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TETRAHEDRON: *ASYMMETRY*

An investigation into the total synthesis of clerocidin: stereoselective synthesis of a clerodane intermediate

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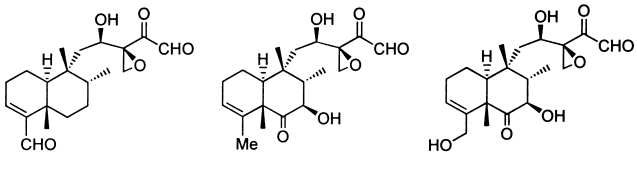
Abstract

A key clerodane intermediate was prepared during the investigation of the total synthesis of clerocidin. The diterpene backbone was synthesized by an enantioselective Robinson annulation followed by trapping of the enolate using allyl bromide. Selective hydrogenation conditions were developed to introduce the axial methyl group at the C_8 position. A palladium-mediated carbonylation reaction was employed to generate the key α,β-unsaturated dialdehyde.

Recent interest in the synthesis of clerodane diterpenes has been stimulated by the potential anticancer and antimicrobial activities displayed by this class of compounds.[1] Clerocidin, a naturally occurring antibiotic isolated from the fungus *Oidiodendron truncatum*, was subsequently identified as a topoisomerase inhibitor.[2] Two additional compounds, terpentecin and UCT4B which have a high degree of structural homology and a similar activity profile to clerocidin,[3] contain several common features which make their synthesis challenging. The unique *trans* configuration present between the C_8 and C_9 methyl groups which is unlike most other clerodanes reported in the literature,[4] and the highly oxygenated side chain which can readily cyclize, hydrate, and dimerize, significantly complicate the synthesis and isolation process of these molecules.[2] The total syntheses of clerodanes possessing *cis* dimethyl stereochemistry at the C_8 and C_9 positions have been reported (*rac*-ajugarin[5] and *rac*-stephalic acid[6]). However, the synthesis of clerodanes with *trans* methyl geometry is largely unreported with the exception of Kobayashi's recent effort towards the total synthesis of terpentecin.[7]



Clerocidin Terpentecin UCT4B

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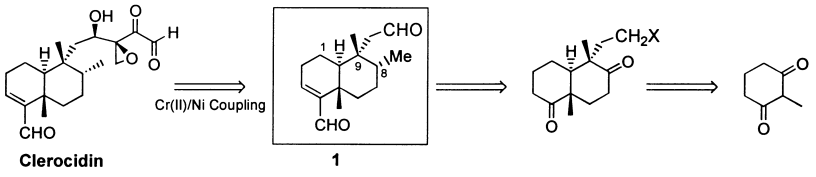
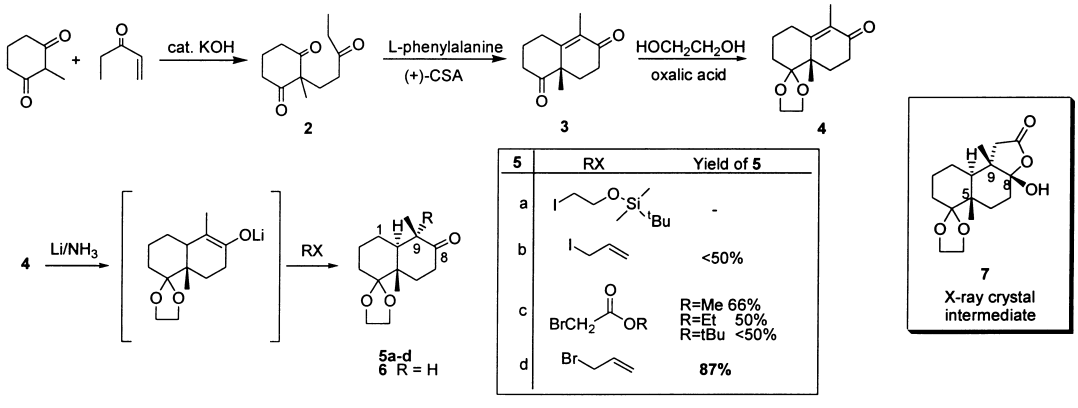
Herein, the synthesis of diterpenoid **1**, a precursor to clerocidin is described. This target molecule was also used as an intermediate in the synthesis of related clerodane analogs of biological interest. The retrosynthetic analysis of clerocidin is shown in Scheme 1.



Scheme 1.

The synthesis begins with the optically pure Wieland–Miescher ketone **3** {$[\alpha]_D^{25}$=+143 (c 1.65, benzene)}[8] which was prepared from triketone **2** in the presence of L-phenylalanine and (+)-camphorsulfonic acid (77% yield)[9] Selective protection of one carbonyl group as the dioxolane **4** was accomplished in the presence of oxalic acid (70% yield). The optical purity of enone **3** was confirmed by resolving the enantiomers of ketone **4** on a chiral cyclodextrin GC column (only a trace of the minor enantiomer was detected).

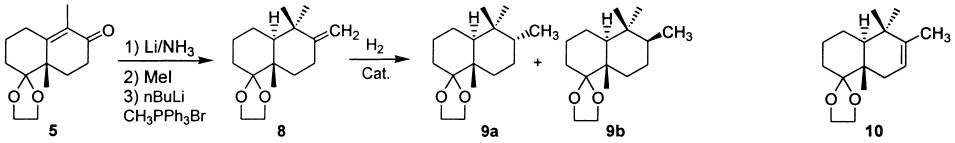
The C_9 substituent was introduced by reductive alkylation of **4** with various electrophiles.[10] The yield was observed to be highly dependent on the steric nature of the electrophile; the silyl ether (a) produced only the protonated product **6**, whereas allyl iodide (b) was prone to overalkylation (table in Scheme 2). Both ethyl bromoacetate and allyl bromide proved to be good electrophiles, providing high isolated yields of the desired products, **5c** and **5d**, respectively. The absolute configuration of the carbon centers C_5, C_9 and C_{10} was independently confirmed by X-ray crystallography of intermediate **7** (generated by oxidation of the aldehyde resulting from ozonolysis of **5d**).[11]



Scheme 2.

The introduction of the axial C_8 methyl group on the diterpene ring was achieved by hydrogenation of the C_8 exocyclic double bond. The hydrogenation reaction of a model substrate was examined in order to determine the optimal reaction conditions to provide the desired diastereomer in excess (thermodynamically less favored, axial product). Model substrate **8** (Scheme 3) containing a *gem*-dimethyl group at the C_9 position was prepared in 59% yield via olefination of the C_8 carbonyl using salt-free Wittig conditions (methyltriphenylphosphonium bromide and *n*-BuLi in benzene at 60°C).[11]

The hydrogenation of **8** was performed in the presence of various catalysts at atmospheric pressure. The ratio of diastereomers **9a**/**9b** was determined by GC analysis and ^{1}H NMR ($CDCl_3$: C_8 CH_3 axial=1.01 ppm and CH_3 equatorial=0.91 ppm). When 5% Pd/C was used as a catalyst, the thermodynamically more stable isomer **9b** with an equatorial methyl group was formed in excess, whereas



Scheme 3.

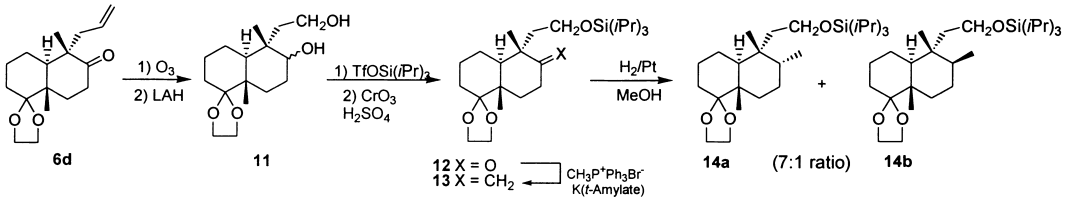
9a was formed in excess in the presence of Pt black catalyst (Table 1). The rate of hydrogenation increased in the following order: Pt/C<Ir black<Pd/C~Pt. Polar, protic solvents such as methanol and ethanol provided higher diastereoselectivity in favor of the desired product **9a**, and increased the rate of hydrogenation when compared to solvents such as benzene and dioxane. A small scale hydrogenation of **8** with Pt in methanol afforded the desired product **9a** quantitatively, at atmospheric pressure in less than 2 h with a diastereoselectivity of almost 9 to 1.

Table 1
Hydrogenation results (NR=no reaction)

Substrate	Catalyst	Solvent	Ratio **9a: 9b**	Conversion
8	Pd/C	EtOH	45 : 55	100%
8	Pt/C	EtOH	-	<15 %
8	Ir	EtOH	73 : 27	100%
8	Os or Rh	EtOH	-	NR
8	Pt black	EtOH	79 : 21	100%
8	**Pt black**	**MeOH**	**89 : 11**	100%
10	Pt black	MeOH	-	<15 %

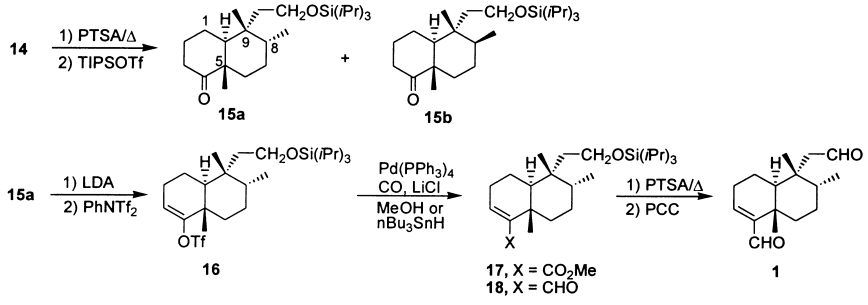
The hydrogenation results demonstrate that the less stable, axial methyl substrate may be formed in excess, possibly under kinetically controlled conditions. In related systems, the thermodynamically more stable product was obtained in excess.[12] The possibility of the double bond isomerization during the hydrogenation step was eliminated by examining the hydrogenation reaction of endocyclic substrate **10** (prepared by MeLi addition to the ketone, followed by dehydration in DMSO). Under the same reaction conditions, only 15% of **10** was hydrogenated after 15 h (ratio of **9a** to **9b** undetermined). In conclusion, the hydrogenation of the exocyclic olefin in **8** was responsible for the observed diastereoselectivity in favor of the desired product, **9a**.

The optimized hydrogenation conditions were applied to the olefin **13** which was prepared in four steps (21% overall yield, Scheme 4). Ozonolysis followed by lithium aluminum hydride reduction of **6d** afforded diol **11** which was selectively protected. Jones oxidation of the secondary alcohol afforded ketone **12** which was subsequently converted to the desired olefin **13**. The hydrogenation of **13** with Pt in methanol gave rise to a mixture of diastereomers **14a** and **14b** in the ratio of 7 to 1 (according to GC and NMR) in almost quantitative yield. The assignment of the stereochemistry by ^{1}H and ^{13}C NMR was made on the mixture of diastereomers **14** since they were not separable by chromatography.[11] However, removal of the dioxolane group afforded silyl ethers **15a** and **15b** (88% yield) which were separable by chromatography (Scheme 5).



Scheme 4.

There are several methods reported in the literature for introduction of α,β-unsaturation into cyclic ketones.[13] We were interested in a versatile yet direct conversion of **15** to either an α,β-unsaturated aldehyde or an ester. This was achieved by a two-step process which successfully utilized a palladium-catalyzed reaction. The ketone **15a** was treated with LDA, and the resulting enolate was trapped in situ with N-phenyl triflamide to provide the enol triflate **16** in 60% yield (Scheme 5). In order to ensure complete enolate formation alpha to a neopentyl center, the reaction mixture was allowed to warm to room temperature. Reaction of the enol triflate with a catalytic amount of tetrakis(triphenylphosphine)palladium and carbon monoxide in the presence of either methanol or *n*-Bu_3SnH provided the CO insertion products, **17** or **18**, respectively (55 or 67% yield). Following the removal of the silyl protecting group from **18** with *p*-toluenesulfonic acid, the resulting alcohol was oxidized with pyridinium chlorochormate to provide the target dialdehyde **1** in 90% yield.



Scheme 5.

The diastereoselective coupling of the dialdehyde with a clerocidin-like side chain can be achieved through a chromium-mediated reaction which has been employed successfully with other systems.[14] The design, synthesis, and scope of the optically active side chain precursor of clerocidin will be described in a separate communication.

In summary, the diterpene backbone was efficiently constructed using an asymmetric Robinson annulation method. Two key reactions made the synthesis of optically active **1** feasible: first, the stereoselective hydrogenation of the exocyclic double bond in **13** provided the less stable product which was crucial to achieving *trans* C_8–C_9 dimethyl stereochemistry and, second, the α,β-unsaturated aldehyde **18** was prepared in two steps via the enol triflate **16** and palladium chemistry.

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