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Iterative Stereospecific Reagent-Controlled Homologation Using a Functionalized α-Chloroalkyllithium: Synthesis of Cyclic Targets Related to Epibatidine

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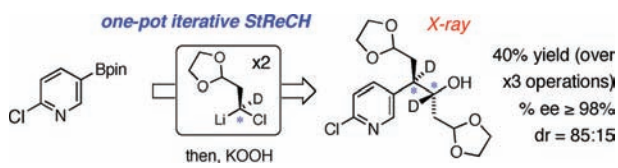
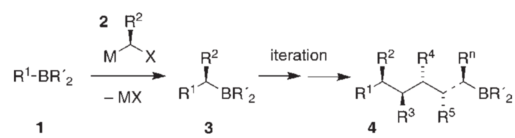
ABSTRACT



Enantioenriched 1-chloro-2-(1,3-dioxolan-2-yl)ethyllithium was generated by PhLi initiated sulfoxide-ligand exchange and deployed in situ for sequential double stereospecific reagent-controlled homologation (StReCH) of *B*-(2-chloro-pyrid-5-yl) pinacol boronate. This process afforded highly functionalized contiguous stereodiad motifs (typically, % ee ≥ 98%, dr ≥ 85:15) amenable to subsequent annulative transformations as demonstrated by the concise synthesis (5−7 steps) of cyclic adducts related to the analgesic alkaloid epibatidine.

Recent advances have seen the successful realization of stereospecific reagent-controlled homologation (StReCH) of organoboron derivatives with various types of enantioenriched chiral carbenoids (**2**),[1] including α-chloroalkyllithiums (and analogous Grignard species),[2] α-lithiated carbamates,[3] α-lithioepoxides/aziridines,[4] and α-lithiated *N*-Boc amines[5] (Scheme 1).[6] Iterative StReCH provides a conceptually simple and wholly programmable approach to carbon−carbon bond formation wherein the carbenoid presentation sequence precisely determines the absolute stereochemical configuration and constitution of a polysubstituted alkylboron intermediate **4**.[7] It is obvious that

Scheme 1. Stereospecific Reagent-Controlled Homologation (StReCH) of Organoborons **1** by Enantioenriched Chiral Carbenoids **2**[a]



[a] M = electrofugal group (e.g., Li, MgCl), X = nucleofugal group [e.g., Cl, OC(O)N(*i*-Pr)$_2$].

(1) For a definition of StReCH and elaboration of the generic attributes of this concept, see ref 2a.
(2) (a) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773–776. (b) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068–3069.
(3) (a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491–7494. (b) Stymiest, J. K.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778–782. (c) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed* **2010**, *49*, 5142–5145. For applications in total synthesis, see:(d) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193–2207. (e) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6317–6319. (f) Robinson, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6673–6675.
(4) (a) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168. (b) Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1149–1152.
(5) Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E.; Adams, H.; Fang, G. Y.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 141–143.
(6) Reviews: (a) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24–29. (b) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704–6716. (c) Capriati, V.; Florio, S. *Chem.—Eur. J.* **2010**, *16*, 4152–4162.

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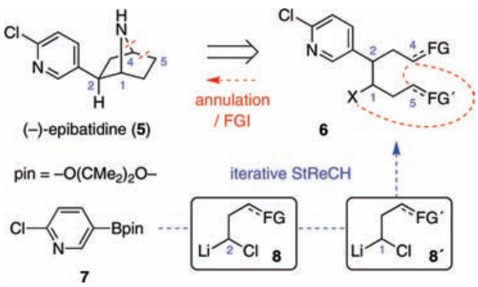
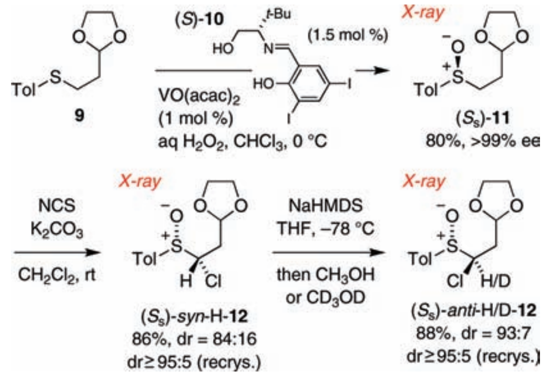
Scheme 2. The Analgesic Alkaloid (−)-Epibatidine (**5**) and an Iterative StReCH Based Synthetic Plan To Access It



this nascent technology could be directed to the synthesis of all manner of acyclic targets; however, it may also be potentially applied to access cyclic compounds providing that the carbenoid building blocks used during iterative assembly bear functionalized substituents. In this manner, following production of an acyclic precursor, annulation processes involving the embedded side-chain functional groups could be triggered to yield some cyclic motif of interest. Herein, we report an exploration of this strategy as it relates to the synthesis of congeners of the analgesic alkaloid (−)-epibatidine using a functionalized α-chloroalkyllithium formed by sulfoxide-ligand exchange.[8]

(−)-Epibatidine (**5**) was first identified by Daly and coworkers as a trace component of the skin extract of the poison tree frog *Epipedobates tricolor*.[9] Isolation of **5** was guided by a mouse Straub-tail bioassay, a response usually associated with opiate induced analgesia. The analgesic action of **5** (estimated to be >200 times that of morphine) was later tracked to its agonism of nicotinic acetylcholine receptors (nAChR's).[10] Given the interesting biological activity of **5** and its intriguing 7-azabicyclo[2.2.1]heptane core, epibatidine has become an inspirational and popular synthetic target[11] and many artificial analogs have been prepared to determine SAR.[12] We desired a versatile route to epibatidine that would enable any of its stereoisomeric forms, and related congeners, to be accessed in a concise fashion. Thus, it was envisioned that sequential StReCH reactions from commercially available pinacol boronate **7** using functionalized scalemic carbenoids **8** would afford an acyclic precursor to epibatidine (**6**) containing preset C1 and C2 stereogenic centers (Scheme 2). Formation of the desired azanorbornane could then be accomplished by engaging the latent reactivity placed at C4 and C5 with a heteroatom (X) at C1, derived from the final site of the boron atom. Four different functional group possibilities (i.e., FG in **8**) were surveyed in pursuit of this aim: FG = ethenyl, ethynyl, benzyloxy, and 1,3-dioxolan-2-yl; only the last one will be detailed in this initial report.

Scheme 3. Enantioselective Synthesis of Chlorosulfoxides **12**



To access a dioxolane substituted chloroalkyllithium, appropriate chlorosulfoxide precursors **12** were prepared from thioether **9** (Scheme 3). A Jackson−Ellman−Bolm[13] catalytic enantioselective sulfoxidation was used as the source of stereochemistry for downstream carbenoids by providing the key asymmetric progenitor **11**. Electrophilic chlorination of this sulfoxide occurred with inversion of stereochemistry on sulfur[14] to provide *syn*-H-**12** which was recrystallized to improve isomeric purity. Curious as to what advantages, if any, *anti* chlorosulfoxides may offer over their better studied *syn* isomers, we prepared *anti*-H-**12** and *anti*-D-**12** by epimerization of *syn*-H-**12**. The absolute and relative stereochemical outcome of all reactions involved in the synthesis of *anti*-**12** from **9** was confirmed by anomalous scattering XRD analysis.

The pivotal sulfoxide-ligand exchange (SLE) process was examined in isolation for each of the three forms of **12** in hand (Table 1). *Syn* and *anti* isomers of H-**12** were treated with PhLi[15] as indicated followed soon thereafter by a deuterium quench to track the final site of lithiation (entries 1 and 2). In each case, the product of SLE (sulfoxide **13**) was found alongside chlorosulfoxide **12** and an

(7) For a substrate-controlled approach to synthesis based on iterative homologation of boronic esters, see ref 6a and: (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607. For recent applications of the Matteson chain extension method, see: (b) Hiscox, W. C.; Matteson, D. S. *J. Organomet. Chem.* **2000**, *614–615*, 314. (c) Davoli, P.; Spaggiari, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 38–47.

(8) For seminal work concerning the generation of scalemic carbenoids via sulfoxide-ligand exchange, see: Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem.—Eur. J.* **2000**, *6*, 3359–3365.

(9) (a) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475–3478. (b) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830–836.

(10) Damaj, M. I.; Creasy, K. R.; Grove, A. D.; Rosecrans, J. A.; Martin, B. R. *Brain Res.* **1994**, *664*, 34–40.

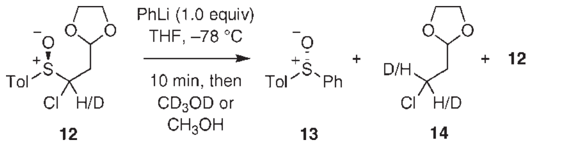
(11) There are over 50 published syntheses of epibatidine. For recent efforts and a review, see: (a) Lee, C.-L. K.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2965–2967. (b) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516–5519. (c) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365–374. (d) Armstrong, A.; Bhonoah, Y.; Shanahan, S. E. *J. Org. Chem.* **2007**, *72*, 8019–8024. (e) Bexrud, J.; Lautens, M. *Org. Lett.* **2010**, *12*, 3160–3163. Review: (f) Olivo, H. F.; Hemenway, M. S. *Org. Prep. Proced. Int.* **2002**, *34*, 1–26.

(12) (a) Carroll, F. I. *Heterocycles* **2009**, *79*, 99–120. (b) Garraffo, H. M.; Spande, T. F.; Williams, M. *Heterocycles* **2009**, *79*, 207–217.

(13) (a) Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221–7223. (b) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019. (c) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed.* **1995**, *34*, 2640–2642.

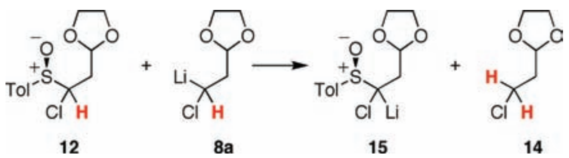
(14) Stereochemical inversion in this reaction is well precedented; see: (a) Calzavara, P.; Cinquini, M.; Colonna, S.; Fornasier, R.; Montanari, F. *J. Am. Chem. Soc.* **1973**, *95*, 7431–7436. (b) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *Tetrahedron Lett.* **1988**, *29*, 313–316.

Table 1. Sulfoxide-Ligand Exchange from Chlorosulfoxides **12**



no.	form of **12** (anti$^{\%D}$:syn$^{\%D}$)	quench	yield **13**	yield **14** (HH:HD:DD)	recovered **12** (anti$^{\%D}$:syn$^{\%D}$)
1	(R_s)-*syn*-H (<5 ^{0}: >95 ^{0})	CD_3OD	47%	28% (>95: <5:0)	20% (78 $^{\geq 99}$:22 $^{\geq 99}$)
2	(R_s)-*anti*-H (93 ^{0}:7 ^{0})	CD_3OD	51%	33% (>95: <5:0)	20% (80 $^{\geq 99}$:20 $^{\geq 98}$)
3	(R_s)-*anti*-D (92 ^{87}:8 $^{\geq 80}$)	CH_3OH	58%	35% (22:50:28)	16% (77 $^{<2}$:23 $^{<2}$)
4	(R_s)-*anti*-D (92 ^{87}:8 $^{\geq 80}$)	CD_3OD	63%	26% (14:59:27)	16% (73 ^{96}:27 ^{89})

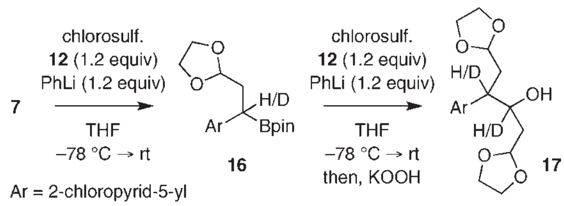
alkylchloride (**14**) derived from protonation of the putative α-chloroalkyllithium **8a**. Of note, the recovered chlorosulfoxide material **12** was fully deuterated in the α-position and had an *anti*/*syn* ratio of ca. 4:1 regardless of whether *anti*-**12** or *syn*-**12** was used as a starting material; furthermore, alkylchloride **14** exhibited essentially 0% D. Evidentally, proton exchange had occurred in the reaction mixture between the carbenoid **8a** and its chlorosulfoxide precursor **12** prior to deuterolysis.[16]



To confirm this hypothesis, a simple reverse labeling experiment was conducted using *anti*-D-**12** (entry 3). Following PhLi treatment as before, protonation led to the generation of alkylchloride **14** with a significant level of DD labeling,[17] as expected, together with undeuterated **12**. Repeating the same experiment with a deuterium quench did not significantly alter the isotopomer composition of **14** revealing that the carbenoid **8a** did not survive 10 min at −78 °C to the quench process (entry 4). The fact that α-chloroalkyllithiums can be protonated by their own α-chlorosulfoxide precursors is of detriment to SLE based StReCH methods. This behavior may account in part for the large variability in yield vs carbenoid type previously observed.[2b]

The StReCH reaction between **7** and **12**, without doubt the most complex such transformation yet attempted, was evaluated next (Table 2). A key finding of the SLE study was that *anti*-D-**12** was more cleanly converted to **13** than either of the protio forms of the same chlorosulfoxide. By implication, the deuteride is a more effective carbenoid precursor (understandable given that the rate of carbenoid quenching from *anti*-D-**12** would be less than that from either H-**12** isomer because of a primary kinetic isotope effect). In the event, *anti*-D-**12** did indeed provide the highest yield of StReCH adduct **16** when reacted with PhLi in the presence of boronate **7** (in THF); however, all three forms of chlorosulfoxide **12** gave acceptable results (entries 1−3). Stereochemical fidelity was excellent with products

Table 2. StReCH of Boronate **7** Using Chlorosulfoxides **12**



1st stage: 7 → 16

no.	chlorosulfoxide **12** form	anti:syn	boronate **16** target	conv	% ee[a]	
1	(R_s)-*syn*-H	<5: >95	(*R*)-H	68%	93	
2	(R_s)-*anti*-H	93:7	(*S*)-H	62%	nd	
3	(S_s)-*anti*-D	95:5	(*R*)-D	79%	89	(53% iso. yield)

2nd stage: (R)-D-16[b] → 17

no.	chlorosulfoxide **12** form	anti:syn	carbinol **17** target	yield	dr (% ee)[c]
4	(S_s)-*anti*-D	96:4	(*R*,*R*)-DD[d]	23%	89 (≥ 98):11 (< 24)
5	(R_s)-*anti*-D	93:7	(*R*,*S*)-DD	22%	90 (≥ 98):10 (~ 2)

one-pot: 7 → [16] → 17

no.	chlorosulfoxide **12** stage 1	stage 2	carbinol **17** target	yield	dr (% ee)[c]
6	(S_s)-*anti*-D[e]	(S_s)-*anti*-D[e]	(*R*,*R*)-DD[d]	40%	85 (≥ 98):15 (< 10)
7	(S_s)-*anti*-D[e]	(R_s)-*anti*-D[f]	(*R*,*S*)-DD	49%[g]	79 (≥ 97):21 (~ 1)

[a] Determined by HPLC analysis of the derived 2° alcohol obtained by KOOH oxidation. [b] (*R*)-D-**16** used had 89% ee. [c] dr = targeted/untargeted diastereoisomer ratio; values in parentheses represent % ee for given isomer as determined by HPLC analysis. [d] Absolute and relative configuration confirmed by X-ray diffraction analysis (see Supporting Information). [e] *Anti*/*syn* = 95:5. [f] *Anti*/*syn* = 93:7. [g] Experiment conducted using 2.5 mmol of **7**; all other reactions performed on ≤0.63 mmol scale.

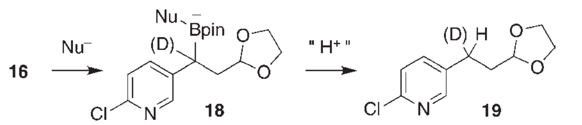
(15) Previously, a combination of *t*-BuLi in PhMe had been regarded as optimal for the generation of α-chloroalkyllithiums via SLE (refs 2b, 16b); however, wary of the pyrophoric nature of *t*-BuLi, an alternative to this hazardous reagent was sought. It has now been discovered that PhLi, a reagent that presents significantly less risk, is superior to *t*-BuLi for SLE based StReCH chemistry. For recent examples of PhLi induced SLE, see: (a) Ferrer, C.; Riera, A.; Verdaguer, X. *Organometallics* **2009**, *28*, 4571–4576. (b) Jarowicki, K.; Kilner, C.; Kocienski, P. J.; Komsta, Z.; Milne, J. E.; Wojtasiewicz, A.; Coombs, V. *Synthesis* **2008**, 2747–2763. (c) Gomez, A. M.; Casillas, M.; Barrio, A.; Gawel, A.; Lopez, J. C. *Eur. J. Org. Chem.* **2008**, 3933–3942.

(16) Carbenoid **8a** can decompose via a variety of pathways that do not lead to **14**; this accounts for the lower isolated yield of **14** vs **13**. See: (a) Köbrich, G. *Angew. Chem., Int. Ed.* **1967**, *6*, 41–52. Lithiated sulfoxide **15** is likely also generated by direct deprotonation of **12** by PhLi. See: (b) Blakemore, P. R.; Burge, M. S.; Sephton, M. A. *Tetrahedron Lett.* **2007**, *48*, 3999–4002.

(17) Incomplete α-deuteration of the starting material used for entries 3 and 4, together with the expected faster H transfer from the minor H-**12** components, accounts in part for the generation of **14** as a mixture of all three (HH, HD, and DD) isotopomers. β-Elimination of HCl from **8a** by the action of another **8a** as base provides a second mechanism for proton transfer that could lead to HD-**14** from D-**12**, see ref 16a.

16 manifested ee's in close accord with the isomeric purity of starting chlorosulfoxides **12**.[18] In all cases, the desired product **16**, which had only limited stability on silica gel resulting in some loss upon chromatographic purification, was accompanied by small quantities of protodeboronated material (**19**, 2−10%).

Restricting attention to the higher yielding deuterated carbenoid precursors, boronate **16** was next advanced to a congested contiguous stereodiad motif (**17**) via a second StReCH reaction (entries 4 and 5). Both diastereoisomers of **17** were individually targeted by use of the appropriate carbenoid presentation sequences, and the stereochemical identity of one product [(*R,R*)-DD-**17**] was confirmed by XRD analysis. Targeted isomers were obtained with good dr, and by virtue of the Horeau effect intrinsic to iterative StReCH, the ee for these products was boosted as compared to intermediate boronate **16** (also as expected, untargeted diastereoisomers exhibited a low ee).[19] Regrettably, protodeboronation was now the dominant pathway and isolated yields of **17** were consistently low in favor of **19** (51−60% yield). Presumably, the pyridyl benzylic nature of boronic ester **16** allows for fragmentation from ate complexes **18**, leading to the formation of **19** after proton transfer.[20]



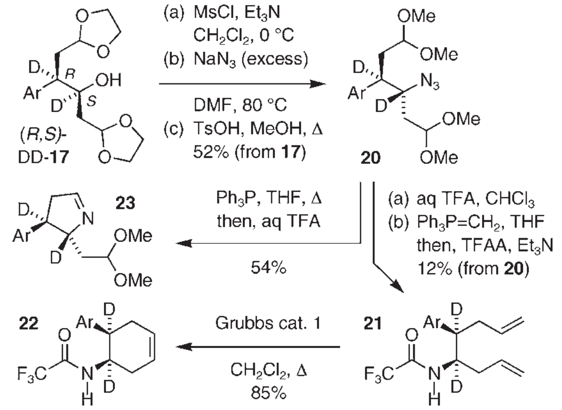
It was later discovered that much better results could be obtained by avoiding isolation of the intermediate boronic ester **16** altogether and instead performing two extensions sequentially from **7** in a one-pot process (entries 6 and 7). In this fashion, the desired densely functionalized product (*R,R*)-DD-**17** was obtained in a 40% overall yield from **7** via an operationally simple process requiring less than 8 h of reaction time. Epimer (*R,S*)-DD-**17** was similarly prepared, albeit with a poorer dr; a likely consequence of unreacted remanents of (S_S)-*anti*-D-**12** from the first stage participating in the second stage of chain elongation.

(18) For a given configuration at sulfur, *syn* and *anti* α-chlorosulfoxides lead to opposite carbenoid enantiomers upon SLE. Thus, in the case of entry 3 (Table 2), a product ee no higher than 90% should be expected given that the dr of the carbenoid source was 95:5.

(19) The amplification in ee for the targeted isomer is readily understood in the following manner. Assume a chiral boronate (of er = x:1) reacts to full conversion and in a purely stereospecific manner with 1 equiv of a chiral carbenoid (of er = y:1). The major result of StReCH would be the targeted diastereoisomer with er = xy:1; the other possible (untargeted) diastereomer will also be produced but with an er = x:y (i.e., racemic if x = y). The overall ratio between targeted and untargeted diastereomers is then (xy + 1):(x + y), and the boost in ee for the targeted isomer is therefore at the expense of the generation of an unwanted minor diastereoisomer. The dr observed in entries 4 and 5 (Table 2) is in line with the expectation given that carbenoids **8a** and intermediate boronate (*R*)-D-**16** had an er ≈ 19:1 (90% ee); thus, the predicted dr = $(19^2 + 1):(2 \times 19)$ = 90.5:9.5. For an early description of this kind of effect, see: Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055–1059.

(20) Related protodeboronations from benzylic positions were recently reported: Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098.

Scheme 4. Advancement of StReCH Derived Stereodiad (*R,S*)-DD-**17** to Epibatidine Congeners[a]



[a] Ar = 2-chloropyrid-5-yl.

The contiguous stereodiad containing StReCH adduct (*R,S*)-DD-**17** was next advanced to azide **20** en route to epibatidine congeners (Scheme 4). A three-step sequence, concluding with ring-closing metathesis of the diene **21** derived from **20** by double acetal hydrolysis and a Wittig−Staudinger reaction, led to cyclohexene **22**. The protio isotopomer of **22** was previously converted to (−)-epibatidine (**5**) in 66% yield by Corey et al.[21] As a prelude to the synthesis of further interesting polycycles, it was demonstrated that bisacetal **20** could be converted efficiently to iminoacetal **23**.[22]

In conclusion, during the pursuit of a popular synthetic target, numerous insightful observations concerning SLE based StReCH methodology have been made. It has been shown that multiple chain extensions can be realized in a convenient one-pot process that allows for a programmed synthesis of nontrivial contiguous stereodiad motifs. The successful use of functionalized substrates and reagents in this study augurs well for future applications of StReCH technologies in the total synthesis of significantly more complex biologically active natural product molecules.

Acknowledgment. Financial support from the National Science Foundation is gratefully acknowledged (via Grant CHE-0906409). The National Science Foundation (CHE-0722319) and the Murdock Charitable Trust (2005265) are also thanked for support of the OSU NMR facility.

Supporting Information Available. Experimental procedures, characterization data, HPLC chromatograms, and NMR spectra for relevant compounds. CIF files for (R_S)-**11**, (S_S)-*syn*-H-**12**, (S_S)-*anti*-D-**12**, and (*R,R*)-DD-**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600–5602.

(22) A pinacol-type reductive cyclization of **23** could lead directly to 5-oxyepibatidines. 5-Hydroxyepibatidines show selective binding affinity for nAChR subtypes; see: Wei, Z.-L.; Xiao, Y.; George, C.; Kellar, K. J.; Kozikowski, A. P. *Org. Biorg. Chem.* **2003**, *1*, 3878–3881.