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Practical and Efficient Multigram Preparation of a Camphor-Derived Diol for the Enantioselective Lewis Acid Catalyzed Allylboration of Aldehydes

Hugo Lachance, Miguel St-Onge, and Dennis G. Hall*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

dennis.hall@ualberta.ca

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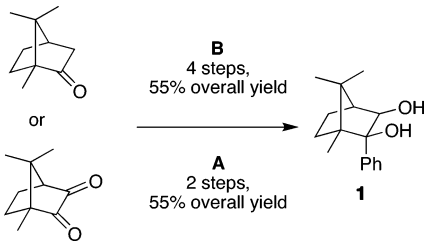
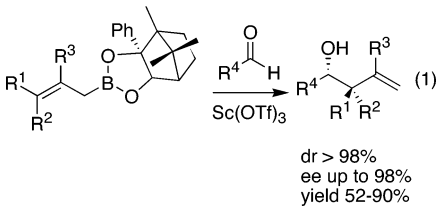


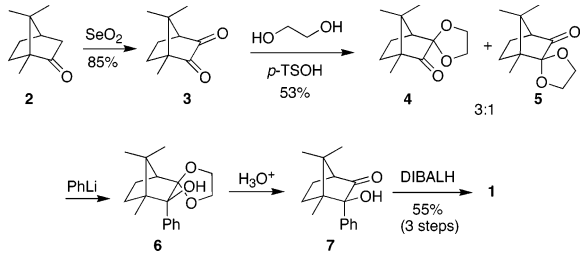
Chiral diols are important molecules with widespread use as chiral auxiliaries and ligands in enantioselective synthesis. Therefore, efficient and practical syntheses of highly dissymmetrical nonracemic diols are still a meaningful pursuit. Two new routes to access camphor-derived chiral diol **1** have been developed. One route employs camphorquinone (**3**) as the starting material, affording in only two steps the desired diol in 55% overall yield. The second route, from camphor (**2**), leads to the desired diol in an efficient four-step synthesis, with an overall yield of 55%.

For many years, the formation of new carbon−carbon bonds has been the driving force behind many discoveries in organic chemistry. In many stereocontrolled processes, a chiral diol is used either as a chiral ligand or a chiral auxiliary.[1] Whereas the use of both natural and synthetic C_2-symmetric diols is widespread, the use of non-C_2-symmetric diols is not as common due to the limited number of naturally occurring diols such as pinanediol. In the domain of stereoselective carbon−carbon bond formation, allylation of carbonyl compounds has attracted a lot of attention.[2] Among these methods, the allylboration of aldehydes stands out as a very successful methodology. It allows formation of homoallylic alcohols containing up to two stereogenic centers with high levels of predictable diastereoselectivity (eq 1). Crotylboron reagents, for example, allow access to the ubiquitous propionate units found in a large number of coveted biologically active natural products. The pioneering work of Hoffmann,[3] Brown,[4] Corey,[5] and Roush[6] has produced useful enantioselective versions with numerous applications in the synthesis of complex natural products.[7]



Recently, our group has reported the first examples of enantioselective Lewis acid-catalyzed allylboration of aldehydes (eq 1).[8,9] This new catalytic allylboration manifold affords excellent enantio- and diastereoselectivities, along with moderate to good yields of products. The camphor-derived allylboronates used in this method tolerate a wide range of conditions, such as air, moisture, and silica chromatography, thereby solving many of the shortcomings of the previously mentioned methods. The required camphordiol precursor, (−)-(1*R*,2*R*,3*R*,4*S*)-1,7,7-trimethyl-2-phenylbicyclo[2.2.1]heptane-2,3-diol (**1**), was originally synthesized[3] in five steps (Scheme 1) from

SCHEME 1. Original Synthesis of Diol 1



camphor (**2**) with a maximum overall yield of 25%. Four of these steps each required a reaction time of over 18 h.

These limitations prompted us to look for a more efficient route to access the Hoffmann camphor-derived diol **1**. The synthetic usefulness of this diol in the Lewis acid-catalyzed allylboration reaction, as well as its potential application to other reactions, made the development of an improved synthetic route a worthwhile endeavor. To be viable, the new route would have to be short, quick, easy to execute, and amenable to multigram preparation of diol **1**.

The current synthesis of **1** begins with a selenium dioxide oxidation[10] of camphor (**2**). In our hands, in addition to the desired product, 4−10% of unreacted camphor is recovered from the reaction. This residual camphor is not easily removed from the product. Another drawback

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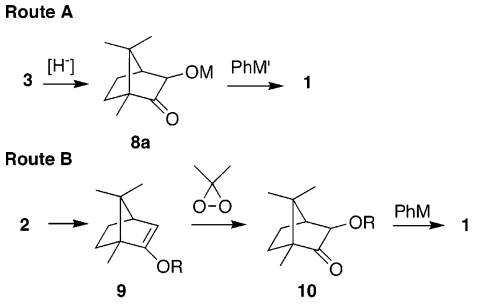
SCHEME 2. Proposed Routes A and B to Diol 1



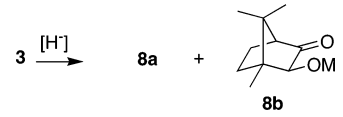
of this synthetic route is the acetal formation step,[11] which consistently gives rise to a 3:1 mixture in favor of the desired product **4** over regioisomer **5**, resulting in a significant loss of material. Herein, two possible alternative routes to access diol **1** were envisaged. Route A (Scheme 2), starting from compound **3**, is an attempt to circumvent the protection and deprotection steps of the original synthesis by performing a selective reduction of the least hindered ketone.[12] The resulting reaction mixture, containing the more hindered unreacted ketone, would then be submitted to the addition of a phenylmetal reagent to afford diol **1**.

Route B (Scheme 2) makes use of camphor (**2**) as a significantly cheaper raw material, which would be first converted to its enol ether, then oxidized by dimethyldioxirane (DMDO),[13] followed by the addition of a phenylmetal species. Like route A, this proposed route would also circumvent the protection scheme of the original synthesis of diol **1**.

In the development of route A, we first investigated the nature of the reducing agent, including common reagents such as DIBALH and Red-Al as well as reagents known to be more sensitive to steric bulk such as L-Selectride, LiAlH(O-*t*-Bu)$_3$, and LiBH(Et)$_3$. The effects of solvent and temperature were also investigated, as well as the rate of addition. The results of these experiments are summarized in Table 1. As seen in entries 1 and 2, the most common reducing agents afforded no selectivity at all, giving rise to low yields or unselective reduction of the carbonyls. In the case of the more sterically sensitive reagents, L-Selectride was found to be markedly more selective than LiAlH(O-*t*-Bu)$_3$ or LiBH(Et)$_3$. The importance of controlling the rate of addition is demonstrated by entry 9, in which the ratio of desired product rises from 7:1 to >9:1.

Following this study, we optimized the addition of the phenylmetal reagent (Table 2), which proved to be more challenging than expected. Phenylmagnesium bromide, phenyllithium, as well as the lesser known phenyl cerium dichloride were examined. To isolate the desired diol **1**, an oxidative workup was needed to break down the borinate generated after the L-Selectride reduction. All attempts to oxidize the borinate prior to the addition of the phenylmetal reagent were unsuccessful. The optimal results were achieved when the addition was performed

TABLE 1. Optimization of Reduction Conditions for Camphorquinone (3), Route A[a]



entry	hydride source [H$^-$]	*T* (°C)	**8a/8b**[b]	yield (%)
1	DIBALH	0	1:1	*c*
2	Red-Al	0	*d*	*c*
3[e]	LiAlH(O-*t*-Bu)$_3$	0	3:2	83
4[f]	LiAlH(O-*t*-Bu)$_3$	0	3:1	*c*
5[e]	LiAlH(O-*t*-Bu)$_3$	−40	4:3	51
6	LiBH(Et)$_3$	0	3:2	49
7	LiBH(Et)$_3$	−40	3:2	*c*
8	L-Selectride	0	7:1	*g*
9	L-Selectride	0	9:1[h]	*g*
10	L-Selectride	0	5:1[i]	*c*

[a] Reactions were performed in THF with 1 equiv of hydride reagent added over 10 min as their commercially available solution; reactions were worked up using 1 M HCl (aq). [b] Ratio determined by ^{1}H NMR of the crude reaction mixture. [c] Product not isolated. [d] Reduction of both carbonyls was observed. [e] LiAlH(O-*t*-Bu)$_3$ was added portionwise as a solid. [f] Hydride reagent was added as a solution in THF. [g] Unpurified product was used directly for the next step. [h] Hydride reagent was added over 40 min. [i] Ether used as solvent.

TABLE 2. Optimization of Addition of Phenylmagnesium Bromide to 8a, Route A

entry	solvent	*T* (°C)	conc (M)	equiv	yield[a] (%)
1	ether	−40	0.4	2	*b*
2	THF	−78	0.4	2	20
3	THF	−40	0.4	2	4
4	THF	0	0.4	2	4
5	THF	−78	0.2	1	6
6	THF	−78	0.2	2	*b*
7	THF	−40	0.2	2	*b*
8	THF[c]	−78	0.5	1.1	*b*
9	THF[d]	−78	0.2	1.1	55

[a] Crystallized from petroleum ether. [b] No product was isolated. [c] Performed using PhLi. [d] Performed using PhCeCl$_2$.

on the crude reaction mixture resulting from the acidic workup following the L-Selectride reduction.

Phenylmagnesium bromide was the first reagent investigated. In most cases, none or very little product was obtained with typical yields between 0 and 20%. Similar results were obtained using phenyllithium. In all of these cases, starting material was the main component of the crude reaction mixture. The phenylcerium reagent,[14] however, proved to be the most efficient reagent and afforded the desired diol **1** in high yield. This was not surprising, as cerium reagents are known to be less basic than Grignard and organolithium reagents. The lack of basicity of the cerium reagent makes it less prone to remove the rigid axial hydrogen α to the carbonyl. When this process happens, the starting material is regenerated upon aqueous workup, which may explain the low conversion observed with PhMgBr and PhLi. In all of these cases, as also observed by Hoffmann,[3] the reagent adds from the least hindered face and none of the other diastereoisomers were detected.

This new route A was found to be optimal (Scheme 3) when the reduction of dicarbonyl **3** is performed by a slow addition of L-Selectride at 0 °C, followed by an acidic workup. The sequence is completed by the addition of phenylcerium reagent to the crude hindered ketone, and

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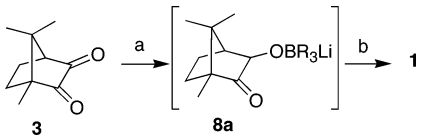
SCHEME 3. Optimal Route A from Camphorquinone[a]



[a] Key: (a) L-Selectride, THF, 0 °C, 1 h; (b) PhMgBr, $CeCl_3$, THF, 0 °C to rt, 3 h.

SCHEME 4. Formation of Enol Ethers of (*R*)-(+)-Camphor (2), Route B

9a, R = Me, quant.
9b, R = Et, quant.
9c, R = *i*-Pr, 0%

the ensuing oxidative workup generates the desired diol **1** with an overall yield of 55% in just two steps from **3**, or 47% including the known oxidation of **2** to **3**. This improved sequence can be accomplished in less than 24 h and was easily performed on more than 5 g of **3** without any purification steps.

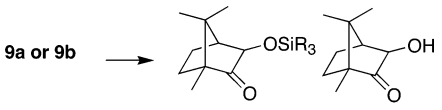
The reaction sequence of route B begins with the method reported in 1969 by House and co-workers[15] (Scheme 4). Thus, (*R*)-(+)-camphor (**2**) is treated with LDA, followed by a trialkylsilyl chloride and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and afforded the desired silyl enol ethers **9a**−**c**. In the case of **9a** (R = Me) and **9b** (R = Et), the product was obtained in quantitative yield. When R = *i*-Pr, no desired product **9c** was observed due to steric bulk.

The crude trimethyl- or triethylsilyl enol ethers were then oxidized using a procedure of Knight and Tchabanencko.[16] This method has certain advantages such as the in situ generation of DMDO, which avoids the distillation of this explosive reagent. Moreover, the reaction can be performed in an open flask. The large volume of solvent needed for the reaction (0.03 M, 120 mL for 1 g), however, makes it inefficient. This procedure also requires a large excess of the solid reagents, Oxone and $NaHCO_3$, which makes the agitation of the heterogeneous reaction mixture difficult. A variety of reaction conditions were investigated and are reported in Table 3. The first conclusion that can be drawn from the results is that the triethylsilyl enol ether **9b**, made using triethylsilyl chloride (TESCl), is more stable to the oxidation conditions as shown by the 10:1 ratio of the desired product **10** over the deprotected alcohol **11** (entry 2). The oxidation of the trimethylsilyl enol ether **9a**, under the same conditions, gave a ratio of 3:1 (entry 3). The reaction efficiency was improved by increasing the concentration from 0.03 to 0.25 M (1 g per 14 mL). Reducing the number of equivalents of oxone and $NaHCO_3$ did not affect the reaction (entry 5).

With the desired alkoxyketone in hand, the following step investigated was the introduction of the phenyl group to the carbonyl. The results of a representative set of conditions tried are summarized in Table 4. The use of either phenyllithium or the phenyl Grignard reagent led to the recovery of a significant amount of starting material (entries 1−4). As previously observed, the phenylcerium reagent was significantly better and gave a ratio of desired product to starting material over 10:1 (entry 5). It was also noted that the ratio of compounds **10** and **1** is greatly improved when the reaction is run using $PhCeCl_2$ made from PhMgBr instead of PhLi (entry 5). In all of these cases, as previously mentioned, none of the other diastereoisomers were detected.

The final step requires the cleavage of the silyl ether. This can be done efficiently with tetrabutylammonium fluoride (TBAF), but on a large scale the cost of TBAF is prohibitive. The procedure of Scheinmann and co-workers[17] was then tested for our sequence. It was found that the silyl ether could be effectively removed by heating compound **12** in a mixture of acetic acid, THF, and water (6.5:3.5:1) at 45 °C for 3 h. The desired diol **1** was obtained in a 55% yield comparable to that of the TBAF procedure. As described in Scheme 5, the optimal route to diol **1** is through the conversion of camphor **2** to its triethylsilyl enol ether **9b** followed by its oxidation to the α-silyloxy ketone **10b**. The sequence is completed by the addition of the phenylcerium reagent and removal of the TES group to afford, as demonstrated on a test sequence with 10 g of camphor, diol **1** in an overall yield of 55% without any purification steps.

TABLE 3. Optimization of Oxidation of Silyl Enol Ethers 9a or 9b, Route B[a]



entry	conc (M)	Oxone (equiv)	$NaHCO_3$ (equiv)	**10/11**[b]	yield (%)
1	0.03	15	5	10:1	71
2[c]	0.1	7.5	2.5	3:1	*d*
3	0.1	7.5	2.5	10:1	81
4	0.25	7.5	2.5	5:1	86
5	0.25	4.5	1.5	10:1	quant
6	0.5	7.5	2.5	5:1	86
7[e]	0.5	4.5	1.5	*f*	*d*

[a] All reactions were performed with **9b** at rt. [b] Ratio determined by ^{1}H NMR of the crude reaction mixture. [c] Done with **9a**. [d] Product not isolated. [e] Solvent was acetone/water 1:1. [f] Reaction was incomplete.

TABLE 4. Optimization of Addition of Phenylmetal Reagents to 10, Route B[a]

entry	metal	solvent	**10/1**[b]	yield[c] (%)
1	Li	THF	5:1	*d*
2	Li	ether	1:1	*d*
3	Mg	THF	*e*	*d*
4	Mg	ether	3:1	*d*
5	Ce[f]	THF	3:1	*d*
6	Ce[g]	THF	>10:1	55

[a] 1.1 equiv of PhM, 0 °C to rt. [b] Ratio determined by ^{1}H NMR of the crude reaction mixture. [c] Crystallized from petroleum ether. [d] Product not isolated. [e] Mostly starting material obtained. [f] Made using PhLi. [g] 1.1 equiv of PhMgBr, 1.15 equiv of anhydrous $CeCl_3$, 0 °C to rt.

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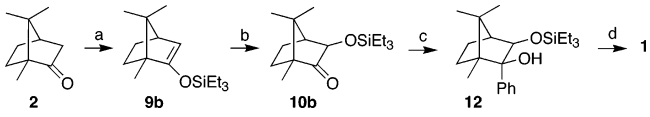
SCHEME 5. Optimal Route B from Camphor[a]



[a] Key: (a) LDA, TESCl, TMEDA, THF, −78 °C, 12 h; (b) Oxone, $NaHCO_3$, acetone, water, rt, 1 h; (c) $CeCl_3$, PhMgBr, THF, −78 °C to rt, 6 h; (d) acetic acid, water, THF, 45 °C, 3 h.

In summary, we have developed and optimized two new short syntheses of (−)-(1*R*,2*R*,3*R*,4*S*)-1,7,7-trimethyl-2-phenylbicyclo[2.2.1]heptane-2,3-diol (**1**) that improve upon the previous literature method of preparation. Route A is performed in two steps from commercially available camphorquinone (**3**) with an overall yield of 55%. Route B involves four steps from the cheap, commercially available camphor (**2**) and gives an overall yield of 55%. These two starting materials can be purchased in both enantiomeric forms, which allow access to either enantiomers of diol **1**. Both of these syntheses are efficient and practical and were successfully performed without any purification steps on multigram scale.

Experimental Section

Method A. A 1 M THF solution of L-Selectride (30.1 mL, 30.1 mmol) was added to a solution of camphorquinone (**3**) (5.0 g, 30.1 mmol) in THF (100 mL) at 0 °C. The temperature was kept below 5 °C throughout the addition. The mixture was stirred for an additional 30 min. THF (100 mL) was added to a separate flame dried round-bottom flask containing $CeCl_3 \cdot 7H_2O$ (13.5 g, 36.1 mmol) dried for 18 h at 140 °C under high vacuum (<1 mmHg). The slurry was stirred at 0 °C, and a 3 M THF solution of phenylmagnesium bromide (12.0 mL, 36.0 mmol) was added slowly. The resulting off-white suspension was stirred for 30 min. (Note: a darker solution indicates water is present.) The reduction reaction mixture was then slowly cannulated to the suspension using a double-ended needle. The resulting suspension was warmed to room temperature and allowed to stir for 3 h. The reaction mixture was poured slowly over a saturated aqueous solution of ammonium chloride, extracted three times with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The resulting oil was then dissolved in a mixture of THF (50 mL), water (25 mL), 1 M aqueous sodium hydroxide (50 mL), and 30% H_2O_2 (20 mL), and the biphasic mixture was stirred at room temperature for 3 h. The mixture was extracted three times with diethyl ether; the combined ether layers were washed once with water and once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The resulting oil was then left under vacuum (<1 mmHg) for 6 h. The resulting product was recrystallized from petroleum ether to afford, after three crops, the desired diol **1** as a white crystalline powder (4.0 g, 55% from (**2**)).

Method B. A 1.59 M hexane solution of *n*-BuLi (50.0 mL, 79.5 mmol) was added slowly to a solution of diisopropylamine (10.6 mL, 75.7 mmol) in THF at −78 °C and stirred for 15 min. A solution of (*R*)-(+)-camphor (**2**) (10.0 g, 65.8 mmol) in THF (100 mL) was added slowly to this mixture at −78 °C and stirred for 1 h. TMEDA (11.4 mL, 75.5 mmol) and TESCl (12.1 mL, 72.3 mmol) were added, and the mixture was kept at −78 °C for another 1 h. The reaction mixture was then warmed to room temperature and stirred for 12 h. The reaction mixture was poured slowly on a saturated aqueous solution of ammonium chloride and stirred for 15 min. The product was extracted three times with ether; the combined layers were washed once with water and once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated to afford the triethylsilyl enol ether **9b** as a yellow clear liquid. It was used without any further purification. Oxone (34.6 g, 56.3 mmol) was slowly added portionwise (over 45 min) to a heterogeneous mixture of **9b** (10.0 g, 37.5 mmol) and $NaHCO_3$ (14.2 g, 169 mmol) in acetone (100 mL) and water (50 mL) in open a flask. The temperature was controlled with a water bath to keep it below 30 °C. (**Caution**: DMDO is an explosive substance that is generated in situ; the reaction should be run in a well-ventilated fume hood using proper safety precautions.) The reaction was left to stir for an additional 30 min at room temperature. The reaction mixture was poured on water (500 mL) and extracted three times with ethyl acetate. The combined organic layers were washed once with a saturated aqueous solution of $Na_2S_2O_3$, once with water, once with brine, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated to afford the triethylsilyl ether ketone **10b** as a yellow clear liquid. It was used without any further purification. THF (100 mL) was added to a separate round-bottom flask containing $CeCl_3 \cdot 7H_2O$ (15.3 g, 43.4 mmol), which was dried for 18 h at 140 °C under high vacuum (<1 mmHg). The slurry was stirred at 0 °C, and a 3 M THF solution of phenylmagnesium bromide (13.9 mL, 41.7 mmol) was added slowly. The resulting off-white to beige suspension was stirred for 30 min at 0 °C. (Note: a darker solution indicates water is present.) The triethylsilyl ether ketone **10b** (10.5 g, 37.8 mmol) in THF (20 mL) was added slowly to the slurry. The resulting suspension was stirred 30 min at 0 °C, warmed to room temperature, and allowed to stir for 6 h. The reaction mixture was poured over a saturated aqueous solution of ammonium chloride. The resulting emulsion was filtered on a pad of Celite, the resulting clear solution was extracted three times with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The resulting oil was then dissolved in a mixture of acetic acid, water, and THF (65 mL, 35 mL, 10 mL) and heated for 3 h at 45 °C. Water (100 mL) and ether (200 mL) were added to the cooled reaction mixture, and solid NaOH was added until the pH of the mixture was >7. The mixture was extracted three times with ether; the combined organic layers were washed once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The resulting oil was stirred and heated to 100 °C under high vacuum (<1 mmHg) for 6 h to remove the leftover triethylsilanol. The resulting sticky solid was recrystallized from petroleum ether to afford, after four crops, the desired diol **1** as a white crystalline powder (5.2 g, 55% overall).

(−)-(1*R*,2*R*,3*R*,4*S*)-1,7,7-Trimethyl-2-phenylbicyclo[2.2.1]-heptane-2,3-diol 1. White powder. Mp: 115−116 °C. $[\alpha]^{25}_D$ −26.34 (*c* = 2.53, $CHCl_3$). IR (CH_2Cl_2 cast, cm^{-1}): 3286, 3055, 2951. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56−7.48 (m, 2H), 7.37−7.20 (m, 3H), 4.40 (s, 1H), 2.75 (br s, 2H), 1.90 (d, *J* = 4.8 Hz, 1H), 1.83−1.69 (m, 1H), 1.30 (s, 3H), 1.20−1.10 (m, 2H), 1.05−0.95 (m, 1H), 0.92 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.5, 127.6, 127.1, 126.6, 84.3, 80.5, 53.2, 51.9, 50.7, 30.4, 24.4, 23.1, 22.3, 9.9. HRMS (EI, *m/z*): calcd for $C_{16}H_{22}O_2$ 246.16215, found 246.16199. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.78; H, 9.24.

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Supporting Information Available: Spectroscopic data for intermediates **8a**, **9a**, and **12** and $[\alpha]^{25}_D$, IR, ^1H NMR, ^{13}C NMR, HRMS, and elemental analyses data for new compounds **9b** and **10b**. Spectral reproductions of **1**, **8a**, **9a**,**b**, **10b**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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