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

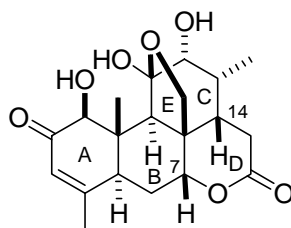
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**Abstract** – Free radical cyclization of **15** provides *trans*-perhydronaphthalene (**16**) in high yield and with much better stereoselectivity than conformationally less constrained analogs.

### INTRODUCTION

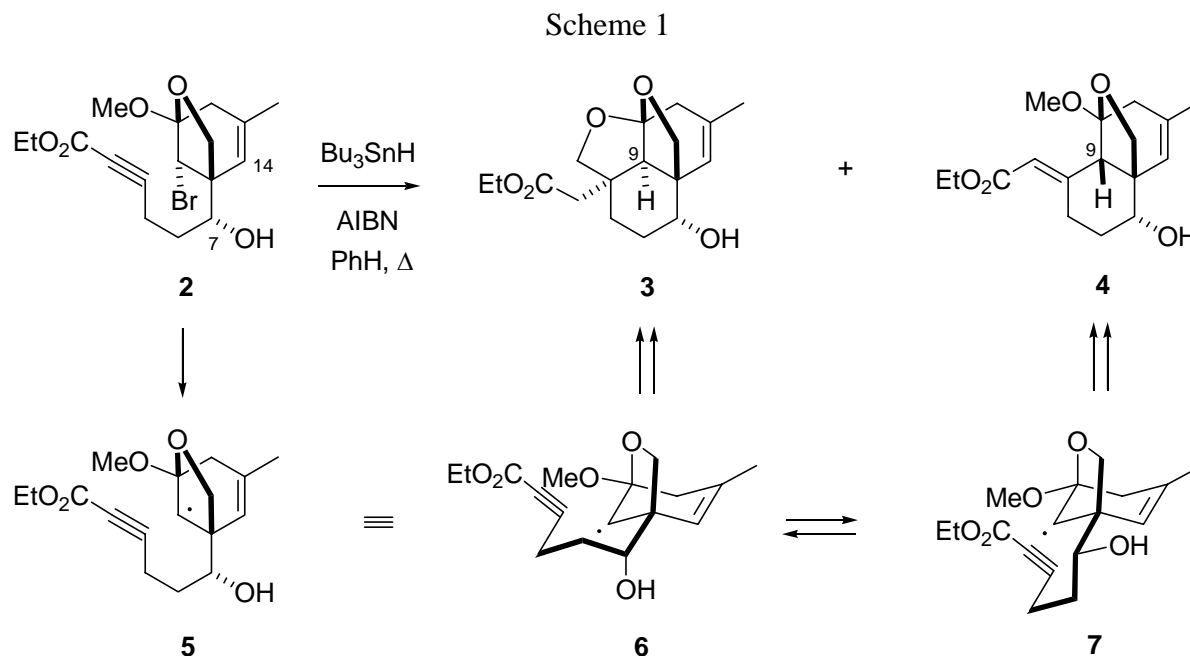
The quassinoids are a large family of terpenoid natural products exemplified by chaparrinone (**1**).<sup>1</sup> The quassinoids have been of long-standing interest to the medicinal chemistry community because of their broad biological activities.<sup>2</sup> Thus, it is not a surprise that the quassinoids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



**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 construct the BC ring system (Scheme 1).<sup>4</sup> 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,<sup>5</sup> and conformation (**7**) provides **4** via cyclization and reduction of the resulting vinyl radical.



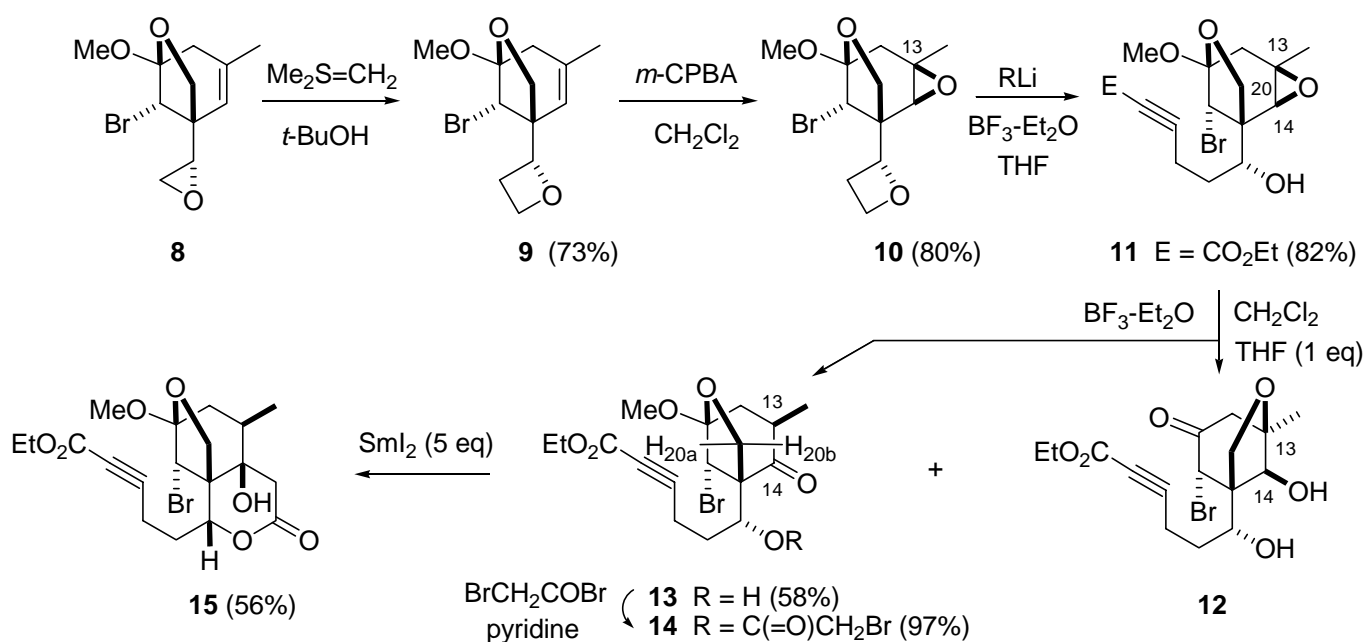
We reasoned that constraining the initially formed radical (**5**) to a conformation of type (**6**) would give better *trans-cis* selectivity in the radical cyclization. We felt that such a constraint could be introduced by linking the C<sub>7</sub> hydroxyl group to C<sub>14</sub>. In other words, 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.<sup>4,6</sup> 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<sub>13</sub> methyl group and the C<sub>20</sub> methylene, and confirmed by subsequent experiments (*vide infra*). Oxetane (**10**) reacted smoothly with an excess of ethyl lithiopropionate (1.5 equiv) in the presence of boron trifluoride etherate (1.5 equiv) to afford epoxy alcohol (**11**) in 82% yield.<sup>7</sup> 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

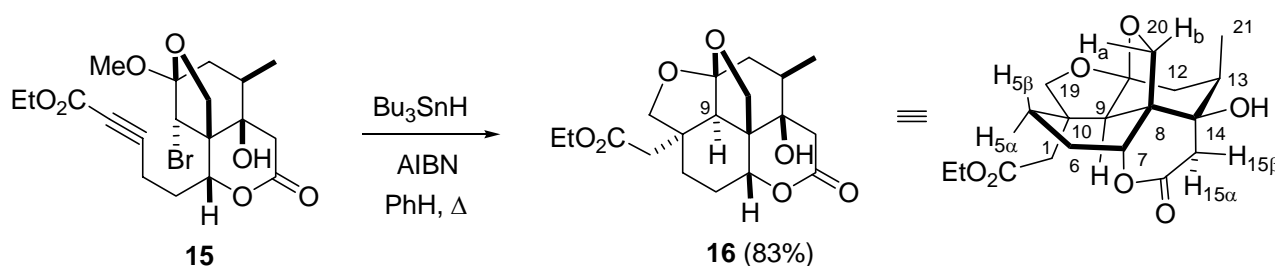
the expected epoxide opening followed by a hydride shift from C<sub>14</sub> to C<sub>13</sub>.<sup>8</sup> Bromoketone (**12**) is presumed to arise from S<sub>N</sub>1 behavior of epoxide (**11**) in which the C<sub>11</sub> ketal is also ionized to provide the nucleophilic oxygen needed to trap an intermediate C<sub>13</sub> carbocation. No reaction was observed when diethyl ether or tetrahydrofuran was used as the solvent for the rearrangement of **11**. The best results were obtained when the rearrangement 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 <sup>1</sup>H NMR spectroscopy. It was hypothesized that complexation between the THF oxygen in **11** (the C<sub>20</sub> oxygen) and the BF<sub>3</sub>-Et<sub>2</sub>O was needed for the conversion of **11** to **12**. We imagine that the added tetrahydrofuran competed with the C<sub>20</sub> 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<sub>13</sub> methyl group upon irradiation of H<sub>20b</sub>, 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.<sup>9</sup>

Scheme 3



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.<sup>10</sup>

## 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<sub>7</sub>-C<sub>14</sub> 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 500 MHz)  $\delta$  0.94 (t,  $J = 7.0$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.10 (d,  $J = 8.0$  Hz, 3H,  $\text{H}_{21}$ ), 1.25 (td,  $J = 10, 3$  Hz, 1H,  $\text{H}_{5\beta}$ ), 1.48 (m, 1H,  $\text{H}_{5\alpha}$ ), 1.49 (m, 1H,  $\text{H}_{6\beta}$ ), 1.50 (m, 1H,  $\text{H}_{13}$ ), 1.75 (m, 1H,  $\text{H}_{6\alpha}$ ), 1.75 (s, 1H,  $\text{H}_9$ ), 2.01 (m, 2H,  $\text{H}_{12}$ ), 2.13 and 2.21 (ABq,  $J = 14.0$ , 2H,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 2.32 and 2.62 (ABq,  $J = 17.5$  Hz, 2H,  $\text{H}_{15\beta}$  and  $\text{H}_{15\alpha}$ , respectively), 2.62 (s, 1H, OH), 3.27 and 4.22 (ABq,  $J = 9.0$  Hz, 2H,  $\text{H}_{20a}$  and  $\text{H}_{20b}$ , respectively), 3.91 (q,  $J = 7.0$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.01 and 4.36 (ABq,  $J = 9.0$  Hz, 2H,  $\text{H}_{19\beta}$  and  $\text{H}_{19\alpha}$ , respectively), 4.40 (dd,  $J = 9.0, 3.5$  Hz, 1H,  $\text{H}_7$ );  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 125 MHz)  $\delta$  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  $\text{C}_{19}\text{H}_{26}\text{O}_7$  ( $\text{M}+\text{Na}$ ) $^+$   $m/z$  389.1576, found  $m/z$  389.1575.  $^1\text{H}$  NMR Assignments were based on  $^1\text{H}$ - $^1\text{H}$  COSY, HMQC and difference nOe experiments.  $^{13}\text{C}$  Multiplicities were based on APT experiments. Critical nOe experiments follow: Irradiation of  $\text{H}_{15\alpha}$ ,  $\text{H}_1$  and  $\text{H}_{12}$  gave enhancements at  $\text{H}_9$ ; Irradiation of  $\text{H}_{20b}$  gave enhancements at  $\text{H}_7$ ,  $\text{H}_{21}$ , the OH and  $\text{H}_{20a}$ ; Irradiation of  $\text{H}_{20a}$  gave enhancements at  $\text{H}_7$ ,  $\text{H}_{6\beta}$ ,  $\text{H}_{5\beta}$ ,  $\text{H}_{19\beta}$  and  $\text{H}_{20b}$ .