Organic Process Research & Development

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Scalable Syntheses of the Vaulted Biaryl Ligands VAPOL and VANOL via the Cycloaddition/Electrocyclization Cascade

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ABSTRACT: Synthetic approaches to the VANOL and VAPOL ligands are developed which are straightforward, inexpensive, efficient, and amenable to large-scale preparation of the ligands since minimum chromatographic purification is required. The key step in each synthesis is a cycloaddition/electrocyclic ring-opening/electrocyclic ring closure/tautomerization cascade that provides a direct one-step route to the monomers from which each ligand is prepared. Improved phenol coupling protocols are developed which provide the racemic ligands. Finally, dramatic improvements in the resolution procedures feature the reduction of the number of chemical steps and the defining of new crystallization protocols that greatly enhance the ease and reliability of the separation of diastereomeric salts.

1. INTRODUCTION

BINOL and its derivatives are among the most important class of ligands for asymmetric synthesis.[1,2] We have introduced the vaulted biaryl ligands VANOL **2** and VAPOL **3** with an eye on redesigning the location of the major groove of the ligand relative to the active site containing the phenol functions.[3,4a] As illustrated for VAPOL **3** in Scheme 1, as a result of the relocation of the major groove, there is a substantially larger chiral pocket around the active site in VAPOL **3** than there is in BINOL **1**. In validation of this design, the VANOL and VAPOL ligands have been shown to be effective in chiral catalysts for a number of reactions. In some, VANOL led to the superior catalyst, and for others it was VAPOL. Aluminum derivatives of VAPOL were more effective than VANOL for Diels−Alder reactions,[4] and zirconium derivatives of VAPOL were more effective than those of VANOL for Mannich reactions.[5] It was interesting to find that VANOL was far more effective than VAPOL in aluminum-mediated Baeyer−Villiger reactions.[6] VANOL and VAPOL have also been incorporated into phosphoric acid esters to produce chiral Brønsted acids, and the VAPOL derivative was shown to be more effective in the amidation[7] and imidation[8] of imines and in the asymmetric reduction of imines,[9] while both showed effectiveness in the desymmetrization of aziridines depending on the nucleophile.[10] The VANOL and VAPOL ligands both showed essentially equal ability to serve in catalysts for the Petasis reaction[11] and the hydroarylation of alkenes.[12] Heteroatom Diels−Alder reactions of imines with Danishefsky's diene were both faster and more enantioselective with a boron-VAPOL catalyst than with the corresponding boron-VANOL catalyst.[13] However, perhaps the most important application of these ligands is the catalytic asymmetric aziridination of imines with diazo compounds which utilizes the same boron-based catalyst as the heteroatom Diels−Alder reaction.[14,15] Recent studies have revealed that this boron-based catalyst is a rather unique chiral polyborate Brønsted acid that contains a boroxine ring in which one of the borons is spiro-fused to the VANOL or VAPOL ligands.[14i,l,m] In the aziridination of imines with diazo compounds, the VANOL catalyst **4** is superior for *trans*-aziridinations,[14k] and the VAPOL catalyst **5** and the VANOL catalyst **4** are essentially equally effective for *cis*-aziridinations.[14g,j] Recent reports have described VAPOL catalysts for the asymmetric catalytic chlorination and Michael reactions of oxindoles[16] and for the benzoyloxylation of oxindoles.[17] Finally, VANOL catalysts have recently been shown to be superior to both VAPOL and BINOL catalysts for the catalytic asymmetric amino-allylation of aldehydes.[18]

The success of asymmetric catalysts derived from the VANOL and VAPOL ligands has resulted in the need for syntheses of these ligands that are more efficient than the original procedures that we first published.[3,4a] In this report we describe cost-effective and scalable racemic syntheses of both the VANOL and VAPOL ligands and, in addition, resolution methods that reliably allow for the separation of the two enantiomers of each ligand by crystallization. The key step in both syntheses is the cycloaddition/electrocyclization cascade (CAEC) that is initiated by the [2 + 2] cycloaddition of phenylacetylene with either phenyl or 2-naphthyl ketene (Scheme 2). Improved procedures are also developed for the oxidative phenol coupling reactions that are used to generate racemic VANOL and VAPOL. Finally, the procedures for the resolution of each ligand involving alkaloid salts of their corresponding hydrogen phosphate derivatives have been improved such that highly reproducible protocols are now available for the crystallization of each of the diastereomeric salts of each ligand.

2. BACKGROUND

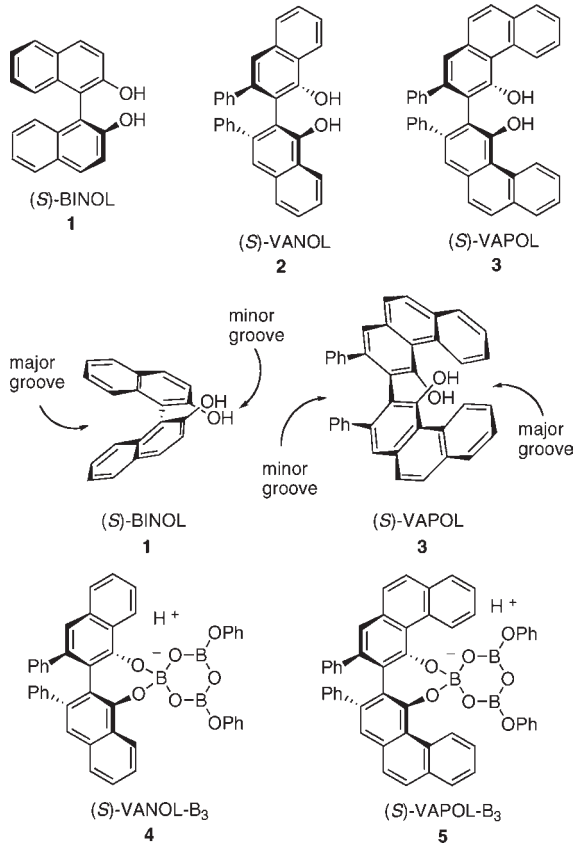
We have recently developed a new synthesis of the VANOL ligand that utilizes inexpensive materials and requires neither special equipment nor low temperatures, which is easy to scale-up since no chromatographic separations are required.[19] This synthesis begins with the chlorination of 1-naphthol, and treatment of the resulting 4-chloro-1-naphthol with $AlCl_3$ in benzene

Special Issue: Asymmetric Synthesis on Large Scale 2011

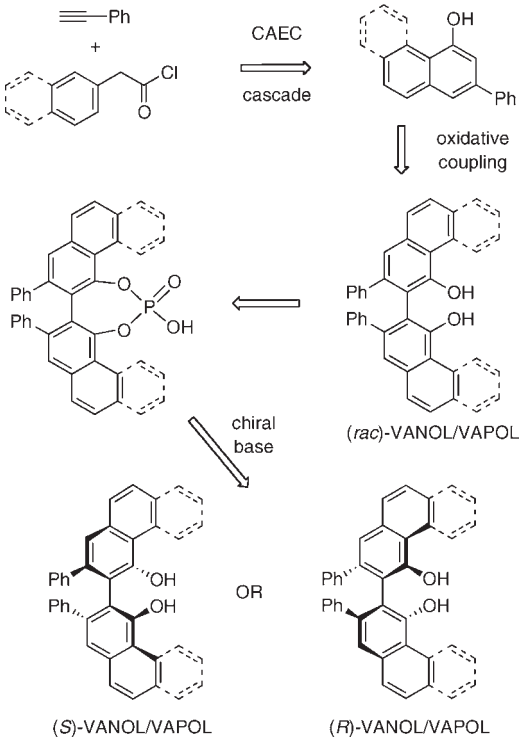
Received: June 7, 2011
Published: July 12, 2011

dx.doi.org/10.1021/op200088b | *Org. Process Res. Dev.* 2011, 15, 1089–1107

Scheme 1



Scheme 2



leads to a dienone−phenol rearrangement of an in situ generated cyclohexa-2,5-dienone and the formation of 3-phenyl-1-naphthol **8** (Scheme 3). The last step is the oxidative phenol coupling of 3-phenyl-1-naphthol **8** with air which gives racemic VANOL in high yield. Considering the fact that the synthesis of 4-chloro-1-naphthol **7** has been reported on a 500 kg (3472 mol) scale,[20] that the remaining two steps in the synthesis of VANOL **2** shown in Scheme 3 employ very inexpensive reagents, and that no chromatographic separations are needed, this synthesis should be scalable for large-scale production of the VANOL ligand.

An attempt to synthesize VAPOL by the approach to VANOL shown in Scheme 3 would begin with the chlorination of 4-phenanthrol **9** (Scheme 4). The key intermediate is 2-phenyl-4-phenanthrol **11** which has been employed in the previous synthesis of VAPOL via an oxidative dimerization.[3] The dienone−phenol type rearrangement set up by the treatment of 1-chloro-4-phenanthrol **10** with $AlCl_3$ in benzene has never been investigated. The reason is that while the chlorination of 4-phenanthrol **9** is known to give 1-chloro-4-phenanthrol **10** (along with 41% of 3-chloro-4-phenanthrol),[21] 4-phenanthrol **9** is not readily available, and the necessity for its synthesis[22] would make this approach far too long to be economical on a large scale.

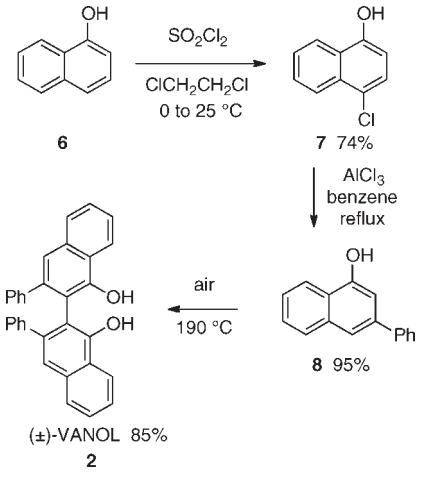
The current method for the synthesis of VAPOL is shown in Scheme 5 and involves the benzannulation of the naphthyl carbene complex **13** with phenylacetylene as the key step.[3] The carbene complex is prepared by the addition of 1-naphthyllithium to chromium hexacarbonyl and then methylation by dimethyl sulfate. The carbene complex is a crystalline red solid and can be readily purified by crystallization, and we have routinely prepared this complex on a 250 g scale. The initial product of the benzannulation is a 1-phenanthrol that is acetylated to give phenanthrene **14**. A thiol will cleave the methyl ether in the presence of aluminum chloride and will simultaneously effect the reductive deacetylation to give 2-phenyl-4-phenanthrol **11** in high yield. This four-step process is quite efficient giving **11** in 52% overall yield from 1-bromonaphthalene and relatively easy to scale up to 100 g or more since chromatography can be avoided in all purifications. For example, the benzannulation reaction of carbene complex **13** and phenyl acetylene has been carried out on a 250 g scale.[23] However, a significant deficit of this approach is the cost of chromium hexacarbonyl, which at $6 per gram is not an issue on small scale, but on a 100 g scale or larger it becomes prohibitive. Thus, a more cost-effective synthesis of VAPOL was sought and is the subject of the present study. We have also examined the synthesis of VAPOL utilizing the Snieckus phenol synthesis, an approach that requires the use of low temperatures (−78 °C) and lachrymators.[24] The yields for the key step fell off when the scale was increased and some of the steps required purification by chromatography, and thus this approach was not considered in seeking a more cost-effective scalable synthesis of VAPOL.

3. CYCLOADDITION/ELECTROCYCLIZATION CASCADE (CAEC) APPROACH TO VANOL AND VAPOL

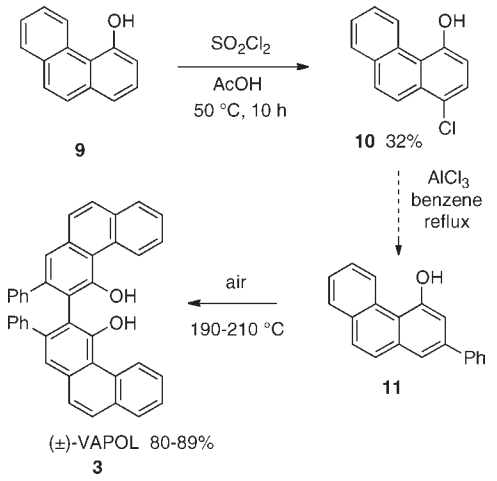
We have previously published[3] the three-step synthesis of 2-phenyl-4-phenanthrol **11** shown in Scheme 6 that begins with the commercially available 2-naphthaleneacetic acid **15**, the parent member of a class of nonsteroidal anti-inflammatory agents such as naproxen.[25] Conversion of the carboxylic acid **15** to its corresponding acid chloride **16** is then directly followed without purification by thermolysis with neat phenyl acetylene

dx.doi.org/10.1021/op200088b |Org. Process Res. Dev. 2011, 15, 1089–1107

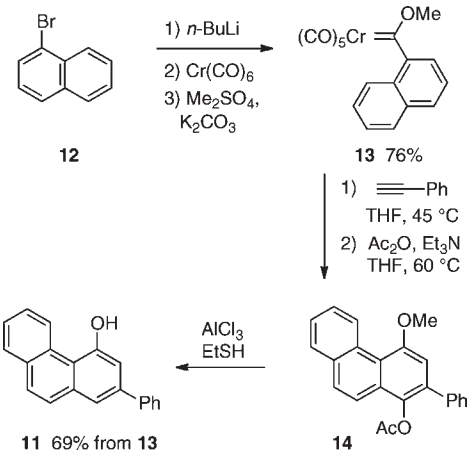
Scheme 3



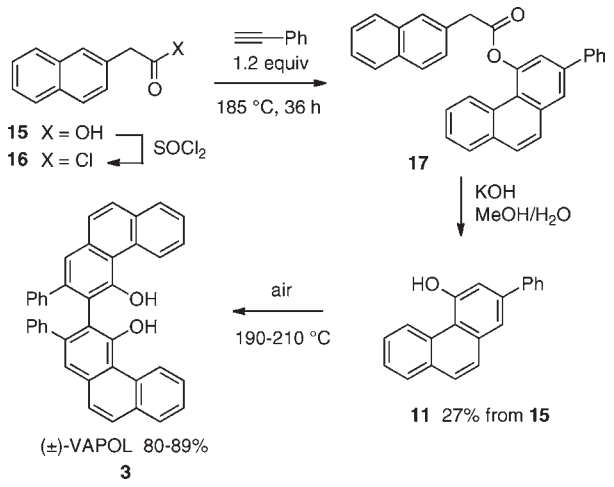
Scheme 4



Scheme 5



Scheme 6



which gives the carboxylic ester **17**. This intermediate also is not purified, and the crude product is directly saponified to give 2-phenyl-4-phenanthrol **11** in 27% yield from the acid **15**. The yield for this process may not be viewed in such a negative light when it is realized that two equivalents of the acid chloride **16** is required for this reaction, one to generate the 2-phenyl-4-phenanthrol **11** and one to trap it to give the ester **17**. While 2-naphthaleneacetic acid **15** can be recovered from the saponification and recycled, the need to do this greatly reduces the efficiency of this synthesis of VAPOL. Despite the flagging interest in this approach that the low yield of **11** engendered, the optimization of this synthesis of VAPOL was undertaken given the simplicity of the chemical steps and the inexpensive nature of the reagents.

In early attempts to scale up the VAPOL synthesis shown in Scheme 6, it was found that the 2-phenyl-4-phenanthrol **11** that was obtained after saponification could only be purified by careful chromatography on silica gel.[3] The crude product was obtained as a black sticky tarry material from which no attempts at crystallization were successful in providing **11** in any form with increased purity. The mechanism by which the transformation of **16** to **17** occurs begins with the loss of HCl from the acid chloride **16** to give the ketene **18** that then is followed by a [2 + 2] cycloaddition with phenyl acetylene to give the cyclobutenone **19** (Scheme 7). The electrocyclization cascade begins with electrocyclic ring opening of the cyclobutenone to give the vinyl ketene **20** which undergoes a $6e^-$ electrocyclic ring closure to give cyclohexa-2,4-dienone **21** and then, upon tautomerization, gives rise to 2-phenyl-4-phenanthrol **11** that is then either trapped by the acid chloride **16** or the ketene **18** to provide the ester **17**.

This cycloaddition/electrocyclization cascade (CAEC) in the past has always been performed without a solvent,[26] but a recent report by Redic and Schuster[27] finds that the yields can be improved somewhat if decalin is employed as a solvent. In our original report[3] of the reaction without solvent, the acid **15** is converted to the acid chloride **16**, and then the excess $SOCl_2$ is removed under high vacuum to leave the acid chloride as a yellow solid. This material is then heated with phenyl acetylene to give the phenanthrol **11** in 27% yield after reductive cleavage of the ester **17** with LAH (Table 1, entry 1). Inspired by the report of Redic and Schuster,[27] we repeated this reaction in decalin to find that the yield slightly increases to 37% (entry 2). It was also found that mineral oil could give

dx.doi.org/10.1021/op200088b |*Org. Process Res. Dev.* 2011, 15, 1089–1107

essentially the same yield (entry 3). The lack of tertiary hydrogens in mineral oil gives it a safety advantage at these high temperatures in that it should be less reactive with air at these higher temperatures. Further optimization found that 190 °C is the optimal temperature, and 1.3 equiv of phenyl acetylene gives material that was much easier to purify and was cleaner after purification.

Given the low yield observed for 2-phenyl-4-phenanthrol **11** and the fact that half of the starting 2-naphthaleneacetic acid **15** is wasted when phenanthrol **11** is trapped, the idea was conceived that a trapping agent could be found that could compete with the in situ generated ketene in the reaction with the phenol function in **11** but not otherwise affect the reaction. In developing a synthesis of any phenol-containing compound, protection of the phenol function is often required to prevent side reactions of the hydroxyl group. The phenol function is most often protected as either an ether or an ester. Formation of ethers usually requires the presence of base since in most cases the hydroxyl group itself is not a strong nucleophile. Another problem associated with ether-forming agents is that they are usually too volatile to be useful for reactions requiring conditions with high temperatures. On the other hand, esterification reagents (acid halides and anhydrides) are generally reactive to the phenol function, thermally stable, and typically inexpensive. A number of such reagents were examined, and the results are summarized in Table 2. All reactions were carried out with 1.3 equiv of phenylacetylene to ensure that there is sufficient alkyne present for the trapping agent to do the job as intended in which case a minimum of 1.0 equiv would be needed. The reaction with $SOCl_2$ as the trap was carried out by not removing the excess $SOCl_2$ from the previous step in which the acid **15** is converted to its acid chloride. This did not lead to the isolation of phenanthrol **11** but rather to the formation of an uncharacterizable black tar (Table 2, entry 1). The reaction with $POCl_3$ added as the trap faired a little better, giving a small amount of **11**. A low yield of **11** was obtained with acetyl chloride, but the quality of the isolated product was significantly improved, as indicated by both the melting point and color of the final product. This low yield could be related to the low boiling point of acetyl chloride which is consistent with the fact that benzoyl chloride gives nearly double the yield as acetyl chloride. Nonetheless, it was still disappointing to find that the 50% yield ceiling could not be overcome. This was to be realized with anhydrides as the trapping agent and, surprisingly, with only one particular anhydride, *iso*-butanoic anhydride which gave the phenanthrol **11** in 75% yield. It is really quite remarkable that it gives a 20% higher yield than the isomeric *n*-butanoic anhydride, and the reason for this is not understood at this time. It was also unexpected that the *n*-butanoic ester would be much more difficult to hydrolyze with aqueous KOH than the *iso*-butanoic ester (entries 9 vs 10). The phenanthrol **11** could be liberated with either KOH or LAH, but the former was deemed to be more desirable on large scale due to cost and to the fact that the latter results in a quite exothermic reaction.

The fact that a 75% yield of phenanthrol **11** is obtained when *iso*-butyric anhydride is used as the trap indicates that at least three-fourths of the carboxylic acid **15** takes part in the cycloaddition/electrocyclization cascade and that a maximum of one-fourth of the phenanthrol **11** comes from the hydrolysis of the 2-naphthaleneacetic acid ester **17** via the trapping of the ketene **18** (Scheme 7) or the acid chloride **16** (Scheme 6). This

Scheme 7

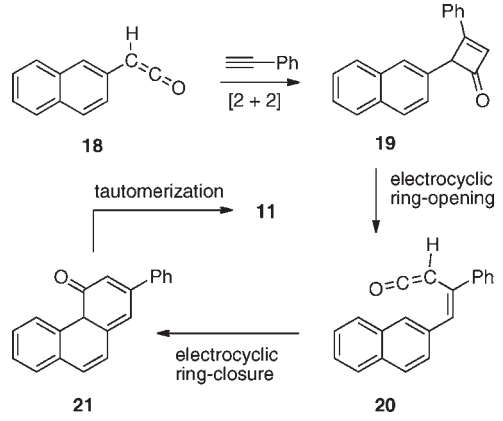
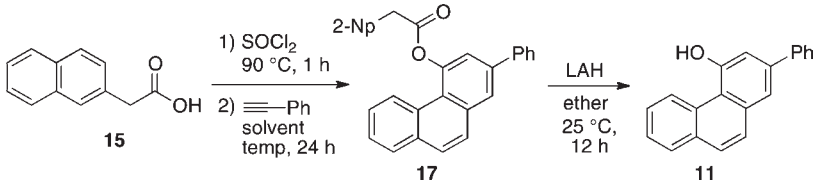


Table 1. Solvents for the Cycloaddition/Electrocyclization Cascade (CAEC)[a]

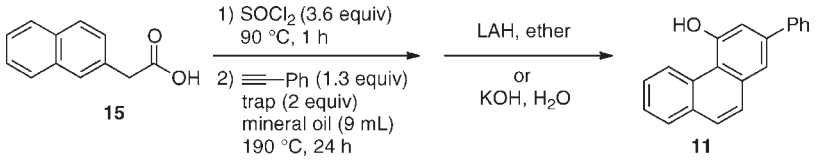


entry	HC≡CPh (equiv)	temp (°C)[b]	solvent (9 mL)	% yield **11**[c]	mp **11** (°C)[d]	color of **11**
1[e]	0.67	185	none	27	nd	brown
2	0.67	190	decalin	37	144−5	brown
3	0.67	190	mineral oil	38	140−1	brown
4	0.67	170	mineral oil	22	150−1	brown
5	0.67	210	mineral oil	37	147−8	brown
6[f]	1.31	190	mineral oil	41	140−1	grey

[a] Unless otherwise specified, each reaction was carried out on 76 mmol of **15** with 3.6 equiv of $SOCl_2$. The phenanthrol **11** was liberated from **17** with 1.1 equiv of LAH in 100 mL of ether. [b] Oil bath temperature. [c] Isolated yield after chromatography on silica gel. [d] mp of **11** is 154−5 °C (ref 3). [e] Data from ref 3: ester was converted to **11** with KOH in MeOH/H_2O for 20 h at 25 °C. [f] 1.72 equiv of LAH used.

dx.doi.org/10.1021/op200088b |*Org. Process Res. Dev.* 2011, 15, 1089–1107

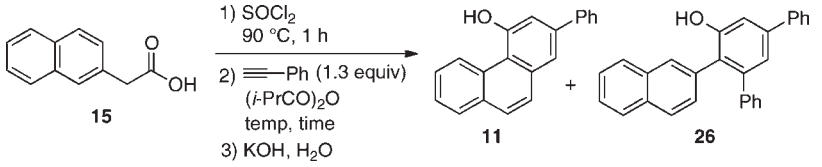
Table 2. Survey of Trapping Agents for Phenanthrol 11[a]



entry	trap	trap bp (°C)	ester cleavage	% yield **11**[b]	mp **11** (°C)[c]	color of **11**[d]
1[e]	$SOCl_2$	76	LAH	ND	nd	nd
2	$POCl_3$	105	LAH	16	128−30	black
3[f]	MeCOCl	51	LAH	23	148−9	light yellow
4	PhCOCl	198	KOH	44	152−4	dk brown
5	*n*-heptylCOCl	196	KOH	51[g]	125−7	chocolate
6	$(MeCO)_2O$	140	LAH	17	152−3	light yellow
7[h]	$(MeCO)_2O$	140	LAH	48	153−5	light yellow
8	$(EtCO)_2O$	168	LAH	31	153−4	yellow
9	$(i\text{-}PrCO)_2O$	182	KOH	75	151−2	orange
10	$(n\text{-}PrCO)_2O$	198	KOH	55[i]	149−50	orange
11	$(ClCH_2CO)_2O$	203	KOH	trace	nd	nd

[a] Unless otherwise specified, each reaction was carried out on 76.4 mmol (14.2 g) of **15** with 3.6 equiv of $SOCl_2$. The phenanthrol **11** was liberated from **17** either with 1.1 equiv of LAH in 100 mL of ether at 25 °C for 12 h or with 4.7 equiv of KOH in 100 mL of H_2O at 100 °C for 12 h. [b] Isolated yield after chromatography on silica gel. ND = not detected. [c] mp of **11** after silica gel chromatography (lit.[3] mp 154−5 °C). nd = not determined. [d] Color of **11** after silica gel chromatography. [e] Excess $SOCl_2$ not removed prior to thermolysis with HC≡CPh. [f] Reaction time is 36 h. [g] Yield of octanoate ester of **11**. [h] Reaction time is 64 h. [i] Hydrolysis performed twice at 120 °C with 11.7 equiv of KOH.

Table 3. Optimization of the Synthesis of Phenanthrol 11 with $(i\text{-}PrCO)_2O$[a]



entry	$SOCl_2$ (equiv)	$(i\text{-}PrCO)_2O$ (equiv)	time (h)	temp (°C)[b]	% yield **11**[c]	mp **11** (°C)[d]	color of **11**[e]	% yield **26**[f]	recovery **15**[f]
1[g]	3.6	2	24	190	68	151−2	brown	nd	nd
2	3.6	2	24	190	71	147−8	orange	nd	nd
3	3.6	1	24	190	43	149−51	orange	nd	nd
4	3.6	4	24	190	55	152−3	orange	nd	nd
5	3.6	2	24	210	51	152−3	orange	nd	nd
6	1.8	2	24	190	65	152−3	orange	nd	nd
7	1.8	2	48	190	81	154−5	yellow	nd	nd
8	3.6	2	48	190	79	152−3	yellow	8	13
9	3.6	2	48	170	67	153−4	orange	11	25
10[h]	3.6	2	48	190	77	156−7	yellow	8	nd
11[i]	3.6	2	48	190	47	nd	brown	ND	ND

[a] Unless otherwise specified, each reaction was carried out on 76.4 mmol (14.2 g) of **15** with no solvent. The phenanthrol **11** was liberated from its *iso*-butyl ester by refluxing with 5.8 equiv of KOH in 100 mL of H_2O for 12 h. [b] Oil bath temperature. [c] Isolated yield after chromatography on silica gel. nd = not determined. [d] mp of **11** after silica gel chromatography (lit.[3] mp 154−5 °C). [e] Color of **11** after silica gel chromatography [f] Isolated yield after chromatography on silica gel. ND = not detected. [g] Reaction performed in mineral oil (9 mL) as solvent, and **11** was liberated by heating with 5.8 equiv of KOH in 100 mL of H_2O at 120 °C (oil bath temperature) for 12 h. [h] The alkyne was added in four equal portions at 0, 6, 12 and 24 h. [i] Alkyne was added by syringe-pump over a period of 30 h, and the scale was 306 mmol of **11**.

was verified by carrying out the reaction without the final hydrolysis which led to the isolation of the *iso*-butyric ester **22** in 74% yield and the 2-naphthaleneacetic acid ester **17** in 7% yield (eq 1).

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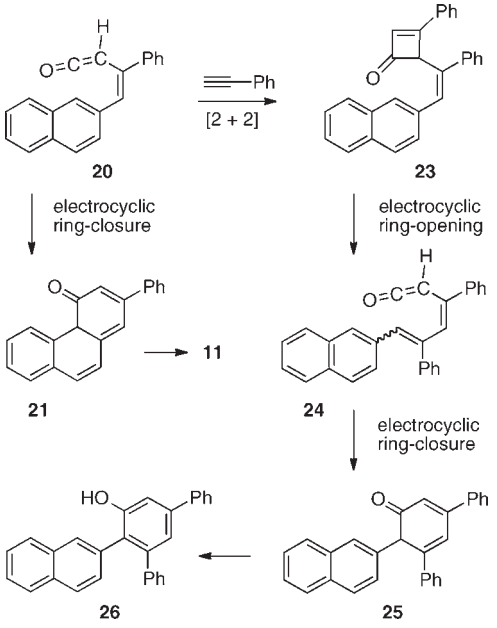
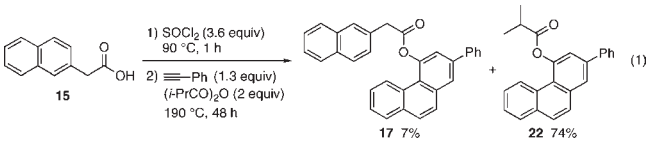
Scheme 8



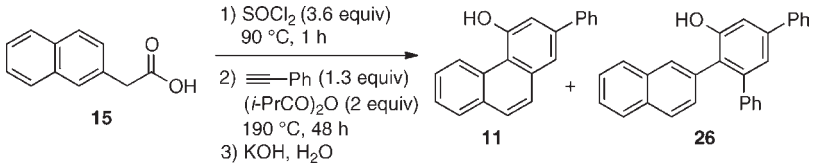


The purpose of the 11 reactions summarized in Table 3 is to identify factors that will lead to optimization of the reaction with *iso*-butyric anhydride as the trapping agent. The first finding is that the use of mineral oil as solvent is unnecessary (entries 1 vs 2), and this is useful in simplifying the purification of the phenanthrol **11**. The results in entries 2−4 served to identify the optimal amount of trapping agent as two equivalents. As was found by the survey of conditions without a trapping agent (Table 1), the optimal temperature for the reaction with the *iso*-butyric anhydride trap is 190 °C (entries 2 and 5 and 8 and 9). A notable decrease in yield (20%, entries 2 vs 5) was observed when the temperature was raised to 210 °C. The reason for this is not clear, but it was observed that *iso*-butyric anhydride (bp 182 °C) began to boil at this temperature, and it is possible that this retarded the condensation of the alkyne (bp 144 °C) and its return to the reaction flask. Finally, it was observed from this study that the amount of excess $SOCl_2$ is not crucial (entries 2 and 6), and a reaction time of 48 h is superior to that of 24 h (entries 6 and 7). The chlorination of acid **15** can also be performed with $(COCl)_2$ instead of $SOCl_2$. When the reaction indicated in entry 2 of Table 3 was repeated with the acid chloride **16** generated from the acid **15** with oxalyl chloride according to the procedure of Bandarage,[28] the phenanthrol **11** was obtained in 67% yield if the oxalyl chloride was added all at once and in a lower yield (47%) if it was added slowly over a period of 1 h. The highly vigorous reaction that ensued when oxalyl chloride was added all at once is a decided detriment, and along with the price difference, thionyl chloride is thus deemed the reagent of choice for the large-scale synthesis of phenanthrol **11**.

The cycloaddition/electrocyclization cascade produces a byproduct which was identified as 2-(2-naphthyl)-3,5-diphenylphenol **26** and which is generally obtained in ∼10% yield (Scheme 8). The origin of this product is most likely from a [2 + 2] cycloaddition of phenylacetylene with the ketene **20**, a process which is in competition with electrocyclic ring closure to give the phenanthrol **11**. The resulting cyclobutenone **23** could then be expected to begin its own electrocyclization cascade that begins with electrocyclic ring opening to give the dienyl ketene **24** and then an electrocyclic ring closure to give the cyclohexadienone **25** and finally tautomerization to the byproduct **26**. The byproduct phenol **26** can be separated from the desired phenol **11** by chromatography on silica gel, but on large scale, it is not clear if the two phenols will be easily separable by crystallization. Thus, some effort was put forth to minimize the formation of this byproduct. Mechanistically, the partition point is the ketene **20**, and the amount of the two phenol products is dependent on the competition between the electrocyclic ring closure to **21** and the [2 + 2] cycloaddition to give **23**. This competition will thus be dependent on the concentration of alkyne, and thus the distribution between the two products was examined as a function of the rate of addition of the alkyne that, in all but the last two entries of Table 3, is added all at once. In entry 10, the alkyne is added in four equal portions over a 24 h period, but the ratio of **11** to **26** is virtually unchanged (entries 8 vs 10). It is not clear why the portion-wise addition did not illicit a change in the ratio of the two products. The formation of the byproduct could be suppressed by the slow addition of the alkyne over a period of 30 h by syringe in a reaction that was carried out on 4-fold increased scale (entry 11). None of the phenol **26** could be detected, but this was gained at an immense price since the yield of the phenanthrol **11** fell to 14%. No further attempts to minimize the formation of **26** were pursued.

The two-alkyne phenol **26** could be separated from the desired phenanthrol **11** by chromatography on silica gel, and on small scale (14.2 g) this proved to be practical (Table 4). The reaction run under the optimal conditions established in Table 3 (entry 8) gave a 75% isolated yield of **11** by chromatography on silica gel (Table 4, entry 1). In an effort to develop a protocol that avoids chromatography, the reaction was repeated (entry 2), and the product was crystallized from the crude reaction mixture from dichloromethane. The first crop gave pure **11** in 37% yield, but it did not prove possible to obtain any additional **11** in pure form by further crystallization under any condition. The second crop was typically impure **26**. However, loading the concentrated mother liquor onto a silica gel column gave additional pure **11** for a total of 57% yield. An additional complication arose from the presence of some nonpolar black impurities that interfered with both chromatographic and crystallization purification techniques. The amount of these impurities and the ultimate quality of the product **11** were found to be dependent on the source of 2-naphthylacetic acid **15**. One particular batch of **15** gave significantly more of these black impurities than others (entry 3). The source of this problem was not obvious since the acid **15** used in entry 3 was nearly white in appearance and had a clean ^{1}H NMR spectrum, and its melting point matched published values. Crystallization of the material used in entry 3 did not markedly reduce the amount of black impurities formed in the reaction. It is suspected without evidence that this compound may have been prepared by a Willgerodt−Kindler reaction[29] from 2-naphthylacetophenone and that residual sulfur is not completely removed by crystallization. The amount of these black impurities was minimal from the reaction performed with the acid **15** obtained from Aldrich Chemical Co. (Table 4, entry 4).

Table 4. Optimization of the Synthesis of Phenanthrol 11 with $(i\text{-PrCO})_2O$



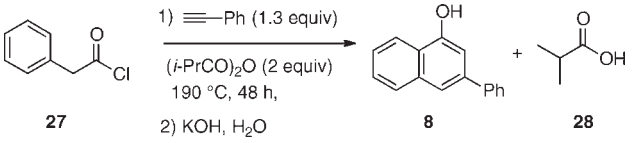
entry	**15** (g)	source of **15**	purification	% yield **11**[a]	% yield **26**
1	14.2	Milestone	column only	75	8
2	14.2	Milestone	crystallization[b]/column	57	7
3	14.2	O-Chem	column only	61	nd
4	14.2	Aldrich	crystallization[b]/column	74	8
5	57	Milestone	crystallization[b]/filter/crystallization[c]/crystallization[d]	57	5
6	57	Milestone	crystallization[b]/filter/crystallization[c]/crystallization[d]	64	5

[a] Combined isolated yield of **11**. [b] The first crystallization gives **11** from CH_2Cl_2. [c] The second crystallization gives **26** from *i*-PrOH. [d] The third crystallization gives additional **11** from hexanes/dichloroethane (2:1).

In an effort to find a method for the separation of **11** and **26** by crystallization, a number of solvents were screened, and it was found that isopropanol was superior to ethanol, methanol, ethyl acetate, and toluene. It was noted that while 157.4 g of **11** would dissolve in 100 mL of boiling *iso*-propanol this stood in stark contrast to only 1.75 g of phenanthrol **26**. This suggested that the byproduct be removed first by initial crystallization from isopropanol. However, all attempts to do this invariably led to the collection of a solid that was a mixture of phenol **26** and phenanthrol **11**. Thus, it was realized that any final protocol would involve collection of the phenanthrol first, and the optimized procedure is shown in entries 5 and 6 in Table 4. The crude product is first crystallized from CH_2Cl_2 to give the phenanthrol **11** (42%, entry 5). It is difficult to crystallize either product from the residue of the mother liquor because of the presence of the nonpolar black impurities. Thus, it was found best to filter the residue through a bed of silica gel in a sintered glass funnel with suction from a water aspirator with a 1:1 mixture of CH_2Cl_2 and hexanes. The first liter of eluent was discarded and consisted of ~10 g (the amount depends on the source of **15**) of a black tarlike substance which contained a small amount of **26**. The remaining material (a mixture of **11** and **26**) was flushed from the silica gel and crystallized from isopropanol to give a 5% yield of the pure phenol **26**. A final crystallization from hexanes and 1,2-dichloroethane gives an additional 15% yield of pure **11**. This protocol proved to be reproducible over a number of runs, and an additional example is given in Table 4 (entry 5). It should be noted that for the 2-naphthylacetic acid **15** obtained from Aldrich Chemical Co. very little of these black impurities were observed (Table 4, entry 4), and thus the crystallization of **11** was not impeded. In this case, crystallization gave a 58% yield of phenanthrol **11** from the first crop from dichloromethane. An additional 16% of **11** was obtained by column chromatography, but it is suspected that additional pure **11** could have been obtained by taking a second crop.

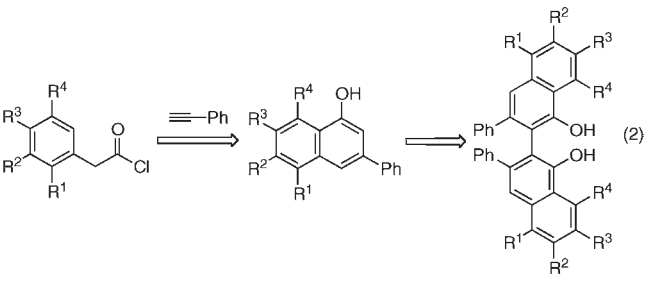
With the successful development of a scalable protocol for the preparation of VAPOL via the CAEC cascade, the immediate question is that would this work as well for the synthesis of VANOL? At first blush, this might be considered as unnecessary since as summarized in Scheme 3 we have recently developed an inexpensive and technically simple synthesis of VANOL in two steps from the commercially available 4-chloro-1-naphthol **7** or three steps from the less expensive 1-naphthol.[19]

Table 5. Optimization of the Synthesis of 3-Phenyl-1-naphthol 8 with $(i\text{-PrCO})_2O$[a]



		% yield of **8**				
entry	**27** (mmol)	1st crop[b]	2nd crop[c]	column[d]	total **8** (%)[e]	total **8** (g)[e]
1	74.7	–	–	70[f]	70	11.5
2	374	43	13	11	67	54.7
3	374	44	17	7	68	56.0

[a] After neutralization, the crude reaction mixture is washed with sat. aq Na_2CO_3 to remove *iso*-butyric acid **28**. [b] The first crystallization gives **8** from hexanes/CH_2Cl_2 (3–4:1). [c] The second crystallization gives **8** from hexanes/CH_2Cl_2 (3:1). [d] The mother liquor is stripped of solvent and loaded onto a silica gel column and eluted with hexanes/CH_2Cl_2 (2:1). Collection of fractions containing **8** gives a yellow solid that is not completely pure. Crystallization from hexanes/CH_2Cl_2 (3:1) gives additional pure **8** in the indicated yield. [e] Total isolated yield of **8**. [f] The *iso*-butyric acid **28** is removed by distillation, and then the entire crude reaction mixture was loaded onto a silica gel column and eluted with hexanes/CH_2Cl_2 (2:1). Collection of the fractions containing **8** gives pure **8** as a biege solid.



However, the CAEC cascade has a potentially significant advantage in a VANOL synthesis in that it can provide for the rapid synthesis of a family of VANOL ligands (eq 2). The commercial availability of a significant number of substituted phenyl acetic acid derivatives empowers the CAEC approach to VANOL since it would enable direct access to a diverse family of chiral ligands. This diversity could, in all likelihood, not be matched by the dienone−phenol approach to VANOL (Scheme 3) given the paucity of substituted 1-naphthols that are commercially available and the fact that the chlorination and dienone−phenol rearrangement steps may be influenced by substituents present in the naphthol.

Thus, it was pleasing to find that the CAEC cascade to VANOL proceeded smoothly with the conditions optimized for VAPOL to provide access to 3-phenyl-1-naphthol **8** in good yields on large scale (Table 5). In this case, the acid chloride **27** is commercially available and inexpensive, and the CAEC reaction is a lot cleaner since the black nonpolar impurities seen in the CAEC cascade in the synthesis of **11** are not observed here. The major side product in this reaction is *iso*-butyric acid **28**, and this can be easily removed by washing the crude reaction mixture with aqueous sodium carbonate. The naphthol **8** is not lost in this extraction, even though it can be extracted into aqueous sodium hydroxide.[3] Two crops of the product can be taken by crystallization from hexanes and methylene chloride which provides the majority of the pure product **8** as a white fluffy solid in 56−61% yield. An additional 7−11% yield of **8** can be obtained from the residue from the mother liquor upon purification by column chromatography on silica gel. The latter may or may not be cost-effective in terms of money and time given the relatively low cost of the starting materials.

4. OXIDATIVE PHENOL COUPLING IN AIR TO GIVE RACEMIC VANOL AND VAPOL

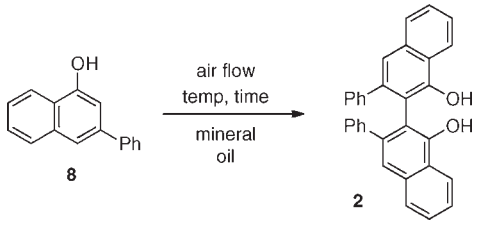
The final step in the synthesis of VANOL and VAPOL is the oxidative phenol coupling of 3-phenyl-1-naphthol **8** and 2-phenyl-4-phenanthrol **11**, respectively. While ferric chloride is the oxidant of choice for the phenol coupling of 2-naphthol in the preparation of BINOL, we found in our initial studies in the synthesis of VANOL and VAPOL that metal oxidants were unsuitable for the related coupling step for these ligands.[3] We took a cue from the total synthesis of gossypol by Edwards and Cashaw in which they found that oxidative phenol coupling of a substituted 1-naphthol was best performed with air as the oxidant.[31] Following their protocol, the first synthesis of VANOL was achieved simply by melting 3-phenyl-1-naphthol **8** in a test tube in the presence of air to give racemic VANOL **2** in 87% yield (1 g scale).[3] The major drawback of this method is that racemic VANOL has a melting point (231−3 °C) that is above the optimal temperature that is needed for the phenol coupling step. This leads to a solidification of the reaction mixture as the reaction progresses and unreacted naphthol **8** becomes trapped and removed from exposure to air. On small scale (1 g), this can be countered by occasionally breaking up the solid mass in small pieces with a stirring rod which allows the reaction to go to completion. This, however, becomes a serious issue when the reaction is scaled up as is illustrated by the 100 g scale reaction shown in entry 1 of Table 6.[32] In this reaction, the melted naphthol **8** is heated under a slow flow of air until the stir bar stops which on a 100 g scale is about 20 h at which time the reaction has gone to about 50−60% completion. It was found best to separate out the product by crystallization of the reaction mixture and then remove the solvent from the mother liquor and subject the oily black residue to the reaction conditions. This procedure was performed a total of six times to give an overall 81% yield of racemic VANOL after a total reaction time of 89 h. The extremely tedious nature of this procedure prompted a search for a suitable solvent for this reaction such that constant contact of the naphthol **8** and air could be maintained.

The provision of a more homogeneous milieu should assist in the more efficient diffusion of air into the reaction mixture and thus hopefully greatly reduced times to effect complete conversion. After consideration of several solvents with suitable high boiling points, the final choice proved to be mineral oil. Given the exposure of the solvent to high temperatures in the presence of air for extended times, it was desired to employ a solvent without tertiary hydrogens to avoid peroxide formation. In addition, mineral oil should be easy to remove by simply washing the crude reaction mixture with hexanes since racemic VANOL and VAPOL are essentially insoluble in hexanes. In this regard, it is interesting to note that optically pure VANOL and VAPOL are highly soluble in hexanes. As indicated by the data in Table 6, the use of mineral oil as solvent for the phenol coupling was very successful and has several advantages over the neat reaction. First the reactions go to completion without stopping half way, and in a much shorter period of time, and unexpectedly, it was found that once the reaction reaches completion the crude product is an orange solid instead of a black tarry material. VANOL can be easily isolated and purified by simple filtration and subsequent crystallization.

Not all of the optimized parameters translated from the neat reaction to the reaction in mineral oil. This was especially true of the reaction temperature which was optimal at 175 °C for the neat reaction; however, in mineral oil the yield sharply fell off at this temperature (46%) (Table 6, entry 7). A survey of temperatures found that reactions at 135 and 145 °C did not go to completion even with extended reaction times (entries 2 and 3). The reaction at 155 °C does go to completion in 38 h, but the reaction at 165 °C was found to be ideal since it goes to completion in only 17 h and gives a higher yield (89%) than the reaction at 155 °C. A reaction at half the concentration gives a slightly lower yield and requires double the reaction time (entries 5 vs 6), and thus the optimal conditions for the reaction in mineral oil are those in entry 5. It was demonstrated that with the optimal conditions the reaction could be readily scaled-up to 50 g, and this proved to be reliably reproducible giving 85−86% yield in three different runs (entries 8, 10, and 11). Thus, in the search for an improved and more general access to VANOL, the possibility that the presence of solvent might ameliorate the destructive effects of the harsh conditions motivated us to carry out the reaction with mineral oil as the reaction media. As a result, the incomplete conversions and associated extended processing time that plagued the earlier studies gave way to this more synthetically useful methodology.

The original procedure[3] for the preparation of VAPOL via the oxidative coupling under neat conditions on large scale was problematic for the same reasons that the original synthesis of VANOL was problematic. With a simple and high-yielding procedure using mineral oil for the synthesis of VANOL (Table 6) in hand, effort was turned to extend the same protocol for the dimerization of 2-phenyl-4-phenanthrol **11**. Indeed, the same protocol applied to the syntheses of racemic VAPOL led to

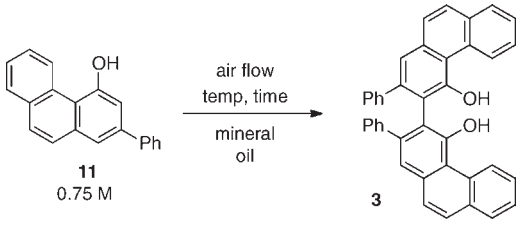
Table 6. Phenol Coupling in the Preparation of Racemic VANOL 2[a]



entry	**8** (g)	time (h)[b]	[**8**] (M)	temp (°C)	% yield crude **2**	mp crude **2** (°C)[c]	% yield **2**[d]	mp **2** (°C)[c]
1[e]	100	89	–	175	nd	nd	81	nd
2[f]	5	72	0.92	135	nd	nd	80	nd
3[f]	5	68	0.92	145	nd	nd	74	nd
4	5	38	0.92	155	nd	nd	80	nd
5	5	17	0.92	165	91	224–9	89	231–2
6	5	40	0.46	165	89	nd	83	nd
7	5	20	0.92	175	nd	nd	46	nd
8	20	32	0.92	165	93	224–9	86	231–2
9[g]	50	24	0.92	165	88	215–7	72	230–1
10	50	32	0.92	165	93	224–7	86	231–2
11	50	24	0.92	165	92	224–9	85	231–2

[a] Unless otherwise specified, each reaction was carried out at the indicated concentration in mineral oil with an air flow of 0.13 L/min directed over the surface of the reaction mixture. [b] Unless otherwise specified, the time is indicated for complete conversion as monitored by TLC. [c] The reported mp for racemic **2** is 231–3 °C (ref 3). [d] The yields are isolated material obtained by crystallization from CH_2Cl_2. [e] This reaction was run neat. The reaction was run until the stir bar stopped (20 h) and then worked up and the product **2** collected by crystallization from CH_2Cl_2. The crude mixture containing unreacted **8** was resubjected to the reaction conditions until the stir bar stopped again at which point more of the product **2** was collected and the unreacted **8** resubmitted to the reaction conditions. This cycle was performed a total of 6 times to give a total of an 81% yield of **2** in 89 h of reaction time. [f] These reactions were stopped prior to full conversion due to the late appearance of byproduct. [g] Reaction was initially stopped after 16 h but was not complete. The crude mixture was then exposed to the same conditions for an additional 8 h at which point the reaction was complete.

Table 7. Phenol Coupling in the Preparation of Racemic VAPOL 3[a]



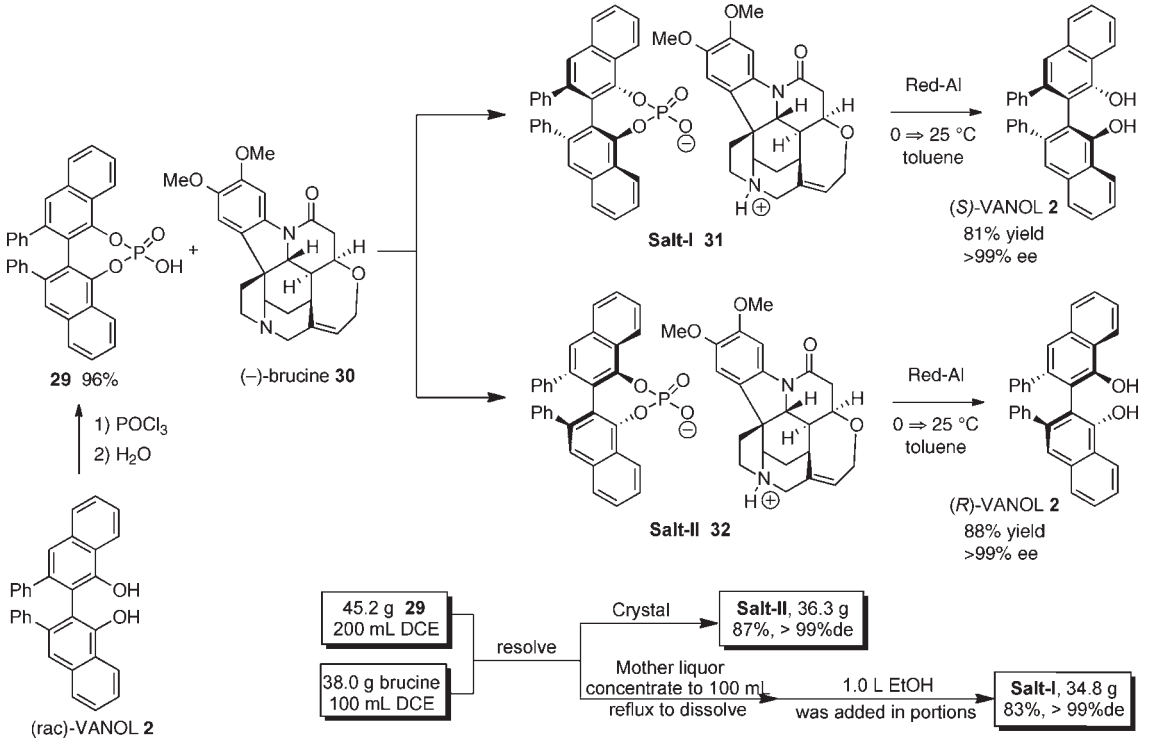
entry	**11** (g)	time (h)[b]	temp (°C)[c]	% yield crude **3**	mp crude **3** (°C)[d]	% yield **3**[e]	mp **3** (°C)[d]
1	4.3	33	190	86	nd	84	nd
2	5	36	180	93	nd	70	nd
3	5	36	170	95	nd	84	nd
4	50[f]	36	170	91	293–5	81[g]	310–1
5	50[f]	36	170	98	297–9	89	308–9
6	50[f]	36	170	91	296–9	93	306–9
7	48[h]	36	170	99	300–1	97	310–1

[a] Unless otherwise specified, each reaction was carried out at 0.75 M in mineral oil with an air flow of 0.15 L/min directed over the surface of the reaction mixture. [b] The time is indicated for complete conversion as monitored by TLC. [c] Oil bath temperature. [d] The reported mp for racemic **3** is 312–313.2 °C (ref 30). [e] The yields are isolated material obtained by crystallization from CH_2Cl_2 (2 crops) in entry 1, from EtOAc (2 crops) in entries 2–3, and from toluene (2 crops) in entries 4–7. [f] **11** prepared as indicated in Scheme 5. [g] 1.6 g of **11** was recovered. [h] **11** prepared as indicated in Table 4.

the same advantages seen for this procedure with VANOL, including a much cleaner reaction and much greater ease in purification of the product (Table 7). Upon completion of the reaction, removal of the mineral oil by washing with hexanes

dx.doi.org/10.1021/op200088b |*Org. Process Res. Dev.* 2011, 15, 1089–1107

Scheme 9



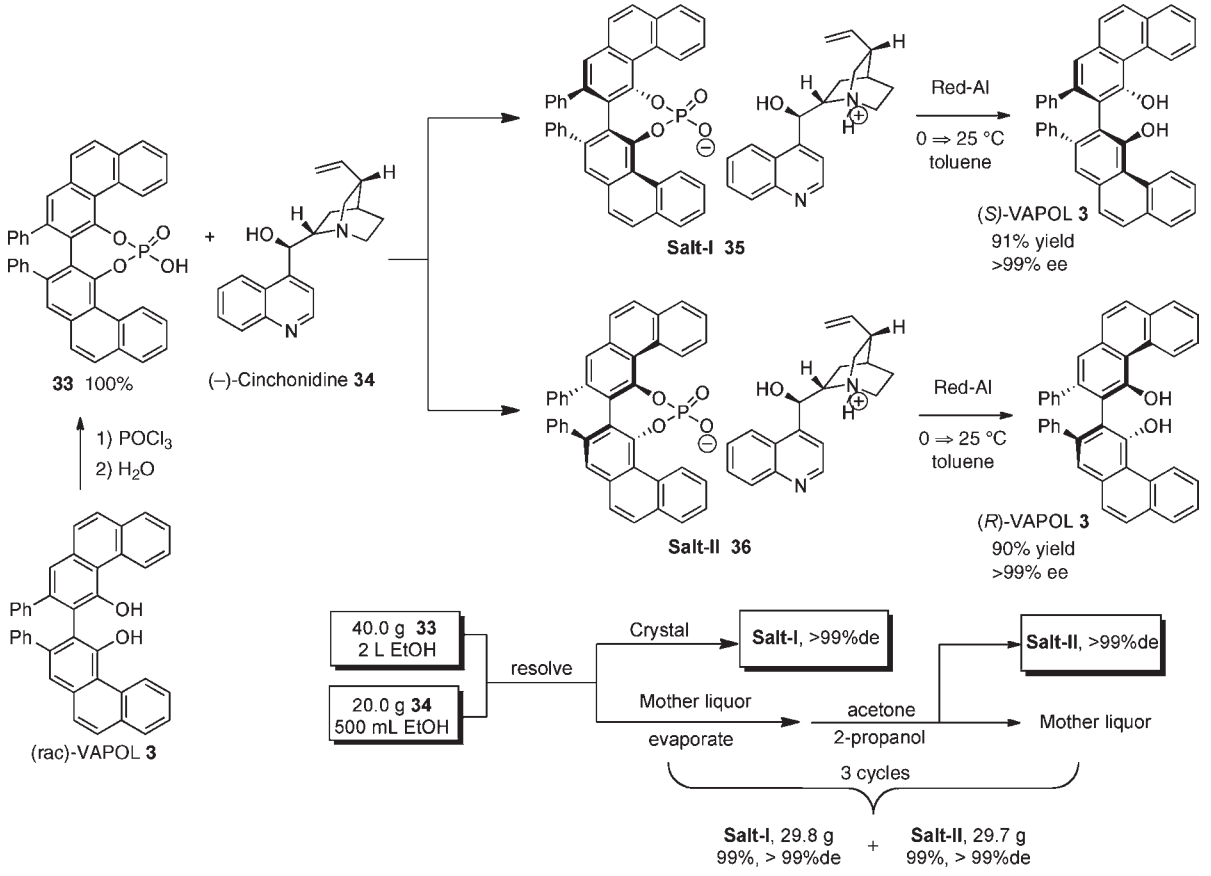
gives the crude product as a brown powder rather than as a black tarry material that is observed under the neat reaction.[3] The temperature is not as crucial to the success of the coupling reaction here as it is for the synthesis of VANOL (entries 1−3), and 170 °C was chosen as optimal for this reaction. The reaction can be scaled up to 50 g with no detrimental effects, and the racemic VAPOL can be purified by crystallization from toluene (2 crops) to give 89−97% yield of **3** as light brown crystals. The cleanest material and highest yield was obtained from the reaction of a batch of 2-phenyl-4-phenanthrol **11** that was produced by the CAEC cascade (Table 4) and gave **3** with a mp of 310−1 °C (lit.[30] 312−313.2 °C). It is interesting to note that racemic VAPOL has a melting point that is 86 °C higher than the optically pure VAPOL, a differential that is among the largest ever recorded for an organic compound.[30]

5. RESOLUTION OF VANOL WITH (−)-BRUCINE

The protocol for the resolution of VANOL outlined in Scheme 9 is the culmination of significant effort over an extended period of time devoted to streamline the process and to make it more reliable for providing access to optically pure VANOL in high yields with crystallization methods alone. Only the final purification of the optical pure ligand employs column chromatography. The resolution is based on the separation of diastereomeric salts formed from the reaction of racemic VANOL hydrogen phosphate **29** with (−)-brucine **30**. The former is generated in high yield from the reaction of racemic VANOL with $POCl_3$ followed by hydrolysis with water. Our original resolution procedure[3] involved heating racemic VANOL with $POCl_3$, but we have since found that this is unnecessary and can on occasion result in the formation of significant unidentified byproduct. The reaction of VANOL with $POCl_3$ at room temperature is sufficient to generate **29** in 96% yield in 6 h. The original method for the separation of the diastereomeric salts was to dissolve both in ethanol and selectively crystallize Salt I (**31**) which contains the (*S*)-enantiomer of the VANOL hydrogen phosphate.[33] With time we found that ethanol did not always give as high of purity of salt I as our original specifications would indicate.[3] We found that the source of variability was the very low solubility of Salt I in ethanol which required the use of undesired large quantities of solvent on large scale. In pursuit of alternative solvents, it was found that both salts are soluble in acetone and toluene, while neither is particularly soluble in ethyl acetate, hexane, and isopropanol. Reasonable solubility differentials were found for dichloroethane and dichloromethane with Salt II being the least soluble. Thus, it was decided to attempt to reverse the order of salt collection.

Extensive studies on dichloromethane as the solvent for resolution never led to the isolation of Salt II in high optical purity in a single crystallization. This repeatedly resulted in a salt that was greatly enriched in Salt II, but one was always left with the need for enhancement strategies. 1,2-Dichloroethane, on the other hand, gave much higher yields of Salt II in the first crop, but the de was only about 95%. This was found to be due to the fact that Salt II was coming out too fast. To slow this down, it was found that the slow addition of a solution of brucine in dichloroethane to a solution of VANOL hydrogen phosphate **29** in dichloroethane gave much higher purity for Salt II. It was also found that performing these manipulations under nitrogen leads to significantly improved yields and purities for Salt II, and this may be related to the formation of a white precipitate when solutions of brucine are overexposed to air. Finally, differences were found between technical grade (−)-brucine and 98% (−)-brucine. The higher purity grade gave lower yields of Salt II but with a higher purity. It was found that a higher purity of Salt II could be

Scheme 10



achieved with the less expensive technical grade brucine if care was taken not to transfer small amounts of insoluble material present in the dichloroethane solutions of brucine. All of these observations taken together lead to the formulation of a protocol that produces an 87% yield of Salt II with greater than 99% de in a single crop. Furthermore, an 83% yield of Salt I of greater than 99% de can be obtained in a single crop from the mother liquor by crystallization from ethanol. Finally, the pure enantiomers of VANOL can be liberated from these salts in a single step by reduction with Red-Al in high yields. This is a dramatic improvement of the original method[3] which involved treatment of the salts with HCl to generate the optically pure enantiomers of VANOL hydrogen phosphate which are then first methylated to give the VANOL methyl phosphates, and these are then finally reduced with Red-Al to give the pure ligands.

6. RESOLUTION OF VAPOL WITH (−)-CINCHONIDINE

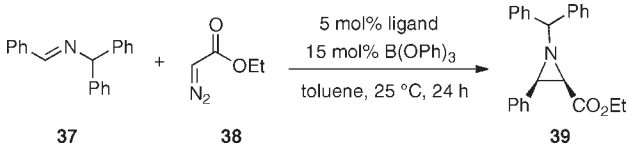
The original method for the resolution of VAPOL is related to that of VANOL but uses (−)-cinchonidine instead of (−)-brucine. The overall process presented in Scheme 10 is a modification of the original version and features a much more reliable crystallization protocol and the same streamlined method for liberation of the optically pure VAPOL ligands that was described above for VANOL. The original crystallization protocol that we published in 1996 involved the crystallization of both salts from ethanol.[3] In practice, we have found that this works much better for Salt I than it does for Salt II. It is often disappointing to find that Salt II is obtained in low yields and with variable de's. A solution to this failing was the finding that Salt II can be much more reliably and efficiently crystallized from a mixture of acetone and isopropanol.[34] After crops of Salt I and Salt II are each collected, this sequence is then repeated until all of the Salts have been collected (usually a total of three cycles). This process has proven to be virtually infallible giving high yields and diastereomeric purity of both salts each time it is performed. Finally, the optically pure (*R*)- and (*S*)-enantiomers of VAPOL can be liberated from Salt I **35** and Salt II **36** with the same procedure described above for VANOL in 90 and 91% yields, respectively.

7. TIME-LAPSED PERFORMANCE OF THE VANOL AND VAPOL LIGANDS IN AN AZIRIDINATION REACTION

The methods described herein for the synthesis and resolution of VANOL and VAPOL involve relatively inexpensive starting materials, are reliable and reproducible, do not involve the chromatographic separation of any intermediate, and thus are imminently suitable for the large-scale preparation of these chiral ligands. It was deemed useful that the development of these efficient methods for the production of VANOL and VAPOL be coupled with an investigation of long-term stability of these ligands which in turn would be reflective of the long-term ability of these ligands to function as effective ligands in asymmetric catalysts. We choose to monitor this effectiveness with time in terms of their ability to provide catalysts for the asymmetric aziridination of imines with ethyl diazoacetate.[14g] This was monitored for the reaction of imine **37** to generate aziridine **39** with catalysts prepared from both the VANOL and VAPOL

dx.doi.org/10.1021/op200088b |*Org. Process Res. Dev.* 2011, 15, 1089–1107

Table 8. Evaluation of Storage Protocols for the VANOL and VAPOL Ligands[a]



37 38 39

			0 years		0.5 years		1.5 years		2.5 years	
	storage conditions[b]	ligand	% yield **39**[c]	% ee **39**	% yield **39**[c]	% ee **39**	% yield **39**[c]	% ee **39**	% yield **39**[c]	% ee **39**
A	refrigerator (3 °C)	VANOL	90	93	86	93	90	93	87	95
	under nitrogen	VAPOL	84	90	81	92	89	92	86	95
B	room temp under argon	VANOL	91	90	91	92	87	94	89	91
	Al foil	VAPOL	85	90	85	92	83	94	85	92
C	room temp	VANOL	83	90	86	92	86	92	84	93
	under argon	VAPOL	83	90	85	91	85	94	87	92
D	room temp	VANOL	83	94	90	93	88	91	91	94
	under air	VAPOL[d]	93	90	85	91	89	92	91	95

[a] Ligand quality was judged by their performance in aziridination reactions which were carried out over a period of 2.5 years. The aziridination catalyst was prepared, and the azirdination reactions were performed by procedure F in ref 14g. Unless otherwise specified, the ligands were all off-white in color, and no change in color or appearance was noted in the course of the study. The VAPOL used in this study was a crystalline form consisting of two molecules of VAPOL and one molecule of CH_2Cl_2. The VANOL did not contain CH_2Cl_2. [b] Condition A: ligands stored in a refrigerator (3 °C) in a brown bottle under nitrogen and sealed with parafilm. Condition B: ligands stored in a cabinet in a brown bottle under argon sealed with parafilm and wrapped in aluminum foil. Condition C: ligands stored on a bench in a brown bottle under argon and sealed with parafilm. Condition D: ligands stored on a bench in a brown bottle under air and sealed with parafilm. [c] Isolated yield after chromatography on silica gel. [d] After 6 months of storage, a thin light orange layer appeared on the surface of the VAPOL sample. This was stirred into the sample and was not observed to reappear after 1.5 or 2.5 years.

ligands over a period of two and a half years (Table 8). This includes samples of each ligand that were stored in four different ways: A, in a refrigerator under nitrogen; B, at room temperature under argon and protected from light by aluminum foil; C, at room temperature under argon; and D, at room temperature stored in the presence of air. It was surprising to find that there was not significant variation in either the yield or asymmetric induction in any of these reactions with either ligand under any of the four conditions of storage, even when stored at room temperature in the presence of air. The color of all samples of the ligands is an off-white, and with a single exception, no change in either the color or appearance of the ligands was observed. For the sample of the VAPOL ligand stored under air at room temperature, a thin orange layer was observed on the top of the ligand sample after 6 months, but this did not appear to have an effect on the aziridination reaction. This small amount of colored material was mixed in with the rest of the sample, and curiously, this discoloration did not make a reappearance after 18 months or after 30 months.

In conclusion, the present work describes a synthesis of the VANOL and VAPOL ligands that represent a dramatic improvement in terms of cost-effectiveness and scalability over our previously published syntheses in 1996.[3] The key step in each synthesis is a cycloaddition/electrocyclization cascade (CAEC) that begins with a [2 + 2] cycloaddition of phenylacetylene with an aryl-substituted ketene. The essential finding that enabled this process as synthetically efficient was that the yields could be improved from 27 to 81% if isobutryic anhydride is added to trap the phenanthrol product **11** before it reacts with the ketene or its acid chloride precursor. The scalability of both syntheses was greatly enhanced by the finding that the air-mediated oxidative phenol coupling step in the formation of the racemic VANOL and VAPOL could be carried out in mineral oil. Finally, more reliable methods for the resolution of each ligand were developed involving VANOL and VAPOL hydrogen phosphate. Classic resolution procedures employing alkaloids (brucine for VANOL and cinchonidine for VAPOL) with the proper solvent systems and proper procedural controls have produced highly reproducible protocols for the separation of the diastereomeric salts for each ligand by crystallization.

8. EXPERIMENTAL SECTION

General Procedure to Prepare Acid Chloride 16. A single-neck 250 mL round-bottom flask equipped with a large 48 × 18 mm oval magnetic stir bar and a condenser was charged with 14.23 g (76.42 mmol, from Milestone Pharm Tech USA Inc., Lot #: T1161) of acid **15** and $SOCl_2$ (20 mL, 274 mmol). The top of the condenser is vented to a bubbler and then into a beaker filled with aq NaOH to trap acidic gases (HCl and SO_2). The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were carefully removed by swirling it under high vacuum (1 mmHg) for 1 h with a second liquid N_2 trap to protect the pump. Crude **16** (ca. 16.7 g) could be obtained as a yellow solid (color was different with **15** from other venders). Spectral data for **16**: white wax-like solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.28 (s, 2H), 7.34−7.37 (dd, 1H, J = 4.5, 1.5 Hz), 7.47−7.52 (m, 2H), 7.35 (s, 1H), 7.98−7.86 (m, 3H).

Preparation of 2-Phenyl-4-phenanthrol 11 on a 14 g Scale with Purification by Chromatography (Table 4, entry 1). Acid **15** (14.23 g, 76.42 mmol) from Milestone Pharm Tech USA Inc. (Lot #: T1161) was used to prepare acid chloride **16** with $SOCl_2$ (20 mL, 274 mmol) in the same manner as described above. The flask containing the resulting **16** (ca. 16.7 g) was filled with argon

and charged with phenylacetylene (11 mL, 100.2 mmol) and $(i\text{-PrCO})_2O$ (25 mL, 146.2 mmol). The flask was fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal.[35] The mixture was heated and stirred in a 190 °C oil bath for 24 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled to below 100 °C (ca. 60 °C, oil bath temperature), and then aqueous KOH (25 g, 445.6 mmol in 100 mL of H_2O) was slowly added. This two-phase mixture was stirred in a 100 °C oil bath overnight (15 h), and the color changed to orange. The mixture was cooled to rt, and ether (100 mL) was added and stirred for 10 min before the organic layer was isolated in a separatory funnel. The water layer was extracted twice with ether (100 mL × 2), and the combined organic layer was washed with brine (100 mL) and dried over $MgSO_4$ and filtered.

The dark-colored solution was combined with silica gel (about 100 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap were put on high vacuum (2 mmHg) for 30 min. A chromatography column (6 cm diameter) was prepared by filling the column with hexanes, and then silica gel was added such that after settling a depth of 15−20 cm (about 350 mL silica gel) had been reached. The dried silica gel with the preadsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the silica gel, and then a layer of sand was applied immediately. The column was then eluted with a 1:2 mixture of CH_2Cl_2:hexanes under gravity (about 1 h). A void volume of about 700 mL was collected and discarded. This was followed by a dark colored (dark brown to black) fast-moving mixture of impurities, which smells strongly like phenylacetylene (about 2 g from 1.5 to 2 L of solution after the solvents were removed). When TLC indicated that the byproduct (**26**) began to elute, a second fraction was collected that contained **26** (about 700 mL, containing 2.24 g, 6.04 mmol, 8%, R_f = 0.50 using 1:3 EtOAc:hexane). When **26** had finished eluting, elution was continued under N_2 pressure to collect the desired product (total of 4−5 L). The product fraction was stripped of solvent by rotary evaporator and then dried in vacuo overnight to afford 15.5 g (57.4 mmol, 75.1%, mp 152−153 °C, lit. value:[3] 154−5 °C) of **11** as a yellow solid. Spectral data for **11**: R_f = 0.33 (1:5 EtOAc:hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71 (s, 1H), 7.18 (s, 1H), 7.35 (t, 1H, J = 7.5 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.72 (t, 1H, J = 7.4 Hz), 7.64−7.70 (m, 5H), 7.84 (d, 1H, J = 7.8 Hz), 9.58 (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 112.20, 118.52, 119.86, 125.99, 126.65, 127.21, 127.62, 128.25, 128.42, 128.89, 130.13, 132.57, 135.27, 139.17, 140.09, 154.61 (2 sp^2 C's not located). Spectral data for **26**: white crystals, mp 207−208 °C; R_f = 0.22 (1:1 CH_2Cl_2:hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.37 (s, 1H), 7.13−7.16 (m, 3H), 7.17−7.20 (m, 3H), 7.35 (dd, 2H, J = 7.5, 2.0 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.48 (s, 1H), 7.50 (s, 1H), 7.51−7.55 (m, 2H), 7.72−7.74 (m, 2H), 7.71 (d, 1H, J = 8.5 Hz), 7.71 (q, 2H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.32, 121.72, 125.75, 126.74, 126.88, 127.37, 127.91, 128.07, 128.20, 129.08, 129.16, 129.21, 129.79, 129.95, 132.76, 132.82, 133.67, 140.70, 141.25, 142.29, 142.96, 153.70, two carbons not located; ^{13}C NMR (d^6-acetone, 75 MHz) δ 113.50, 120.14, 126.03, 126.11, 126.76, 126.90, 127.20, 127.87, 127.99, 128.13, 128.22, 129.42, 130.12, 130.29, 130.42, 132.26, 133.36, 135.29, 140.84, 141.11, 142.17, 143.53, 156.30, one carbon not located; IR (thin film) 3522 br vs, 1701 w, 1684 w, 1653 m, 1558 m, 1506 w, 761 w, 700 m cm^{-1}; mass spectrum, m/z (% rel intensity) 373.8 (30), 372.5 M$^+$ (100), 371.3 (15), 352.2 (13), 326.3 (8), 265.3 (10), 252.2 (8), 175.1 (10), 91.1 (5). HRMS calcd for $C_{28}H_{19}O$ m/z 371.1436, meas 371.1430.

Preparation of 2-Phenyl-4-phenanthrol 11 on a 14 g Scale with Purification by Crystallization and Chromatography (Table 4, entry 4). Acid **15** (14.23 g, 76.42 mmol from Sigma-Aldrich Inc., Lot #: 03824CE) was used to prepare **16** with $SOCl_2$ (20 mL, 274 mmol) in the same manner as described above. The flask containing the resulted white solid was filled with argon and charged with phenylacetylene (11 mL, 100.2 mmol) and $(i\text{-PrCO})_2O$ (25 mL, 146.2 mmol). The flask was fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal.[35] The mixture was heated and stirred in a 190 °C oil bath for 48 h with a gentle nitrogen flow across the top of the condenser. The orange reaction mixture was cooled to below 100 °C (ca. 60 °C, oil bath temperature), and then aq KOH (25 g, 445.6 mmol in 100 mL H_2O) was added. After stirring in a 100 °C oil bath overnight (15 h), the orange solution was cooled to 25 °C, and ether (150 mL) was added and stirred for 10 min before the organic layer was isolated in a separatory funnel. The water layer was extracted twice with ether (150 mL × 2), and the combined organic layer was washed with brine (100 mL) and dried over $MgSO_4$ and filtered. The solvent was completely removed in vacuo, and the brown solid (22 g) was crystallized under N_2 as follows: to a 250 mL round-bottom flask was added a stir bar and 50 mL of CH_2Cl_2. The flask was equipped with a condenser (flushed with N_2 in advance) and heated to reflux. Then CH_2Cl_2 (60 mL) was added slowly via syringe until a clear dark brown solution formed, which was cooled to 25 °C then to −20 °C overnight. The crystals of **11** (11.92 g, 44.15 mmol, 57.8%, mp 156−7 °C) were collected by filtration and washed with 15 mL of CH_2Cl_2/hexanes (1:2).

The dark-colored mother liquor was combined with silica gel (about 100 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap were put on high vacuum (0.5 mmHg) for 30 min. A chromatography column (6 cm diameter) was prepared by filling the column with hexanes, and then silica gel was added such that after settling a depth of 15−20 cm (about 350 mL silica gel) had been reached. The dried silica gel with the preadsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the silica gel, and then a layer of sand was applied immediately. The column was then eluted with a 1:2 mixture of CH_2Cl_2:hexanes under gravity (about 1 h). A void volume of about 700 mL was collected and discarded. This was followed by a yellow fast-moving mixture of impurities (1.7−1.8 L). When TLC indicated that the byproduct (**26**) began to elute, a second fraction was collected that contained this byproduct (about 700−800 mL, containing 2.3 g), followed by an overlapping third fraction containing a mixture of the two products (300−400 mL, from which 1.1 g of solid could be isolated after removal of solvents). This material contained 0.71 g of **11** based on its ^{1}H NMR spectrum and could be further purified by either crystallization from CH_2Cl_2 or column (under the same conditions). When **26** had finished eluting, elution was continued under N_2 pressure to collect a fourth fraction containing the pure desired product (total of 3−3.5 L), which was stripped of solvent by rotary evaporator and then dried in vacuo overnight to afford 3.45 g (12.7 mmol, 16.6%, mp 151−3 °C) of **11** as an orange solid. The combined yield was 74.4%.

Isolation of the Ester Intermediates of 17 and 22 (No KOH Workup). Acid **15** (14.23 g, 76.42 mmol) from Milestone Pharm Tech USA Inc. (Lot #: T1161) was used to prepare acid chloride **16** with $SOCl_2$ (20 mL, 274 mmol) in the same manner as described above. The flask containing the resulting **16** (ca. 16.7 g) was filled with argon and charged with phenylacetylene (11 mL, 100.2 mmol) and $(i\text{-PrCO})_2O$ (25 mL, 146.2 mmol). The flask was fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal.[35] The mixture was heated, and the contents were stirred in a 190 °C oil bath for 48 h and then cooled to 25 °C. The volatiles were removed under high vacuum (1 mmHg), and the residue (27 g) was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford a fraction of the first component (**22** was the major component) and then a fraction of the second component (**17** was the major component). Both compounds were crystallized from boiling CH_2Cl_2 saturated with hexanes by cooling to 25 °C and then −20 °C to get pure **17** (2.34 g, 5.34 mmol, 7.0%) as white cotton-like crystals and **22** (19.3 g, 56.8 mmol, 74.3%) as yellow leaf-like crystals. The byproduct **26** was not located. Spectral data for **17**: mp 177−8 °C; R_f = 0.22 (1:1 CH_2Cl_2: hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.32 (s, 2H), 7.07 (t, 1H, J = 7.0 Hz), 7.40 (t, 1H, J = 7.0 Hz), 7.45−7.51 (m, 3H), 7.52−7.56 (m, 2H), 7.57 (d, 1H, J = 1.5 Hz), 7.66 (dd, 1H, J = 8.5 Hz, J = 2.0 Hz), 7.72−7.78 (m, 4H), 7.83−7.84 (d, 1H, J = 7.5 Hz), 7.88−7.90 (m, 2H), 7.93 (d, 1H, J = 7.5 Hz), 8.00 (s, 1H), 8.01 (d, 1H, J = 2.0 Hz), 8.78 (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.73, 121.07, 122.45, 125.17, 126.41, 126.68, 126.75, 126.82, 126.89, 127.43, 127.60, 127.84, 128.02, 128.07, 128.58, 128.93, 129.18, 130.55, 133.02, 133.16, 133.88, 135.28, 139.35, 139.77, 149.17, 170.05, four carbons not located; ^{13}C NMR (d^6-acetone/d^6-DMSO 75 MHz) δ 41.86, 121.23, 122.41, 124.82, 126.37, 126.68, 126.74, 127.12, 127.37, 127.65, 128.03, 128.04, 128.38, 128.46, 128.58, 128.61, 128.74, 129.04, 129.16, 129.44, 131.66, 133.00, 133.22, 133.93, 135.37, 139.13, 139.27, 149.64, 170.40, one carbon not located; IR (salt plate) 1745 vs, 1622 w, 1454 m, 1385 m, 1235 m, 1116 m, 812 m, 753 m cm^{-1}; mass spectrum, m/z (% rel intensity) 438.1 M$^+$ (8), 271.2 (18), 270.0 (100), 238.9 (15), 168.0 (10), 140.9 (44), 114.9 (12); HRMS calcd for $C_{32}H_{23}O_2$ m/z 439.1698, meas 439.1702. Spectral data for **22**: yellow crystal; mp 121−2 °C; R_f = 0.50 (1:3 EtOAc: hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54 (d, 6H, J = 7.0 Hz), 3.14−3.2 (m, 1H), 7.44 (t, 1H, J = 7.5 Hz), 7.54 (t, 2H, J = 7.5 Hz), 7.58 (d, 1H, J = 2.0 Hz), 7.62−7.68 (m, 2H), 7.77−7.82 (m, 4H), 7.92−7.94 (m, 1H), 8.04 (s, 1H), 9.18 (d, 1H, J = 8.0 Hz); ^{1}H NMR (d^6-acetone, 500 MHz) δ 1.48 (d, 6H, J = 7.0 Hz), 3.21 (octet, 1H, J = 7.0 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.53 (t, 2H, J = 7.5 Hz), 7.65 (td, 1H, J = 7.0 Hz, J = 1.0 Hz), 7.69−7.73 (m, 1H), 7.75 (d, 1H, J = 1.5 Hz), 7.81−7.90 (m, 4H), 7.97 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 2.0 Hz), 9.22 (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.33, 35.13, 121.11, 122.67, 125.00, 126.84, 126.88, 127.58, 127.65, 128.06, 128.52, 129.09, 129.14, 129.19, 130.09, 133.27, 135.29, 139.46, 139.94, 149.42, 175.83; ^{13}C NMR (d^6-acetone, 75 MHz) δ 19.33, 34.77, 121.09, 122.70, 124.66, 126.74, 127.10, 127.16, 127.26, 127.37, 127.63, 128.07, 128.19, 128.47, 129.06, 129.16, 129.30, 133.32, 135.38, 139.30, 139.50, 149.82, 175.45; IR (salt plate) 2973 w, 1754 s, 1453 m, 1386 m, 1176 m, 1107 vs, 882 m, 749 m, 695 m cm^{-1}; mass spectrum, m/z (% rel intensity) 341.3 (6), 340.1 M$^+$ (30), 270.3 (35), 270.1 (100), 239.0 (60), 165 (10), 138.8 (10), 119.6 (17), 70.9 (22), 43.0 (58). Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.34; H, 5.86.

Preparation of 2-Phenyl-4-phenanthrol 11 on a 57 g Scale with Purification by Crystallization (Table 4, entry 5). A single-neck 1 L round-bottom flask equipped with a large 48 × 18 mm oval magnetic stir bar and a condenser was charged with 57 g (306 mmol, Milestone Pharm Tech USA Inc., Lot #: T1161) of acid **15** and $SOCl_2$ (45 mL, 618 mmol). The top of the condenser is vented to a bubbler and then into a beaker filled with aqueous NaOH to trap acidic gases (HCl and SO_2). The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were distilled off. It was then put on high vacuum (2 mmHg) and swirled until the residue solidified with a second liquid N_2 trap to protect the pump. The extra liquid N_2 trap was then removed, and the residue was kept under vacuum for 1 h. The flask containing the yellow crude acid chloride **16** was filled with argon, and then phenylacetylene (45 mL, 410 mmol) and $(i\text{-PrCO})_2O$ (100 mL, 603 mmol) were added. The flask was fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal.[35] The reaction mixture was heated and stirred in a 190 °C oil bath for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled to about 60 °C (oil bath temperature), and aq KOH (100 g, 1.8 mol in 400 mL of H_2O) was slowly added. After stirring in a 100 °C oil bath overnight (15 h), the orange solution was cooled to rt, ether (400 mL) added, and the mixture stirred for 30 min before the organic layer was isolated in a 2 L separatory funnel. The water layer was extracted twice with ether (400 mL × 2), and the combined organic layer was washed with brine (400 mL), dried over $MgSO_4$, and filtered. The dark-colored organic solutions were combined together (5 drops were collected for ^{1}H NMR analysis), and the solvents were removed in vacuo. The residue was collected in a 500 mL flask and dried under high vacuum (1 mmHg) overnight to give ca. 80 g of the dark brown crude product. The ^{1}H NMR spectrum of the crude product indicated it was a mixture of **11** and **26** with a 1:0.15 ratio.

To the crude mixture in the 500 mL flask was added a stir bar and 100 mL of CH_2Cl_2, and the resulting solution was brought to a boil under an atmosphere of N_2. More CH_2Cl_2 was then added in 50 mL aliquots until all was dissolved (total of 200 mL). The solution was allowed to cool to rt and then to −20 °C in a refrigerator overnight. The mixture was filtered and the solid washed with a mixture of CH_2Cl_2:hexanes (1:2, 15 mL × 2) to give 34.4 g (127.2 mmol, 41.5%) of **11** as beige crystals (mp 156−7 °C, lit.[3] 154−5 °C). The dark-colored mother liquor was collected in a 500 mL flask and combined with silica gel (ca. 150 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap were put on high vacuum (0.5 mmHg) for 1 h. The mixture was filtered through a short column of silica gel as follows. A short pad of Celite (30 g) was prepared in a sintered glass funnel (OD 10 cm, 18 cm long), and then silica gel (400 mL) was added followed by the crude mixture absorbed on silica gel and finally a thin layer of sand (2−3 cm). The mixture was then eluted with hexanes:CH_2Cl_2 = 1:1 with a vacuum produced by a water aspirator. The first fraction of ca. 1 L was discarded. This fraction by TLC contains fast running impurities (ca. 10 g, black material) and a small amount of double-inserted byproduct **26**. An additional 2.5 L of hexanes: CH_2Cl_2 = 1:1 was passed through and collected, and this product-containing fraction was concentrated on a rotary

evaporator to afford a mixture of **11** and **26** (~25 g) as an orange solid.

This solid was refluxed with 10 mL of *i*PrOH under N_2 to effect dissolution, cooled to 25 °C, and then to −20 °C overnight. The solid was filtered and washed with *i*PrOH (3 × 10 mL) to give pure **26** (5.93 g, 15.9 mmol) as a white solid. The mother liquor was stripped of solvent in vacuo, and to the orange residue (22 g, mp 146−7 °C) was added 100 mL of a 2:1 mixture of hexanes and 1,2-dichloroethane. The mixture was brought to a boil under an atmosphere of nitrogen. More of this solvent mixture was added (in 50 mL aliquots, total of about 350 mL) until all was dissolved. The mixture was cooled to 25 °C and then to −20 °C to give a second crop of **16b** (12.4 g, 45.9 mmol, 15%, mp 157−8 °C). The total yield was 56.5%.

The $SOCl_2$ (50 mL) could be recovered from this process. Acid **15** could be recovered from aqueous KOH as follows: after acidification with HCl (6 N) to pH~1 and extraction with ether (3 × 100 mL), the combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, and filtered. Ether was removed via a rotary evaporator, and the remaining orange oil was a mixture of **15** in ca. 90 mL of isobutyric acid. The isobutyric acid was distilled off under a vacuum produced by a water aspirator (80 mmHg/81−2 °C) to give 7.20 g of crude **15** as an orange solid. This material was crystallized from EtOH/H_2O to give 5.15 g (27.5 mmol, 9%) of the acid starting material **15** as yellow leaf-like crystals.

Preparation of 3-Phenyl-1-naphthol 8 on a 59 g Scale with Purification by Crystallization (Table 5, entry 2). To a flame-dried single neck 2 L flask equipped with a magnetic stir bar was added 2-phenylacetyl chloride (50.5 mL, 59.0 g, 374 mmol), phenyl acetylene (55 mL, 501 mmol), and isobutyric anhydride (125 mL, 731 mmol). The flask was fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal.[35] The mixture was stirred at 190 °C for 48 h with a gentle nitrogen flow over the top of the condenser. The reaction was cooled to room temperature, and aq KOH (125 g, 2.23 mol in 500 mL of H_2O) was added. The reaction mixture was stirred at 100 °C overnight (13−15 h). The solution was cooled to 0 °C and acidified with 6 N HCl to pH ~ 6 (100−110 mL). The mixture was then transferred to a separatory funnel using 400 mL of ether. The organic layer was separated, and the aqueous layer was washed with ether (3 × 100 mL). The combined organic layers were washed with sat Na_2CO_3 (3 × 100 mL) and brine (100 mL) and dried over $MgSO_4$. After filtration through Celite, the solvent was removed by a rotary evaporator to give a dark brown oil. Hexanes (3 × 50 mL) were added and then removed by a rotary evaporator to give a dark brown solid (92 g) with a mp of 84−89 °C (begins to soften at 71−73 °C). The crude product was taken up in 900 mL of refluxing hexanes/CH_2Cl_2 (4:1), and the hot solution was poured into a 1 L Erlenmeyer flask leaving some white solid behind (1−2 g) which was taken up in a small amount of hot dichloromethane. Both solutions were covered and allowed to cool to room temperature overnight, and then the solids from each were collected together in a 5 in. Buchner funnel and rinsed with cold hexanes (0 °C, 2 × 200 mL) to give the first crop of **8** as a white fluffy solid in 43% yield (34.9 g, 159 mmol) with a mp of 98.5−99.5 °C. The mother liquor was concentrated to dryness, and the product was crystallized again using hexanes/CH_2Cl_2 (3:1, 400 mL) to give a second crop of **8** as a white fluffy solid in 13% yield (10.37 g, 47 mmol) with a mp of 98.5−99.5 °C.

Collection of a third crop gave material that was not sufficiently pure by ^{1}H NMR. Therefore, the third crop and mother liquor residue were combined (~35 g) and purified via column chromatography on silica gel. This mixture was dissolved in CH_2Cl_2 and added to 40 mL of silica gel. After removal of volatiles, the silica gel mixture was loaded onto a silica gel column (5 × 25 cm) that was wet loaded with hexanes. Elution with hexanes/CH_2Cl_2 (2:1) and combining the fractions containing the product gave 18 g of an off-white solid that was shown to contain small amounts of impurities by ^{1}H NMR. This material was crystallized from 80 mL of a 3:1 mixture of hexanes and CH_2Cl_2 to give the pure product **8** in 11% yield (9.41 g, 43 mmol) with a mp of 97.5−98 °C. Spectral data for **8**: white solid; mp 98.5−99.5 °C (lit.[3] 96−97.5 °C); R_f = 0.48 (1:3 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.32 (s, 1H), 7.06 (s, 1H), 7.34 (t, 1H, J = 9 Hz), 7.41−7.50 (m, 4H), 7.62−7.64 (m, 3H), 7.82 (d, 1H, J = 10 Hz), 8.13 (d, 1H, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.41, 118.73, 121.39, 123.47, 125.34, 126.86, 127.20, 127.37, 127.99, 128.75, 134.85, 138.73, 140.67, 151.47; mass spectrum, m/z (% rel intensity) 220 M^+ (100), 191.0 (45), 189.0 (30), 165.0 (23), 95 (23), 55 (21), 43 (25).

Preparation of Racemic VANOL 2 on a 50 g Scale with Purification by Crystallization (Table 6, entry 11). An oil bath (19 cm id containing 1.5 L oil) was heated to 165 °C and stirred with a magnetic stirrer. The naphthol **8** (50.05 g, 227.5 mmol) was introduced by a funnel into a 2 L 3-necked round-bottom flask equipped with a 60 × 18 mm oval magnetic stir bar and a 400 mm Allihn water-cooled condenser. This was followed by the addition of 250 mL of light mineral oil through the same funnel. A glass tube (6 mm id) was introduced into the flask via the second neck to about 5 cm above the surface of the aphthol solution and was used to provide a stream of house air which is maintained at a flow rate of 0.15−0.20 L/min.[36] The third neck was sealed with a rubber septum. The stir bar in the oil bath was removed before the flask was introduced into the oil bath to warm it up for about 15 min until the solid was melted. Airflow was allowed to flow into the flask while the molten **18** was stirred as fast as possible. The airflow was switched to N_2 after the reaction was kept at 165 °C for 24 h. The flask was removed from the oil bath and cooled to ambient temperature before hexanes (500 mL) were added to the flask. The mixture was stirred for 30 min, and then it was cooled to −20 °C overnight (12 h) before the solid was collected by suction filtration. The crude product (about 46 g, brown powder, softened at 216−219 °C and melted at 224−227 °C) was dried on high vacuum and crystallized from 600 mL of hot CH_2Cl_2. The dark-colored solution was cooled to room temperature and then to −20 °C overnight (12 h). The brown crystals were collected via suction filtration, washed with hexanes (3 × 50 mL), and dried under vacuum to give the first crop product of (±)-VANOL (37.4 g, 85.3 mmol, 74.7%, mp 231−232 °C, lit.[3] 231−233 °C). The mother liquor was dried, and the residue was crystallized from 60 mL of hot CH_2Cl_2 and cooled to −20 °C overnight to give 5.04 g of additional (±)-VANOL as brown crystals (11.5 mmol, 10.1%, mp 230−231 °C). The combined yield was 42.4 g (96.8 mmol, 85.2%).

Preparation of Racemic VAPOL 3 on a 50 g Scale with Purification by Crystallization (Table 7, entry 4). An oil bath (19 cm id containing about 1.5 L of oil) was heated to 170 °C while the oil was stirred with a magnetic stirrer. Phenanthrol **11** (50.0 g, 185.2 mmol) was introduced by a funnel into a 2 L 3-necked round-bottom flask equipped with a 60 × 18 mm oval magnetic stir bar and a 400 mm Allihn water-cooled condenser.

This was followed by the addition of 250 mL of light mineral oil through the same funnel. A glass tube (6 mm id) was introduced into the flask via the second neck to about 5 cm above the surface of the solution of **11** and was used to provide a stream of house air, which was maintained at a flow rate of 0.15−0.20 L/min.[36] The third neck was sealed with a rubber septum. The stir bar in the oil bath was removed before the flask was introduced to warm the mixture for about 30 min until the solid melted. Airflow was allowed to flow into the flask while the solution of **11** was stirred as fast as possible. The airflow was switched to N_2 gas after the reaction was kept at 170 °C for 36 h. The flask was removed from the oil bath and cooled to ambient temperature before hexane (500 mL) was added to the flask. The mixture was stirred for 30 min, and then it was cooled to −20 °C overnight (12 h) before the solid was collected by suction filtration. The crude product (45.1 g, brown powder, softened at 286−287 °C and melted at 293−295 °C) was dried under high vacuum and crystallized from a minimum amount of boiling toluene (about 1 L). The dark-colored solution was cooled to room temperature and then to −20 °C overnight. The liquid portion of the solution was filtered without disturbing the precipitate to collect the fine suspension of particles in solution, and then a new piece of filter paper was used to collect the brown crystals via suction filtration. This solid was washed with hexanes (2 × 50 mL) and dried over vacuum to give the first crop of (±)-VAPOL (33.3 g, 61.9 mmol, 66.8%, mp 310−311 °C, lit.[30] 312−313.2 °C). The mother liquor was dried, and the residue was crystallized from 150 mL of hot toluene and then cooling to room temperature for 12 h followed by cooling to −20 °C overnight to give an additional 7.0 g of (±)-VAPOL (13.0 mmol, 14.0%, mp 298−299 °C). The combined yield was 40.3 g (74.9 mmol, 80.9%).

Preparation of Racemic VANOL Hydrogen Phosphate 29. To a single-necked 500 mL round-bottom flask flushed with N_2 was added 40.0 g (91.3 mmol) of racemic VANOL via a powder funnel. As the contents of the flask were stirred with a 48 × 18 mm oval magnetic stir bar, 150 mL of pyridine was added and used to rinse the funnel. The flask was fitted with a rubber septum and a nitrogen balloon. To the transparent brown solution was added phosphorus oxychloride (17.0 mL, 182.4 mmol) dropwise over a period of 10 min via a plastic syringe. Upon addition of $POCl_3$, the flask becomes hot, and a beige precipitate forms but does not stop the stirrer. The resulting suspension was stirred for 6 h at room temperature. Water (120 mL) was added slowly in 3 to 4 portions, and the addition of each subsequent portion was delayed until boiling had subsided. The resulting biphasic suspension was stirred at room temperature for 2 h. The pyridine was removed by rotary evaporator, and the residue was dissolved in 250 mL of CH_2Cl_2 to give a brown solution which was washed twice with 500 mL of 1 N HCl. The solution was dried over $MgSO_4$ and filtered through Celite. The solvent was removed to give the crude product, which was dried overnight under high vacuum. This left the crude racemic VANOL hydrogen phosphate as a yellow amorphous solid which was used directly in the resolution without further purification. The yield: 44.0 g (87.9 mmol, 96.4%). Spectral data for **29**: white solid, mp 245−250 °C dec; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 5.80 (br s, 1H), 6.45 (d, 4H, J = 7.5 Hz), 6.88 (t, 4H, J = 7.4 Hz), 7.06 (t, 2H, J = 7.2 Hz), 7.47 (s, 2H), 7.49−7.51 (m, 4H), 7.77 (d, 2H, J = 7.4 Hz), 8.46 (d, 2H, J = 7.3 Hz).

Resolution of Racemic VANOL Hydrogen Phosphate 29 with (−)-Brucine. The hydrogen phosphate **29** (45.2 g, 90.3 mmol) was placed in a 500 mL 3-necked round-bottom flask that was equipped with a condenser and a stir bar (48 × 18 mm) and which had been flushed with a N_2 stream that was introduced via a needle in a septum on one of the necks and monitored by a bubbler attached to the condenser. To the flask was added dichloroethane (200 mL), and the contents of the flask were stirred and brought to a boil by heating the flask with a heating mantel. To a separate 250 mL pear-shaped flask was added brucine dihydrate (38.0 g, 88.6 mmol, technical grade, 92.6%) and 90 mL of dichloroethane. The contents of the flask were purged with N_2 for about 2 min, and then the flask was sealed with a rubber septum which was fitted with a nitrogen balloon. This flask was heated by swirling in hot flowing water (50 °C) until a clear colorless solution (volume about 110 mL) resulted which had a small amount of grey insoluble impurities floating on top. The resulting brucine solution was placed in a hot water bath (50 °C), and 60 mL of the solution was removed by a syringe equipped with a 12 gauge needle and added to the solution of **29** over a period of about 1 min to give a brownish clear solution. The remainder of the brucine solution (about 50 mL) was loaded into the syringe leaving the insoluble material in the flask. The brucine solution was slowly added to the solution of **29** via syringe pump (addition rate: 100 mL/h). Solid began to form when about 22 mL of the solution was left in the syringe. The addition was paused while the suspension was refluxed for 15 min, and then the addition was resumed to complete the addition to the suspension. An additional portion of dichloroethane (10 mL) was used to rinse the pear flask leaving the insoluble material in the flask. The final washing was added over a period of one minute. The resulting suspension was cooled slowly to room temperature and allowed to settle for 48 h without disturbance. The white solid was collected by filtration through a Buchner funnel and washed three times with dichloroethane (25 mL) and then dried over high vacuum for 12 h to afford 36.3 g (40.5 mmol, 87%, >99% de) of the Salt II **32**.

The dark yellow mother liquor was stripped of volatiles by rotary evaporator and combined with 100 mL of dichloroethane in a 2 L single-necked round-bottom flask fitted with a condenser. The resulting mixture was stirred and brought to a boil to dissolve the solid residue. A total of 1000 mL of ethanol was added in portions as follows: first, 300 mL of ethanol was added, and the resulting solution was returned to a boil and then additional ethanol (200 mL) was added and again returned to a boil. At this point, another 200 mL portion of ethanol was added, and the mixture was refluxed for 15 min until it appeared that no further accumulation of precipitate was occurring. Finally, an additional 300 mL portion of ethanol was then added, and the mixture was refluxed for 10 min before being allowed to cool to room temperature overnight undisturbed. The beige solid was isolated by filtration in a Buchner funnel and dried over high vacuum for 12 h to afford 34.8 g (38.9 mmol, 83%, >99% de) of Salt I **31**. The filtrate was stripped of volatiles to give 10.50 g of a light brown solid (Salt I, 32% de).

Liberation of (*R*)-VANOL by Reductive Cleavage of the Brucine Salt II. To an oven-dried 1 L round-bottom flask was added Salt II **32** (52.7 g, 58.8 mmol), 250 mL of reagent-grade toluene, and a 48 × 18 mm oval magnetic stir bar. The flask was equipped with a 1 L pressure compensating addition funnel which was sealed with a rubber septum. The system was flushed with N_2 for at least 30 min, and then the mixture was cooled to 0 °C. A nitrogen balloon was used to balance the pressure. Red-Al (75 mL, 65 wt % in toluene, 246 mmol) was added to the funnel and then slowly added to the flask over 3 h with stirring. After

addition, the flask was warmed to room temperature for 4.5 h. The flask was then cooled to 0 °C, and chilled (0 °C) HCl (6 N, 500 mL) was added slowly to quench the reaction as follows: the first 20 mL of HCl was added a pipet full at a time down inside the wall of the flask, and the remainder was added in 3−5 portions over 10 min. The mixture was put into a 2 L separatory funnel, and the organic layer was collected. The water layer was extracted three times with 500 mL of ethyl acetate. The combined organic layer was washed with 400 mL of brine, dried over $MgSO_4$, and filtered through Celite. Upon removal of the solvent the residue (ca. 25 g) was dissolved in a minimum amount of CH_2Cl_2 (ca. 50 mL) and loaded onto a silica gel column (4.5 cm OD, silica gel was filled to a depth of 40 cm) and eluted by hexanes:CH_2Cl_2 (1:2). When TLC indicated that VANOL had begun to elute, a 2 L round bottomed flask was used to collect all of the VANOL. When the elution was complete (ca. 2 L), 5 drops of this solution was saved for HPLC analysis. The rest of solution was stripped of solvents to give a foamlike solid. This solid was dissolved in a minimum (ca. 50 mL) of CH_2Cl_2, and then 300 mL of hexanes was added. The solution was slowly evaporated by a rotary evaporator to dryness. The residue was again taken up in a minimum of (ca. 50 mL) of CH_2Cl_2, and then 300 mL of hexanes was added. The resulting mixture was shaken vigorously under a strong N_2 flow until a solid crashed out. This mixture was then slowly evaporated to dryness. This process gave (*R*)-VANOL as a white powder-like solid that was more stable to long-term storage if this procedure were not employed. Yield: 22.7 g (51.9 mmol, 88.1%); mp 199−201 °C, $[\alpha]_D$ 316 ($CHCl_3$, *c* 1.0) on 99% ee material. Spectral data for (*R*)-VANOL: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (s, 2H), 6.63 (d, 4H, *J* = 7.5 Hz), 6.94 (t, 4H, *J* = 8.0 Hz), 7.07 (t, 2H, *J* = 7.5 Hz), 7.32 (s, 2H), 7.54−7.56 (m, 4H), 7.78 (d, 2H, *J* = 7.0 Hz), 8.35 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.72, 122.03, 122.79, 122.92, 125.66, 126.61, 127.44, 127.51, 127.68, 128.89, 134.62, 140.19, 140.70, 150.37. The optical purity of (*R*)-VANOL was determined as follow: 5 drops of the saved (*R*)-VANOL solution was diluted with 2 mL of hexanes, from which ca. 4 μL was injected into an HPLC with a Pirkle D-phenylglycine column and eluted with a 98:2 mixture of hexane/isopropanol (254 nm, flow rate: 2 mL/min over 30 min). Under these conditions, the retention time of (*R*)-VANOL was 18.3 min, and that of (*S*)-VANOL was 20.6 min. The ee of (*R*)-VANOL was >99%. The same procedure can be applied to obtain (*S*)-VANOL from the reductive cleavage of Salt I **31** in 81% yield and >99% ee, mp 200−201 °C, $[\alpha]_D$ −319 ($CHCl_3$, *c* 1.0).

Preparation of Racemic VAPOL Hydrogen Phosphate 33. To a 500 mL round-bottom flask charged with N_2 was added 30.91 g (57.4 mmol) of racemic VAPOL and pyridine (170 mL). As this mixture was stirred, phosphorous oxychloride (10.7 mL, 114.8 mmol) was added dropwise over a period of 10 min. After all the solid had dissolved, the resulting solution was stirred for 6 h at room temperature (a lot of solid formed after about 45 min). Water (75 mL) was added slowly, and the resulting biphasic suspension was stirred at room temperature for 2 h. Pyridine was removed by rotary evaporator, and the residue was combined with 250 mL of 1 N HCl and then was filtered and washed twice with 250 mL of 1 N HCL. The crude product was dried over high vacuum overnight and used directly for resolution without further purification. The yield: 34.35 g (54.4 mmol, 100%). The spectrum of **33**: ^{1}H NMR ($CDCl_3$) δ 6.51 (d, 4H, *J* = 7.2 Hz), 6.93 (t, 4H, *J* = 7.3 Hz), 7.09 (t, 2H, *J* = 7.5 Hz), 7.23 (s, 4H), 7.52−7.55 (m, 4H), 7.66 (d, 2H, *J* = 8.8 Hz), 7.76 (d, 2H, *J* = 9 Hz), 7.87 (d, 2H *J* = 7.5 Hz), 9.87 (d, 2H, *J* = 8.5 Hz). White solid, mp > 350 °C.

Resolution of Racemic VAPOL Hydrogen Phosphate 33 with (−)-Cinchonidine. To a boiling suspension of **33** (40.0 g, 66.7 mmol) in 2 L of absolute ethanol in a 4 L Erlenmeyer flask was added (−)-cinchonidine (20.0 g, 68.0 mmol), while the solution was stirred on a hot plate (Corning) with a 60 × 18 mm oval magnetic stir bar. Ethanol (500 mL) was used to rinse all (−)-cinchonidine into the suspension, which was gently boiled for 30 min before it was cooled to room temperature overnight. The solution was filtered without disturbing the solid until most of the liquid went through the Buchner funnel. Then the filter paper was replaced by a new one, and the remaining solid was broken, filtered, and washed with ethanol (50 mL). This solid (17.6 g, 19.7 mmol, 58%) was revealed by its ^{1}H NMR spectrum to be Salt I **35**. The mother liquor was dried by a rotary evaporator and combined with 2 L of 2-propanol, which was heated to a boil in a 4 L Erlenmeyer flask. Acetone was added slowly with stirring until the solid dissolved (about 500 mL). This solution was cooled to room temperature overnight and then to −20 °C. Crystals (26.1 g, 28.7 mmol, 87%) were collected and ^{1}H NMR revealed that were pure Salt II **36**. The filtrate was dried and dissolved in a minimum amount of boiling CH_2Cl_2 (about 50 mL), to which ethanol (100 mL) was added in two portions and heated for 15 min until a solid crashed out. More ethanol was then introduced (400 mL in two portions) and heated to a boil and then allowed to cool to room temperature overnight. The solid was filtered and washed twice with 25 mL of ethanol and was identified as pure Salt I **35** by ^{1}H NMR (9.24 g, 10.3 mmol, 31%). The mother liquor was dried by rotary evaporator and combined with 500 mL of 2-propanol, which was heated to a boil, and acetone was slowly added while stirring until the solid dissolved (about 50 mL). This solution was cooled to room temperature overnight and then to −20 °C. Crystals (3.58 g, 4.0 mmol, 12%) were collected, and ^{1}H NMR showed them to be pure Salt II **36**. The filtrate (a 3:1 mixture of Salt I and Salt II by ^{1}H NMR spectrum, total of 8.6 g) was dried and dissolved in a minimum amount of boiling CH_2Cl_2 (15 mL), to which ethanol was added in three portions (25 + 25 + 50 mL), and after each addition the solution was returned to a boil for 10 min. A solid crashed out, and more ethanol (150 mL, which made the total volume of ethanol at 250 mL) was introduced and heated to a boil and then cooled to room temperature overnight. The solid was filtered and washed with 25 mL of ethanol, which was confirmed to be pure Salt I **35** by ^{1}H NMR (2.96 g, 3.31 mmol, 10%). The total amount of Salt I and Salt II: 29.8 g (99%) and 29.7 g (99%), respectively. Spectral data for Salt I **35**: white solid; ^{1}H NMR ($CDCl_3$ 500 MHz) δ 0.75−0.85 (m, 1H), 1.50−1.80 (m, 6H), 2.28 (s, 1H), 2.38 (s, 1H), 2.62−2.81 (m, 2H), 4.10 (s, br, 1H), 4.70 (d, 1H, *J* = 17.1 Hz), 4.83 (d, 1H, *J* = 10 Hz), 5.08−5.12 (m, 1H), 5.92 (s, 1H), 6.49 (d, 4H, *J* = 7.8 Hz), 6.60 (br s, 2H), 6.77 (t, 1H, *J* = 7.7 Hz), 6.85 (t, 4H, *J* = 7.6 Hz), 7.01 (t, 2H, *J* = 7.3 Hz), 7.15 (m, 3H), 7.19−7.27 (m, 4 H), 7.43 (s, 2H), 7.55−7.61 (m, 6H), 7.75 (d, 1H, *J* = 8.4 Hz), 8.67 (d, 1H, *J* = 4.4 Hz), 10.08 (d, 2H, *J* = 8.6 Hz), 11.79 (s, br, 1H). Spectral data for Salt II **36**: light yellow crystal; ^{1}H NMR ($CDCl_3$ 500 MHz) δ 0.97−1.05 (m, 1H), 1.20−1.29 (m, 1H), 1.50−1.58 (m, 1H), 1.62−1.73 (m, 2H), 1.98−2.07 (m, 1H), 2.18−2.19 (m, 1H), 2.40−2.50 (m, 3H), 3.10−3.15 (m, 1H), 4.05−4.15 (m, 1H), 4.75 (d, 1H, *J* = 17.2 Hz), 4.81 (d, 1H, *J* = 10.4 Hz), 5.22−5.32 (m, 1H), 6.39 (s, 1H), 6.55 (d, 4H, *J* = 7.4 Hz), 6.61 (br s, 1H), 6.89 (t, 4H, *J* = 7.6 Hz), 6.98 (t, 2H, *J* = 7.8 Hz), 7.04

(t, 2H, J = 7.3 Hz), 7.36−7.31 (m, 4H), 7.50 (s, 2H), 7.59−7.68 (m, 6H), 7.75 (d, 2H, J = 7.8 Hz), 8.16 (d, 1H, J = 7.7 Hz), 8.40 (d, 1H, J = 7.9 Hz), 8.69 (d, 1H, J = 5.0 Hz), 9.94 (d, 2H, J = 8.6 Hz), 11.85 (s, 1H).

Liberation of (*S*)-VAPOL by Reductive Cleavage of the Cinchonidine Salt I 35. A 500 mL 3-necked round-bottom flask equipped with a stir bar was sealed with one rubber septum and two adapters. One adapter was connected to a bubbler, and the flask was flushed with N_2 for 1 h via the other adapter. Salt I **35** (36.3 g, 40.6 mmol) was put into the flask, and the adapters were switched to two rubber septums. A N_2 balloon was connected to the flask via a needle. Toluene (200 mL) was added followed by a 48 × 18 mm oval magnetic stir bar. The mixture was cooled in an ice−water bath for 1 h and then stirred while Red-Al (54 mL, 177.0 mmol as a 65 wt % solution in toluene) was added via syringe pump over 3 h using a 12-gauge needle. The suspension was allowed to stir at room temperature overnight and then was chilled in an ice−water bath for 1 h. Precooled HCl (6 N, 150 mL, 0 °C) was added, and the mixture was stirred at room temperature for 5 min before it was poured into a 1 L separatory funnel. The organic layer was separated, and the aqueous layer was extracted three times with 100 mL of ethyl acetate. The combined organic layer was washed with brine (100 mL) and then dried over $MgSO_4$. After filtration through Celite, the solvent was removed in vacuo. The residue (ca. 20 g) was dissolved in a minimum amount of CH_2Cl_2 (about 110 mL, a heat gun may help dissolution) and was loaded onto a chromatography column (6 cm diameter) prepared by filling the column with a 1:20 mixture of CH_2Cl_2 and hexanes and then the addition of silica gel such that after settling a depth of ca. 15 cm had been reached. When the solvent level was lowered to the top of the silica gel, the column was eluted with a 1:1 mixture of hexanes and CH_2Cl_2 and tracked with TLC until the product had eluted. All of the fractions containing the product were combined together (about 1.5 L), from which 5 drops was collected by pipet which was later used for optical purity determination. The solvent was slowly removed by a rotary evaporator to give shiny yellow crystals. To remove the color, the crystals were combined with 30 mL of CH_2Cl_2 and swirled for about 1 min, and then 100 mL of hexane was added; this mixture was filtered and rinsed with hexanes (2 × 25 mL). The solid (19.8 g, 36.8 mmol, 90.6% as light yellow crystals) was collected and dried overnight on high vacuum. The optical purity of (*S*)-VAPOL (*S*-**3**) was determined to be >99% by HPLC using a Pirkle D-phenylglycine column as described below: the 5 drops of solution saved from above were diluted with 5 mL of hexanes, from which 4 μL was injected onto the HPLC with the following conditions: 260 nm, 2 mL/min, 25:75 mixture of 2-propanol and hexanes, and the t_R = 14.0 min for (*S*)-VAPOL and t_R = 23.9 min for (*R*)-VAPOL.

The (*S*)-VAPOL obtained as described above exists as a solvate with CH_2Cl_2 containing two molecules of VAPOL per molecule of CH_2Cl_2.[30] To remove the CH_2Cl_2 all of the material above was taken up in 250 mL of hexanes, and then the volatiles were removed by rotatory evaporation and then under high vacuum (0.1 mmHg) for 48 h. This gave an off white powder with mp 223−226 °C (lit.[30] 226.2−227.9 °C) and $[\alpha]_D$ 143.5 ($CHCl_3$ *c* 1.0). Spectral data for (*S*)-VAPOL: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.60 (s, 2H), 6.69 (d, 4H, J = 8.0 Hz), 6.96 (t, 4H, J = 8.0 Hz), 7.07 (t, 2H, J = 7.5 Hz), 7.45 (s, 2H), 7.63 (t, 2H, J = 8.5 Hz), 7.67−7.71 (m, 4H), 7.83 (d, 2H, J = 8.5 Hz), 7.94 (d, 2H, J = 8.5 Hz), 9.75 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 115.84, 118.16, 123.25, 126.36, 126.83, 126.99, 127.03, 127.54, 128.44, 128.85, 128.86, 129.30, 130.33, 132.86, 135.32, 139.77, 141.59, 153.44.

(*R*)-VAPOL can be obtained from the reductive cleavage of salt II **36** with Red-Al utilizing the same procedure described above in 90% yield and >99% ee. After removal of the CH_2Cl_2 as described above, (*R*)-VAPOL was obtained as a white powder with mp 223−227 °C (lit.[30] 226.2−227.9 °C) and $[\alpha]_D$ −148.3 ($CHCl_3$ *c* 1.0).

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ACKNOWLEDGMENT

This work was supported by a grant from the National Science Foundation.

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■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on July 12, 2011, with a production error in Table 8. The value for % ee **39** (0 years) has been corrected for Al foil. The corrected version was reposted on July 22, 2011.