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### Benzylic Bromination by Bromotrichloromethane. Dependence of the Identity of the Chain-Carrying Radical(s) on the Method of Initiation<sup>1</sup>

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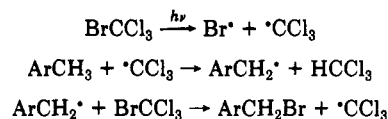
#### Introduction

The photoinitiated free-radical reactions of bromotrichloromethane date back to 1947 when Kharasch and co-workers reported its addition to a series of olefins.<sup>2</sup> These reactions proceed by a mechanism which involves addition of the trichloromethyl radical as the rate-determining step. Bromotrichloromethane has also been used to effect benzylic brominations.<sup>3</sup> As might be expected, analogous allylic bromination is complicated by the competing addition to the double bond.<sup>4</sup> Even in allylic systems, however, hydrogen atom abstraction, which is the rate-determining step in the bromination process, may become comparable to addition if the lability of the allylic hydrogen atom is increased or the accessibility of the double bond is decreased.<sup>5</sup>

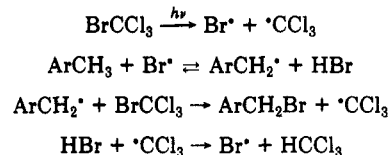
The study of substituent effects in the course of benzylic brominations has led to a natural utilization of Hammett type relationships. While an earlier study by Kooyma, van Helden, and Bickel reported no dependence of rate on substituent,<sup>6</sup> a later study by Huyser has shown that a substantial substituent effect ( $\rho = -1.46$ , correlated with  $\sigma^+$ ) is associated with the photoinitiated reaction of a series of substituted toluenes with bromotrichloromethane at 50 °C.<sup>7</sup> A generalized mechanism, Scheme I, has been proposed which involves the trichloromethyl radical as the chain carrying (hydrogen atom abstracting) species in this benzylic bromination. Support for this mechanism has come from gas-phase reactions of bromotrichloromethane with alkanes in which only brominated products and chloroform were observed.<sup>8</sup>

A second possible mechanism of photoinitiated benzylic bromination by bromotrichloromethane has been postulated on several occasions, Scheme II.<sup>9-10</sup> Although initially discounted as a major pathway based on observed products<sup>8</sup> and selectivities,<sup>9</sup> support for this mechanism, which involves chain propagation by the bromine atom, has been presented by Tanner and co-workers.<sup>10,11</sup> A

#### Scheme I. Mechanism Involving Hydrogen Atom Abstraction by the Trichloromethyl Radical in the Photoinitiated Benzylic Bromination of Toluene by Bromotrichloromethane



#### Scheme II. Mechanism Involving Hydrogen Atom Abstraction by the Bromine Atom in the Photoinitiated Benzylic Bromination of Toluene by Bromotrichloromethane



repetition of Huyser's study produced similar results ( $\rho = -1.24$ , correlated with  $\sigma^+$ ). It was shown, however, that when these brominations were carried out in the presence of a hydrogen bromide trap such as ethylene oxide or potassium carbonate, the sensitivity to substituents decreased markedly ( $\rho = -0.69$ , again correlated with  $\sigma^+$ ). Furthermore, under normal photoinitiation conditions (no hydrogen bromide trap), substantial hydrogen/deuterium exchange is observed when mixtures of toluene and toluene-*d*<sub>3</sub> are used. This scrambling is completely suppressed upon addition of ethylene oxide. Both of these observations are consistent with the reversibility of the hydrogen abstraction step in the bromine atom propagation mechanism.

Is hydrogen atom abstraction by bromine atom the sole chain-carrying step? Several studies on substituted alkylbenzenes have been carried out which show distinctly different selectivities for bromotrichloromethane brominations and brominations using either molecular bromine or *N*-bromosuccinimide (NBS).<sup>12</sup> On the basis of bond energies (enthalpies of reaction), hydrogen atom abstraction from toluene by trichloromethyl radical (10.8 kcal/mol) should be favored over that by bromine atom (2.4 kcal/mol).<sup>14</sup> For the Scheme II mechanism to be the only one operative also requires the trichloromethyl radical to react in an unusually selective fashion. It demands exclusive reaction with a small, steady-state concentration of hydrogen bromide even though that of the benzylic substrate is several orders of magnitude greater at any given time of the reaction.

Neither of the two mechanisms, when considered alone, is able to account for all of the observations which have been reported for these photoinitiated brominations. A possible adjudication of the question may be found through generation of the trichloromethyl radical in a less ambiguous fashion.

#### Results and Discussion

Initial attempts to generate the trichloromethyl radical in an unambiguous fashion were not successful. Trichloriodomethane was deemed to be a suitable precursor

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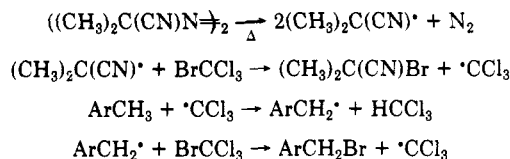
(11) Tanner, D. D.; Wada, N. *J. Am. Chem. Soc.* 1975, 97, 2190.

(12) Series of meta- and para-substituted ethylbenzenes, neopentylbenzenes, allylbenzenes, and cumenes have all shown selectivities that are dependent on the method of bromination. These data have been summarized by Russell.<sup>13</sup> Each of these studies predates Tanner's work.<sup>10,11</sup>

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**Scheme III. Benzylic Bromination of Alkylbenzenes by Bromotrichloromethane under Conditions of Thermal Initiation**



of this radical.<sup>15</sup> The high photolability of the material, however, led to an inability to obtain kinetic data. Likewise, attempts to prepare the trichloroacetoxy radical (which is expected to rapidly decarboxylate to form the trichloromethyl radical and carbon dioxide) from the parent acyl peroxide failed. This precursor is also too unstable to be useful. A general approach has been developed by Barton to prepare alkyl radicals from the acyl derivatives of hydroxamic acids.<sup>16</sup> Although his group has extended this methodology to the generation of the trifluoromethyl radical,<sup>17</sup> we were unable to utilize this approach. In each of these three attempts, hydrogen atom abstraction from an added toluene proved to be a very minor reaction. The first two approaches led to the formation of high yields of hexachloroethane. In the last method the trichloroacetoxy radical underwent rapid decarboxylation; however, the trichloromethyl radical apparently preferred to react with the precursor thiohydroxamic ester. Minisci has shown that the reaction of aqueous hydrogen peroxide with acetone is a convenient source of methyl radicals.<sup>18</sup> Extension of this method to hexachloroacetone produced trichloroacetic acid and chloroform via an ionic pathway analogous to the haloform reaction. No evidence for the formation of trichloromethyl radicals was found.

Attention was eventually shifted from attempts to develop new precursors toward carrying out the same benzylic brominations with bromotrichloromethane under conditions in which only the trichloromethyl radical may be operative. While photoinitiation generates both bromine atom and trichloromethyl radical, other methods of initiation can be free of this complication. We chose to utilize the thermal decomposition of azobisisobutyronitrile (AIBN) for such a process. The overall process is shown in Scheme III. This approach proved to be successful.

All of the following results are based on competitive studies. Pairs of substituted toluenes were utilized directly. The long half-life of AIBN at 50 °C necessitated the use of a higher temperature (70 °C) in this study. In order to allow for direct comparison of results, the corresponding light-induced reactions of bromotrichloromethane and NBS with the same series of compounds were reinvestigated at this temperature. Each pair of substrates was studied in replicate, usually five or more runs. The results of these brominations are given in Table I. Because of relatively poor GC separability of toluene from bromotrichloromethane, the parent compound was not among the systems utilized.

Application of the Hammett equation led to optimum correlation with  $\sigma^+$  constants for each of these brominations. Differences in  $\rho$  values were observed. The AIBN initiated reactions gave a  $\rho$  value of only  $-0.38$  ( $r = 0.98$ ),

**Table I. Relative Rates for Reactions of Substituted Toluenes with Bromotrichloromethane or NBS at 70 °C**

substrate	BrCCl <sub>3</sub> , AIBN	BrCCl <sub>3</sub> , <i>h</i> $\nu$	NBS, <i>n</i> $\nu$
<i>p</i> -methoxytoluene <sup>a</sup>	1.38 ± 0.15	2.08 ± 0.11	3.88 ± 0.33
<i>p</i> -xylene	1.00	1.00	1.00
<i>p</i> - <i>tert</i> -butyltoluene	0.97 ± 0.07	0.96 ± 0.05	1.05 ± 0.04
<i>m</i> -xylene <sup>b</sup>	0.69 ± 0.06	0.55 ± 0.04	0.68 ± 0.09
<i>p</i> -chlorotoluene	0.68 ± 0.06	0.53 ± 0.06	0.41 ± 0.05
<i>m</i> -chlorotoluene <sup>b</sup>	0.45 ± 0.01	0.42 ± 0.05	0.10 ± 0.02
<i>m</i> -trifluoromethyltoluene <sup>b</sup>	0.48 ± 0.11	0.25 ± 0.03	0.09 ± 0.02
<i>p</i> -cyanotoluene <sup>b</sup>	0.35 ± 0.06	0.12 ± 0.01	0.13 ± 0.02
3,5-dibromotoluene <sup>b</sup>	0.44 ± 0.01	0.29 ± 0.01	0.05 ± 0.01

<sup>a</sup> Corrected for reaction at the ether methyl group. <sup>b</sup> Run relative to *p*-chlorotoluene.

**Table II. Effect of Reaction Conditions on the Relative Rate of Photoinitiated Bromination by Bromotrichloromethane for *p*-Methoxytoluene and *p*-Xylene**

BrCCl <sub>3</sub> : <i>p</i> -methoxytoluene: <i>p</i> -xylene	temperature, °C	<i>k</i> <sub>rel</sub>
A. Effect of Bromotrichloromethane Concentration		
16:1:1	70	2.39 ± 0.07
10:1:1	70	2.39 ± 0.11
2:1:1 <sup>a</sup>	70	2.36 ± 0.06
1:1:1 <sup>a</sup>	70	2.33 ± 0.15
0.5:1:1 <sup>a</sup>	70	2.39 ± 0.16
B. Effect of Temperature		
10:1:1	70	2.39 ± 0.11
10:1:1	60	2.62 ± 0.11
10:1:1	50	2.79 ± 0.04
10:1:1	40	2.95 ± 0.40

<sup>a</sup> Concentration of substrates maintained by adding carbon tetrachloride.

and the photoinitiated bromotrichloromethane brominations gave a  $\rho$  value of  $-0.69$  ( $r = 0.95$ ). The NBS brominations gave a corresponding  $\rho$  value of  $-1.19$  ( $r = 0.97$ ). These values are in good agreement with previously reported values when the temperature differences are considered.<sup>19</sup> These results suggest that both the trichloromethyl radical and the bromine atom participate in benzylic hydrogen atom abstraction for the photoinitiated reaction.<sup>20</sup> Furthermore, a semiquantitative estimate of the relative participation of either radical can be made by interpolation of the  $\rho$  values. This indicates that an average of approximately 62% of chain propagation is due to the trichloromethyl radical at 70 °C. There may be variation in this value as a function of substituent.

Although  $\rho$  values were not obtained at lower temperatures (for the AIBN initiated reaction this would be impractical), photoinitiated reactions with bromotrichloromethane for a selected pair of toluenes were examined over a 30-deg temperature range. Selectivity increased linearly with decreasing temperature, linking the present results with previous studies done at 50 °C (Table IIA). The effect of variation of the bromotrichloromethane/substrate concentration ratio was also investigated. All of the bromotrichloromethane reactions discussed above were run with this species in a 10-fold excess. Reactions in which the bromotrichloromethane concentration was the limiting reagent, however, gave similar relative rates within experimental error (Table IIB). These reactions also showed no dependence on the extent of reaction. Each reaction

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**Table III. Relative Rates for Reactions of Unsubstituted Alkylbenzenes with Bromotrichloromethane at 70 °C<sup>a</sup>**

substrate	photoinitiated <sup>b</sup>	AIBN initiated
cumene	6.49 ± 0.42	4.51 ± 0.24
sec-butylbenzene	3.12 ± 0.26	2.02 ± 0.08
3-phenylpentane	1.10 ± 0.13	0.57 ± 0.03
ethylbenzene	1.00	1.00
n-propylbenzene	0.79 ± 0.06	0.61 ± 0.02
isobutylbenzene	0.27 ± 0.02	0.43 ± 0.03
neopentylbenzene	0.02 ± 0.0002	<0.006

<sup>a</sup> All results statistically corrected for number of benzylic hydrogen atoms. <sup>b</sup> Taken from ref 22.

was run from between 10% and 90% completion with highly reproducible results. The lack of variation with bromotrichloromethane concentration and extent of reaction suggest that the relative importance of each chain propagating radical is a constant throughout the reaction.

The Hammett studies indicate that the trichloromethyl radical is, as Tanner first proposed, less sensitive to electronic variation than photoinitiation results originally suggested.<sup>10</sup> The trichloromethyl radical is a larger species than bromine atom.<sup>21</sup> The question might be raised as to whether differences in selectivity could be related to the greater steric demands of the former species.

The photoinitiated reaction of bromotrichloromethane with several unsubstituted alkylbenzenes has shown a sensitivity to the size of the alkyl group.<sup>22</sup> This sensitivity has been explained in terms of the steric demands of the trichloromethyl radical. Participation of a bromine atom in the hydrogen abstraction step (vide infra) could, however, complicate the interpretation of these results. For this reason, we have reinvestigated these brominations under AIBN initiation.

Table III contains the results of bromination of a series of unsubstituted alkylbenzenes with bromotrichloromethane at 70 °C (reported on a per hydrogen basis), initiated with either light or AIBN. The original, photochemical results showed increased reactivity for tertiary as distinct from secondary or primary benzylic positions.<sup>22</sup> The series cumene, ethylbenzene, toluene had previously been investigated by both Russell and DeBoer,<sup>9</sup> and Tanner and Wada<sup>11</sup> who obtained similar findings. Interestingly, however, there were significant variations among the reactivities of sets of tertiary and secondary systems. The reactivity of 3-phenylpentane was, for example, only slightly greater than that of ethylbenzene whereas cumene was more than six times as reactive. sec-Butylbenzene showed an intermediate reactivity. This could be equated to steric hindrance at the reaction site. While this factor should be particularly important for tertiary systems, its occurrence is also observed in the reactivity of secondary systems. Ethylbenzene is 50 times more reactive than neopentylbenzene. Other secondary alkylbenzenes are also less reactive than ethylbenzene as expected based on the relative size of the alkyl groups.

What should be the effect of AIBN initiation? Although the trichloromethyl radical is less sensitive to electronic variation than bromine atom, the inherent size difference should increase its sensitivity to steric bulk at the reaction site. Most of the reactions indeed show a moderate decrease in selectivity when initiated with AIBN. For example, cumene is only 4.5 times more reactive than ethylbenzene. In some cases, however, the effect of steric bulk is more dramatic. 3-Phenylpentane is only half as

reactive as ethylbenzene despite being a tertiary benzylic compound. Neopentylbenzene shows no measurable reactivity under these conditions. An upper limit on the neopentylbenzene reactivity of 0.006 relative to ethylbenzene punctuates the result of eliminating bromine atom participation from the reactions and highlights the large steric demands of the trichloromethyl radical.

It must be recognized that a majority of the products formed from the secondary and tertiary alkylbenzenes investigated have the potential of eliminating hydrogen bromide under the reaction conditions employed.<sup>23</sup> The trace amounts of this material present could lead to modest participation in hydrogen atom abstraction by the more selective bromine atom. The above results for 3-phenylpentane and neopentylbenzene suggest, however, that the part played by this pathway is very minor.

### Conclusion

The photoinitiated reaction of bromotrichloromethane with benzylic substrates involves two chain-carrying species: the trichloromethyl radical and bromine atom. AIBN initiates a simplified mechanism involving exclusive hydrogen atom abstraction by the trichloromethyl radical. This method allows a more specific characterization of the reactivity of this radical. The trichloromethyl radical, while less sensitive to electronic factors than bromine, is more sensitive to steric factors caused by introduction of large groups at the reaction site.

### Experimental Section

All of the compounds were purified by standard procedures before use.<sup>24</sup> Compounds: When available, compounds were obtained commercially. For this study, 3,5-dibromotoluene and *m*-trifluoromethyltoluene were synthesized.

**Preparation of 3,5-Dibromotoluene.** This compound was prepared from *p*-toluidine by the sequence: bromination, diazotization, and deamination after the method of Coleman and Talbot.<sup>25</sup> The solvent for bromination was changed from water to glacial acetic acid, and the bromine was added dropwise. This effectively eliminated the formation of tar which we observed under the former conditions. Recrystallization from ethanol gave 3,5-dibromotoluene, mp 35–36 °C (lit.<sup>26</sup> 36.8–37.0 °C).

**Preparation of *m*-Trifluoromethyltoluene.** This compound was prepared directly from *m*-bromobenzotrifluoride by addition of 1.1 equiv of methyllithium (1.0 M in ether) at –100 °C. After 10 min the reaction mixture was warmed slowly to 0 °C. Distillation gave *m*-trifluoromethyltoluene, bp 125–127 °C (lit.<sup>27</sup> bp 127 °C).

**Kinetics.** All kinetic studies were run on pairs of substituted toluenes or unsubstituted alkylbenzenes. The reactions were run in a thermostated oil bath. The reaction times were varied to insure from 10% to 90% reaction for each substrate. The reaction mixtures (see below) were divided among several ampoules which were then sealed under a reduced pressure of nitrogen after three freeze–thaw cycles. In each case, one of the sealed ampoules was reserved for analysis of starting material.

**Photoinitiated Reactions of Bromotrichloromethane.** Reaction mixtures contained a pair of substituted toluenes, an internal standard (either *p*-di-*tert*-butylbenzene or *p*-bromo-*tert*-butylbenzene), and bromotrichloromethane in an approximate molar ratio of 1:10:0.5:10. The ampoules were placed in the bath, just below the surface of the oil, and irradiated with a Ken-Rad 275-W sun lamp. Reaction times ranged from 2 to 5 h.

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**AIBN-Initiated Reactions of Bromotrichloromethane.** Reaction mixtures were prepared as above using a pair of substituted toluenes or a pair of unsubstituted alkylbenzenes, an internal standard, and bromotrichloromethane. To this, 10–15% azobisisobutyronitrile was added. The sealed ampoules were wrapped in foil and submerged in the oil bath. Reaction times ranged from 48 to 336 h.

**Photoinitiated Reactions of *N*-Bromosuccinimide (NBS).** Reaction mixtures contained a pair of toluenes, NBS, an internal standard, and carbon tetrachloride in a ratio of 1:1:0.75:10. The ampoules were sealed and irradiated as above for 3 h.

**Analysis.** All analyses were carried out using a Varian 3400 gas chromatograph equipped with a flame ionization detector and an autosampler. The capillary columns used were DBWax, DB-5, and DB-225 to insure maximum separation.

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### An Enantioselective Synthesis of D(-)- and L(+)-2-Amino-3-phosphonopropanoic Acid

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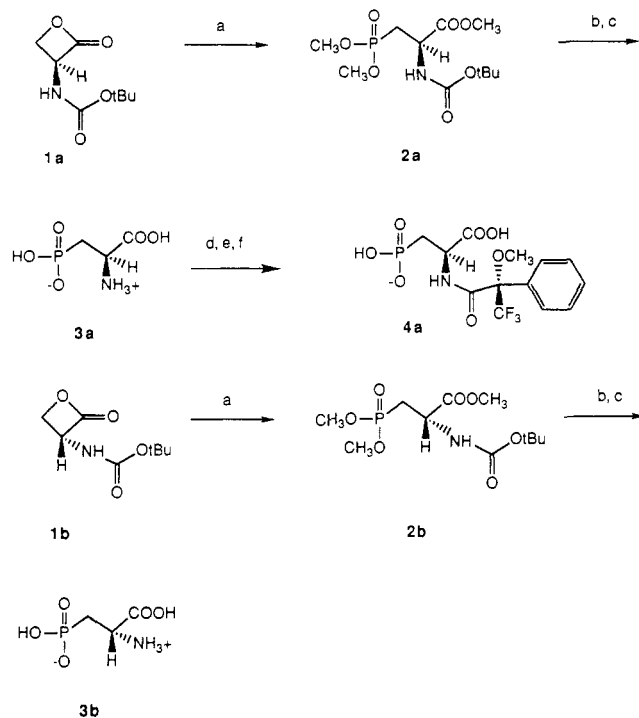
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As a result of the observation that 2-amino-3-phosphonopropanoic acid (AP-3) is a selective, potent modulator of the quisqualic acid/phosphoinositide coupled metabotropic excitatory amino acid receptor subtype,<sup>1,2</sup> it became desirable to obtain the individual enantiomers of AP-3 for pharmacological evaluation. A previous report by Villanueva et al.<sup>3</sup> described the preparation of (*S*)-AP-3 from an optically active amino nitrile prepared by reaction of (diethylphosphono)acetaldehyde with hydrogen cyanide and (*S*)-(-)- $\alpha$ -methylbenzylamine. Acid hydrolysis, enrichment of the diastereomers by fractional recrystallization, and debenzoylation led to the isolation of (*S*)-AP-3 in 86% enantiomeric excess.

Our desire to prepare the enantiomers of AP-3 in a more efficient, enantioselective fashion lead us to explore the feasibility of addition of triethyl phosphite to (*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate (**1a**)<sup>4</sup> (Scheme I). Vederas and co-workers have reported on the addition of a number of nucleophiles to various derivatives of enantiomerically pure 3-amino-2-oxetanones to give products of corresponding stereochemical purity.<sup>4,5</sup> In fact, upon engaging in this chemistry, we became aware that they had conducted a preliminary investigation into the addition of trimethyl phosphite to *N*-BOC-3-amino-2-oxetanone (**1a**) and were able to suggest appropriate experimental conditions.<sup>5</sup> We found that the nucleophilic addition of trimethyl phosphite to **1a** gave (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate (**2a**) in excellent yields. Similarly, the addition of trimethyl

Scheme I<sup>a</sup>



<sup>a</sup> (a) (CH<sub>3</sub>O)<sub>3</sub>P, 70 °C, 42 h; (b) 6 N HCl, reflux; (c) propylene oxide, EtOH, 50 °C; (d) BSTFA; (e) (*R*)-(+)-MTPA-Cl; (f) H<sub>2</sub>O.

phosphite to **1b** afforded the *R* isomer **2b**.

The enantiomeric purity of **2a** and **2b** was confirmed by <sup>1</sup>H NMR studies with a chiral shift reagent. Addition of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TAE) to a 1:1 mixture of **2a** and **2b** in CDCl<sub>3</sub> affected the separation of the C-3 methylene protons at ~2.25 ppm as well as the diastereotopic methoxy signals of the dimethyl phosphonate moiety at ~3.6 ppm. Each methoxy signal appears as a doublet due to <sup>1</sup>H-<sup>31</sup>P coupling but provided the best handle for determination of enantiomeric purity (supplementary material). The absence of observable antipode in the <sup>1</sup>H NMR spectrum of **2a** or **2b** containing TAE made it possible to establish the enantiomeric purity of **2a** and **2b** as greater than 97%. Additionally, optical rotations of **2a** and **2b** were approximately equal and opposite.

Exhaustive acid hydrolysis of the (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate (**2a**) followed by treatment with propylene oxide afforded (*S*)-2-amino-3-phosphonopropanoic acid (**3a**) as its zwitterion. The *R* isomer was prepared in an analogous fashion. The optical rotation value of [ $\alpha$ ]<sub>365</sub><sup>24</sup> = +61.7° (*c* = 2, 1 N NaOH) for the *S* isomer **3a** compared favorably with that reported by Villanueva<sup>3</sup> ([ $\alpha$ ]<sub>365</sub><sup>25</sup> = +56° (*c* = 2, 1 N NaOH)) for a (*S*)-AP-3 sample of 86% enantiomeric excess. Inexplicably, the optical rotation of **3a** observed at 589 nm ([ $\alpha$ ]<sub>D</sub><sup>24</sup> = +13.8°) was not in accordance with that reported by Villanueva ([ $\alpha$ ]<sub>D</sub><sup>25</sup> = +44°).

Our desire to further quantitate the stereochemical purity of **3a** led us to first attempt the reconversion of **3a** to **2a**. Unfortunately, the clean reconversion of **3a** to **2a** by *N*-*tert*-butoxycarbonylation with BOC-ON and esterification with diazomethane proved difficult, so alternative methods of determining the stereochemical purity of **3a** were explored. Racemic AP-3 (**3c**) was prepared by modification of the method of Soroka and Mastalerz<sup>7</sup> as

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