1. nOe enhancements for the tetracyclic compounds **12a** and **12c**.

The major tetracyclic compounds **12a** and **12c** are thought to arise via the *endo* chair-like transition states (TS) **A**, where the methyl and *t*-butyldimethylsilyloxy groups are oriented in equatorial positions (Figure 2). Note that this preference occurs *regardless of the stereochemistry at* C_{14} . The *exo*-TS **C** is invoked to explain the formation of the minor isomer **12b**.

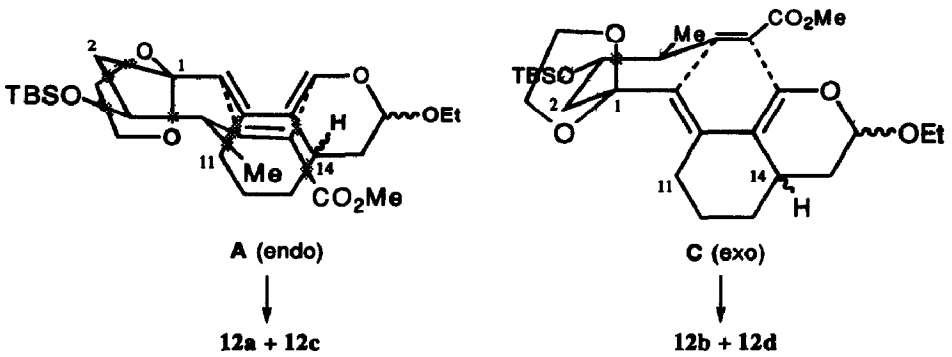


Figure 2. Transition states for the intramolecular cycloaddition of **11**.

In conclusion we have demonstrated that chiral substituents on the chain can control the stereochemistry of the intramolecular cycloaddition in our diene-transmissive strategy. The ring A in these advanced intermediates have several functional groups adequately positioned for elaboration into several natural quassinoids.

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2. For a review of the intramolecular Diels-Alder reaction and the effect of chain substituents see: Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.
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7. Addition to both aldehydes occurred, with the addition to the α,β-unsaturated aldehyde predominating. Complete chemoselective addition to the saturated aldehyde was possible in the unsubstituted dialdehyde analog described in ref. 1.
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10. The proton and carbon NMR spectra of **12b** showed two distinct conformations at -30°C. The two conformations slowly equilibrate at 25°C as shown by the broadening of peaks which become sharp again above 50°C. This is indicative of a *cis* -fusion between ring A and B, as proposed, imparting two conformations to the molecule. The stereochemistry at $C_{14,16}$ had to be the same as **12a** since their added ratio is equal to that of **12c**. Comparisons of its proton NMR with that of other analogous tetracycles of known structure confirmed this affirmation.
11. The small discrepency may be explained from partial loss of one diastereomer during the purification steps in the transformation of **10** to **12**.

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