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QUASSINOID SUPPORT STUDIES: INCREASING STEREOCONTROL IN A PERHYDRONAPHTHALENE SYNTHESIS BY RESTRICTING CONFORMATIONAL DEGREES OF FREEDOM

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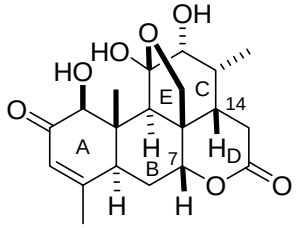
Abstract – Free radical cyclization of **15** provides *trans*-perhydronaphthalene (**16**) in high yield and with much better stereoselectivity than conformationally less constrained analogs.

INTRODUCTION

The quassinoids are a large family of terpenoid natural products exemplified by chaparrinone (**1**).[1] The quassinoids have been of long-standing interest to the medicinal chemistry community because of their broad biological activities.[2] Thus, it is not a surprise that the quassinoids have attracted the attention of synthetic organic chemists for a period of approximately 50 years.[3]

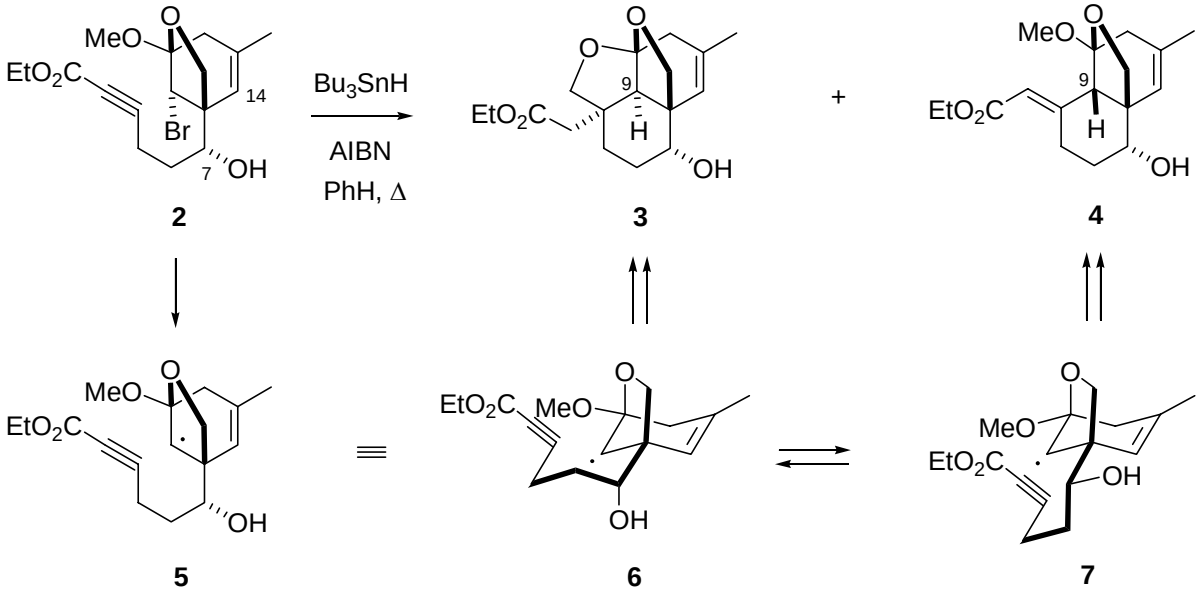


1 (chaparrinone)

A *trans*-fused perhydronaphthalene constitutes the BC ring system of most quassinoids and a variety of approaches to this substructure have been reported. We recently described an approach that relied on a free radical cyclization to contruct the BC ring system (Scheme 1).[4] Treatment of bromoalkyne (**2**) with tri-*n*-butyltin hydride gave *trans*-perhydronaphthalene (**3**) and *cis*-perhydronaphthalene (**4**) as the major products. These products arise from cyclization of intermediate radical (**5**). We suspect that cyclization

of **5** from conformation (**6**) affords **3** via a cyclization-hydrogen atom transfer-cyclization sequence,[5] and conformation (**7**) provides **4** via cyclization and reduction of the resulting vinyl radical.

Scheme 1



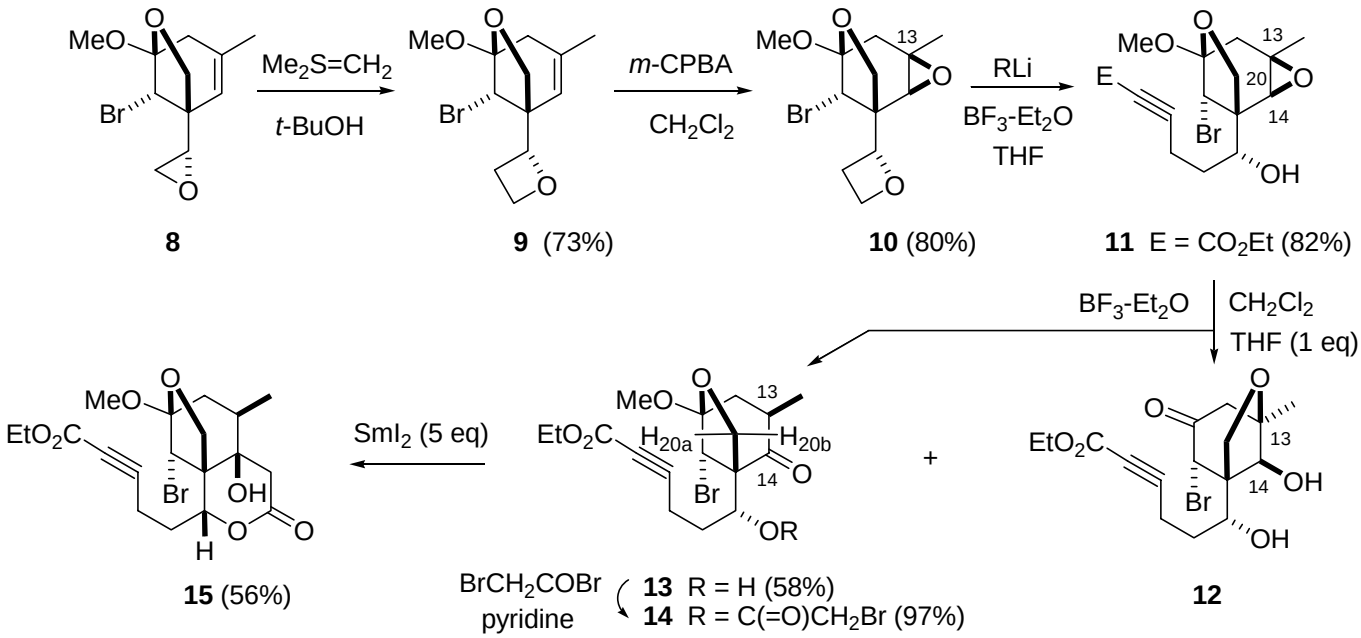
We reasoned that constraining the initially formed radical (**5**) to a conformation of type (**6**) would give better *trans-cis* selectivity in the radical cyclization. We felt that such a constraint could be introduced by linking the C_7 hydroxyl group to C_{14}. In other words, introduction of the quassinoid D-ring prior to the free radical cyclization (introduction of the B-ring) would improve stereoselectivity in this route to perhydronaphthalenes. A test of this hypothesis is presented herein.

RESULTS AND DISCUSSION

Cyclization precursor (**15**) was prepared as described in Scheme 2. Treatment of the known epoxide (**8**) with dimethylsulfonium methylide gave oxetane (**9**) in 73% yield.[4,6] Epoxidation of the olefin using *m*-chloroperoxybenzoic acid provided **10** in 80% yield. The stereochemical course of the epoxidation was suggested by the lack of an nOe between the C_{13} methyl group and the C_{20} methylene, and confirmed by subsequent experiments (*vide infra*). Oxetane (**10**) reacted smoothly with an excess of ethyl lithiopropiolate (1.5 equiv) in the presence of boron trifluoride etherate (1.5 equiv) to afford epoxy alcohol (**11**) in 82% yield.[7] Treatment of **11** with boron trifluoride etherate (2.0 equiv) in dichloromethane gave a 2:1 mixture of ketones (**13**) and (**12**), respectively, in modest yield. Ketone (**13**) most likely results from

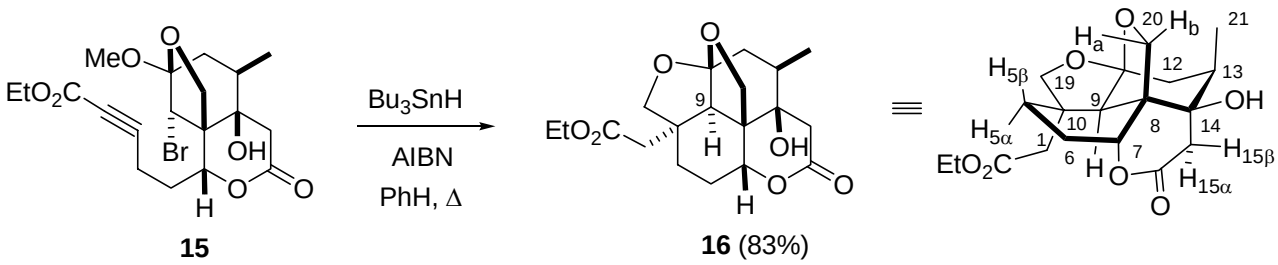
the expected epoxide opening followed by a hydride shift from C_{14} to C_{13}.[8] Bromoketone (**12**) is presumed to arise from S_N1 behavior of epoxide (**11**) in which the C_{11} ketal is also ionized to provide the nucleophilic oxygen needed to trap an intermediate C_{13} carbocation. No reaction was observed when diethyl ether or tetrahydrofuran was used as the solvent for the rearrangment of **11**. The best results were obtained when the rearrangment was conducted in dichloromethane with tetrahydrofuran (1.0 equiv) as an additive. Under these conditions, the isolated yield of **13** was 55-58% and the ratio of **13**:**12** prior to purification was 5:1 by ^{1}H NMR spectroscopy. It was hypothesized that complexation between the THF oxygen in **11** (the C_{20} oxygen) and the BF_3-Et_2O was needed for the conversion of **11** to **12**. We imagine that the added tetrahydrofuran competed with the C_{20} oxygen and thus, slowed the rate of rearrangement of **11** to **12** relative to the rearrangement of **11** to **13**.

Scheme 2



Esterification of **13** using bromoacetyl bromide in pyridine gave ester (**14**). The stereochemistry of **14** was apparent from a 3.5% nOe observed at the C_{13} methyl group upon irradiation of H_{20b}, providing support for the presumed stereochemical course of the epoxidation (*vide supra*). The esterification was followed by an intramolecular Reformatsky-type reaction of **14** to give cyclization substrate (**15**) in 56% overall yield.[9]

Scheme 3



15 **16** (83%)

Cyclization substrate (**15**) was converted to **16** in 83% yield upon treatment with tri-*n*-butyltin hydride (2.5 equiv) and AIBN (0.2 equiv) in benzene under reflux (Scheme 3). Thus, the anticipated increase in selectivity was realized upon subjecting an intermediate radical of type (**5**) to conformational constraints. Once again the stereochemistry of **16** was supported by extensive nOe studies.[10]

CONCLUSIONS

This study supports the hypothesis that, through imposition of conformational constraints, this free radical cyclization route to perhydronaphthalenes can be rendered highly *trans*-selective. This guiding principle should not be restricted to the D-ring substitution pattern used in this study, but should be extendable to other C_7-C_{14} bridges that might be better suited for the synthesis of quassinoids or other perhydronaphthalenes.

DEDICATION

This paper is dedicated to the memory of Professor Ivar Ugi.

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10. Spectral data for **16**: IR (neat) 3438, 1738, 1714 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.94 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.10 (d, *J* = 8.0 Hz, 3H, H_{21}), 1.25 (td, *J* = 10, 3 Hz, 1H, $H_{5\beta}$), 1.48 (m, 1H, $H_{5\alpha}$), 1.49 (m, 1H, $H_{6\beta}$), 1.50 (m, 1H, H_{13}), 1.75 (m, 1H, $H_{6\alpha}$), 1.75 (s, 1H, H_9), 2.01 (m, 2H, H_{12}), 2.13 and 2.21 (ABq, *J* = 14.0, 2H, CH_2CO_2Et), 2.32 and 2.62 (ABq, *J* = 17.5 Hz, 2H, $H_{15\beta}$ and $H_{15\alpha}$, respectively), 2.62 (s, 1H, OH), 3.27 and 4.22 (ABq, *J* = 9.0 Hz, 2H, H_{20a} and H_{20b}, respectively), 3.91 (q, *J* = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 4.01 and 4.36 (ABq, *J* = 9.0 Hz, 2H, $H_{19\beta}$ and $H_{19\alpha}$, respectively), 4.40 (dd, *J* = 9.0, 3.5 Hz, 1H, H_7); ^{13}C NMR (C_6D_6, 125 MHz) δ 13.8 (q), 18.7 (q), 27.1 (t), 27.5 (t), 38.2 (d), 39.4 (s), 40.0 (t), 43.3 (t), 43.4 (t), 49.8 (s), 52.3 (d), 60.3 (t), 69.0 (t), 72.4 (d), 74.5 (s), 82.0 (t), 116.8 (s), 169.0 (s), 171.0 (s); exact mass calcd. for $C_{19}H_{26}O_7$ $(M+Na)^+$ *m/z* 389.1576, found *m/z* 389.1575. ^1H NMR Assignments were based on ^1H-^1H COSY, HMQC and difference nOe experiments. ^{13}C Multiplicities were based on APT experiments. Critical nOe experiments follow: Irradiation of $H_{15\alpha}$, H_1 and H_{12} gave enhancements at H_9; Irradiation of H_{20b} gave enhancements at H_7, H_{21}, the OH and H_{20a}; Irradiation of H_{20a} gave enhancements at H_7, $H_{6\beta}$, $H_{5\beta}$, $H_{19\beta}$ and H_{20b}.