JOC The Journal of Organic Chemistry

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Scope of Stereoselective Mn-Mediated Radical Addition to Chiral Hydrazones and Application in a Formal Synthesis of Quinine

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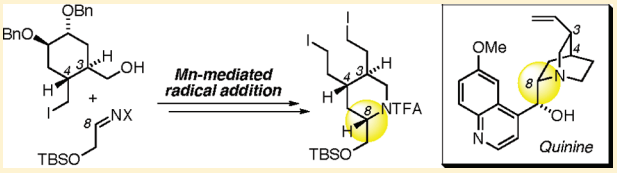
Supporting Information

ABSTRACT: Stereocontrolled Mn-mediated addition of alkyl iodides to chiral *N*-acylhydrazones enables strategic C−C bond constructions at the stereogenic centers of chiral amines. Applying this strategy to quinine suggested complementary synthetic approaches to construct C−C bonds attached at the nitrogen-bearing stereogenic center using multifunctional alkyl iodides **6a−d** as radical precursors, or using multifunctional chiral *N*-acylhydrazones **26a−d** as radical acceptors. These were included among Mn-mediated radical additions of various alkyl iodides to a range of chiral *N*-acylhydrazone radical acceptors, leading to the discovery that pyridine and alkene functionalities are incompatible. In a revised strategy, these functionalities are avoided during the Mn-mediated radical addition of **6d** to chiral *N*-acylhydrazone **22b**, which generated a key C−C bond with complete stereochemical control at the chiral amine carbon of quinine. Subsequent elaboration included two sequential cyclizations to complete the azabicyclo[2.2.2]octane ring system. Group selectivity between two 2-iodoethyl groups during the second cyclization favored an undesired azabicyclo[3.2.1]octane ring system, an outcome that was found to be consistent with transition state calculations at the B3LYP/6-31G(d) level. Group differentiation at an earlier stage enabled an alternative regioconvergent pathway; this furnished the desired azabicyclo[2.2.2]-octane ring system and afforded quincorine (**21b**), completing a formal synthesis of quinine.



INTRODUCTION

The long-established antimalarial properties of quinine (Figure 1) have fueled great interest in synthetic efforts toward this target since the very early days of natural product synthesis,[1] including a surge of media attention that accompanied the 1944 Woodward−Doering formal synthesis of quinine.[2] Despite practical improvements led by Uskokovic, Taylor, and Gates[3] in the 1970s for access to quinine and quinidine, no total synthesis offered complete configurational control until that reported by Stork in 2001.[4] Quinine syntheses by Jacobsen[5] and Kobayashi[6] appeared in 2004, followed by the Williams route to 7-hydroxyquinine in 2006.[7] More recently Krische reported a racemic formal synthesis of quinine,[8] and Aggarwal[9] and Hatakeyama[10] disclosed organocatalytic approaches to quinine and quinidine. Along with the plethora of interesting chemistries to emerge from these studies was an historically significant controversy regarding the validity of the 1944 Woodward−Doering formal synthesis.[11] This route relied upon the Rabe conversion of quinotoxine to quinine,[12] the authenticity of which was for some time questioned[13] but then ultimately verified by Smith and Williams,[14] confirming the claims of Woodward and Doering.

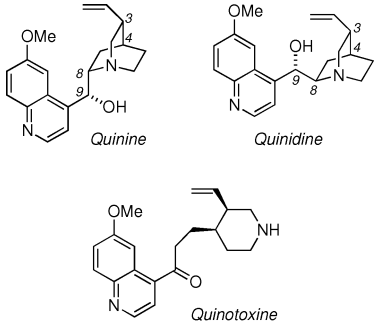
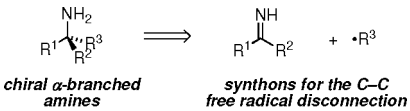


Figure 1. Structures of quinine, quinidine, and quinotoxine.

Quinine attracted our interest in the course of our program to develop new C−C bond construction approaches to chiral amines.[15] Asymmetric preparation of amines presents challenges in the synthesis of nitrogen-containing natural products,[16] particularly alkaloids and peptides derived from unusual amino acids. While numerous indirect methods involving C−N bond construction are available, an attractive alternative is a C−C bond construction via addition to the C═N bond of carbonyl imino derivatives (Scheme 1),[17] which efficiently generates both a stereogenic center and a C−C bond. Since two or three different C−C bonds could be chosen for disconnection in the retrosynthetic direction (Scheme 1), an

Scheme 1



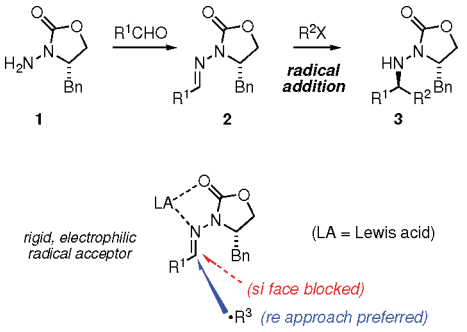
Received: December 20, 2011
Published: February 13, 2012

   dx.doi.org/10.1021/jo2026349 | J. Org. Chem. 2012, 77, 3159−3180

ideal methodology for this bond construction would avoid limitations on the scope in both precursors. In seeking this ideal, we have introduced Mn-mediated free radical additions to chiral *N*-acylhydrazones, achieving excellent acyclic stereocontrol in intermolecular C−C bond couplings which are compatible with complex multifunctional precursors.[18] As an alkaloid of some complexity and synthetic challenge, quinine presented a worthy test of the strategic application of these Mn-mediated coupling reactions in a multifunctional molecular setting.

Beginning in 2000, we introduced novel chiral *N*-acylhydrazones[19] prepared from *N*-aminooxazolidinones (e.g., **1**, Scheme 2) and carbonyl compounds, and their use in several

Scheme 2



types of Lewis acid promoted addition reactions, both radical[20,21] and nucleophilic.[22−24] The *N*-acylhydrazone motif has also recently been exploited for asymmetric α-alkylation.[25]

Among the aforementioned addition reactions were the first examples of highly stereoselective free radical coupling of alkyl iodides and chiral *N*-acylhydrazones.[21] In general, radical additions at the carbon of imino compounds[26] are attractive complements to polar methods for reasons of functional group compatibility, but despite seminal work by Naito[27] and Bertrand[28] as well as more recent efforts by Tomioka,[29] Porta,[30] and Jang[31] to develop such reactions, applications to total synthesis have lagged because methods exhibiting versatility with respect to both radical and acceptor are limited. A key problem has been the difficulty in achieving synthetically useful yields in the addition reactions of primary alkyl iodides. This problem was the inspiration for our development of Mn-mediated radical additions of alkyl iodides to chiral *N*-acylhydrazones, substantially broadening the versatility of radical additions to imino compounds.[18] Still, few synthetic methods gain wide acceptance without demonstrations of the methodology in the arena of natural product synthesis, where multifunctional precursors challenge the scope and versatility of new methods. Therefore we embarked upon an application of Mn-mediated coupling of alkyl halides and *N*-acylhydrazones to a synthesis of quinine, full details of which are discussed here.[32]

RESULTS AND DISCUSSION

Mn-Mediated Coupling Methodology. The growing potential of organomanganese reagents in synthesis[33] rests upon interesting reactivity attributes, such as the generation of carbon-centered radicals using dimanganese decacarbonyl [$Mn_2(CO)_{10}$].[34] The weak manganese−manganese single bond (38 kcal mol^{-1})[35] in this commercially available yellow solid is easily photolyzed (λ_{max} 324 nm, cyclohexane),[36] and in the presence of alkyl halides the resulting ·$Mn(CO)_5$ abstracts halogen atoms to produce alkyl radicals and X−$Mn(CO)_5$ (eq 2).[37,38] This reactivity profile bears some resemblance to stannyl radicals.[39]

$$(CO)_5Mn{-}Mn(CO)_5 \xrightarrow{h\nu} 2(CO)_5Mn\cdot \quad (1)$$

$$(CO)_5Mn\cdot + I{-}R \rightarrow (CO)_5Mn{-}I + \cdot R \quad (2)$$

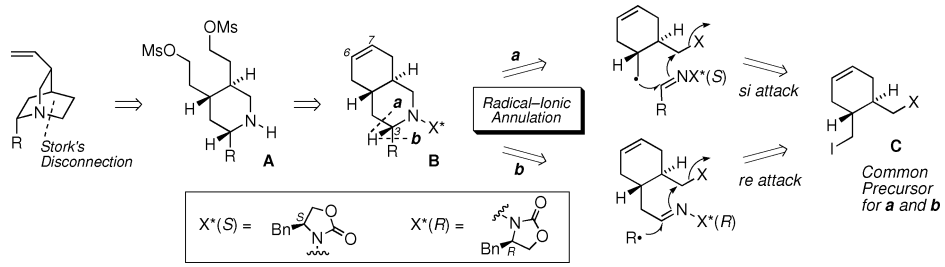
Examples of the utility of Mn-mediated photolytic radical generation are found in Wurtz-type homocoupling,[40] radical cyclizations,[41] TEMPO trapping,[41b] and polymerization.[42] These examples expose a couple of interesting attributes of $Mn_2(CO)_{10}$: (a) The success of Wurtz coupling upon photolysis with $Mn_2(CO)_{10}$ suggests production of significant concentrations of carbon-centered radicals.[37a] (b) The reaction of ·$Mn(CO)_5$ with primary halides has been noted to be more facile than with secondary or tertiary halides.[41b] This latter point contradicts the usual order of reactivity for generation of alkyl radicals yet is in agreement with Brown's assessment of the importance of steric hindrance in the halogen atom transfer reactions of Mn(0)-centered radicals.[39b]

Further practical considerations also warrant mention. Unlike the organotin reagents, $Mn_2(CO)_{10}$ is a solid; it may be easily handled for short periods in ambient laboratory atmosphere (e.g., for measurement and transfer) and stored for long periods under inert atmosphere in the freezer without decomposition. In contrast to tin halides such as Bu_3SnBr, the manganese(I) halide byproducts obtained from atom abstraction reactions with alkyl halides are relatively easy to remove.

Taking advantage of the above considerations, we have shown that photolysis of dimanganese decacarbonyl holds great promise for generating a broad range of alkyl radicals and expanding the synthetic potential of radical additions to imino compounds.[18]

Synthetic Strategy. In its conception, our approach to quinine focused upon strategic application of Mn-mediated hybrid radical−ionic annulation, a tandem reaction involving Mn-mediated radical addition followed by S_N2 ring closure. We had previously described examples of this reaction, an example

Scheme 3



dx.doi.org/10.1021/jo2026349 | J. Org. Chem. 2012, 77, 3159−3180

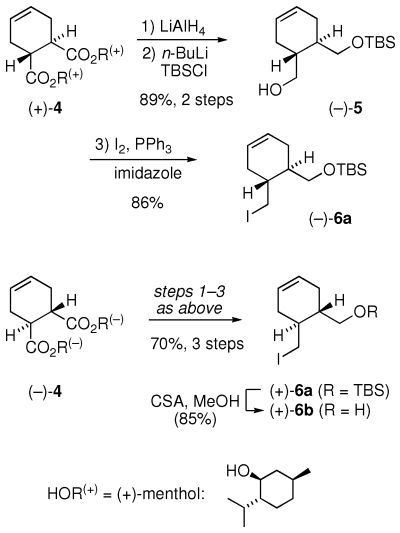
of a radical−polar crossover reaction,[43] for preparation of simple pyrrolidines and piperidines.[18a,b,e] Employing Stork's disconnection of the *aza*-bicyclo[2.2.2]octane ring system suggested a 2,4,5-trisubstituted piperidine[44] precursor **A** (Scheme 3), which in turn would derive from oxidative cleavage of the C6−C7 bond of a tetrahydroisoquinoline such as **B**. We envisaged an efficient access to the isoquinoline ring system through Mn-mediated radical addition to construct either of the two C−C bonds at the C3 stereogenic carbon (disconnections ***a*** and ***b***). The stereoselective radical addition would be followed by closed-shell S_N2 displacement of a leaving group X by the imino nitrogen to complete the radical−ionic annulation and furnish the tetrahydroisoquinoline heterocycle.

Some important aspects of the strategy depicted in Scheme 3 warrant specific mention. First, the Mn-mediated coupling enables interchange of the iodide and hydrazone functionality, such that either component could serve as radical precursor or acceptor. Thus the choice of path ***a*** or ***b*** is flexible, to be defined at the benchtop according to optimal yields or selectivities. Second, the strategy reveals a common precursor **C**, for which C_2-symmetry could be exploited in an efficient access to both sets of coupling components. Third, if the chiral auxiliary X* is the dominant control element (as was expected from all available precedent), then the enantiomeric iodide (e.g., *ent*-**C**) could generate the C8−C3/4 stereochemical relationship of quinidine. Finally, the group selectivity implied in the ring closure of a structure exemplified by **A**, which bears two primary alkyl halides or their equivalents, presented an intriguing question that was, to our knowledge, without close precedent: Would the cyclization afford a azabicyclo[3.2.1]-octane or the desired azabicyclo[2.2.2]octane ring system?

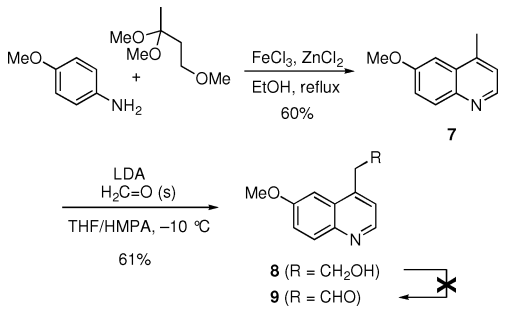
Initial Synthetic Efforts. Testing the synthetic strategy began with preparation of an iodide encompassing the structural features of **C**. We envisioned using the known enantioselective Diels−Alder reactions of dimenthyl fumarate[45] to generate the disubstituted cyclohexene of **C**, and both enantiomeric menthol esters of fumaric acid were readily available. Thus, both enantiomeric forms of **C** could be accessed, and this would enable a test of the impact of the configuration of the radical on stereocontrol in radical addition to a chiral hydrazone. Diesters (+)-**4** and (−)-**4** (Scheme 4, containing (+)- and (−)-menthol, respectively) were acquired in quantitative yield via the known Diels−Alder reactions. From (+)-**4**, reductive removal of the (+)-menthol with $LiAlH_4$ and monosilylation of the resulting C_2-symmetric diol furnished desymmetrized (−)-**5**. The free hydroxyl was readily converted to the corresponding iodide, affording (−)-**6a** in 76% overall yield for four steps from commercial dimenthyl fumarate. The same sequence was applied to prepare (+)-**6a** in 70% overall yield. The silyl ether of (+)-**6a** was cleaved by acidic methanolysis to afford the corresponding alcohol (+)-**6b**.

The initially envisaged *N*-acylhydrazone coupling partner for radical precursors **6a,b** incorporated the 6-methoxyquinoline fragment of quinine. Early attempts to prepare this hydrazone (Scheme 5) began with condensation of *p*-anisidine with 1,3,3-

Scheme 4



Scheme 5



trimethoxybutane in the presence of $FeCl_3$ and $ZnCl_2$ to afford 6-methoxy-4-methylquinoline (**7**),[46] followed by homologation (LDA, paraformaldehyde) furnishing primary alcohol **8**. Unfortunately, a wide range of oxidation methods failed to provide the aldehyde **9** required to prepare the *N*-acylhydrazone.[47] Attempts to modify the homologation by replacing paraformaldehyde with electrophiles at higher oxidation state (HCO_2Et, DMF, $ClCO_2Me$) were also unsuccessful.

Attention then turned to homologation via olefination (Scheme 6). Oxidation of 6-methoxy-4-methylquinoline according to Minisci et al.[48] afforded quininaldehyde (**10**)[49] in 77% yield. Wittig reaction of **10** with (methoxymethyl)-triphenylphosphorane provided the corresponding methyl enol ether **11**, which was then subjected to condensation with *N*-aminooxazolidinone (*S*)-**1** in acidic ethanol to afford hydrazone **12** in modest yield (22%, 2 steps). After further exploration aimed toward more efficient material throughput, finally, a preferred route to **12** emerged via two consecutive condensation reactions of 6-methoxy-4-methylquinoline, first with Bredereck's reagent[50] (**13**) to afford enamine **14**, then with *N*-aminooxazolidinone (*S*)-**1** in acidic ethanol to furnish hydrazone **12** in 62% yield for two steps.

With hydrazone **12** now available, the stage was set to attempt the $Mn_2(CO)_{10}$-mediated coupling with iodide (−)-**6a** (Scheme 7); to our dismay we observed no coupling product. It was noted that a precipitate was formed from a mixture of hydrazone **12** with $InCl_3$ in 10:1 PhH/MeCN. This precipitate was not soluble, even upon further addition of MeCN.

This anomalous failure of the Mn-mediated coupling of (−)-**6a** and **12** led us to consider which structural features of the chiral *N*-acylhydrazone partner might be interfering with the reaction. Mn-mediated radical additions of iodides containing the silyl ether moiety had previously been successful in various contexts,[18b−e] so we turned our attention to the

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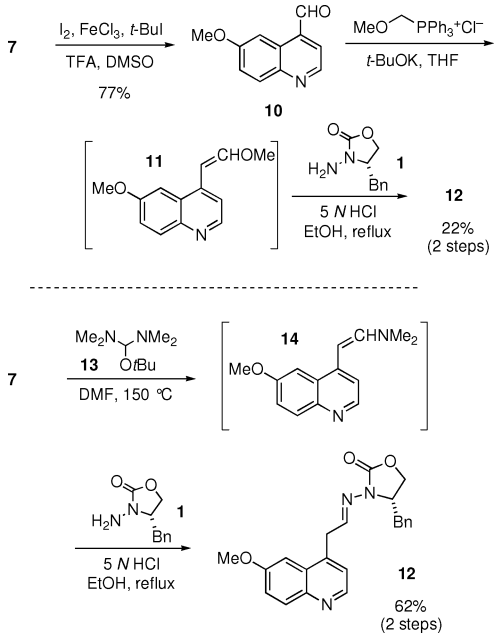
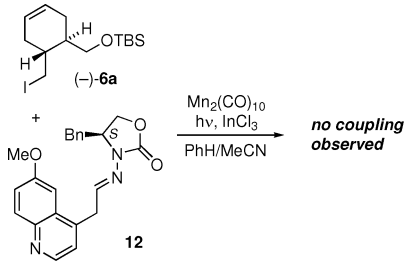
Scheme 6



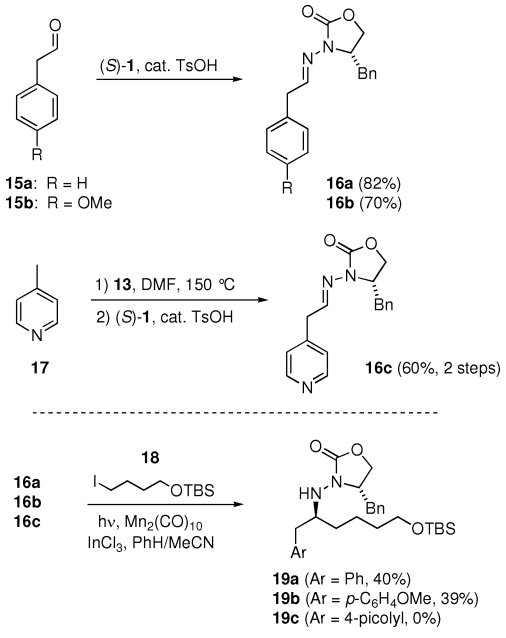
Scheme 7



functionalized aryl unit. We began to question whether complexation of the *N*-acylhydrazone with $InCl_3$, usually a prerequisite for efficient radical addition, was disrupted by the presence of the basic methoxyquinoline. A second concern was that the compatibility of the electron-rich methoxyphenyl group with the Mn-mediated radical additions had not previously been established.

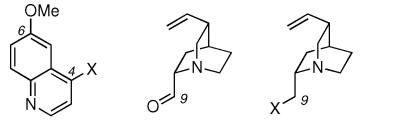
The compatibility of the methoxyquinoline substructure with the Mn-mediated coupling was addressed by a series of control experiments with aromatic hydrazones. Two hydrazones **16a** and **16b** (Scheme 8) were prepared by condensation of **1** with the corresponding arylacetaldehydes **15a** and **15b**, which lacked the basic heteroaromatic amine. A third hydrazone **16c** was prepared in 60% yield from 4-picoline (**17**) via the same Bredereck condensation sequence described above for hydrazone **12**. When hydrazones **16a** and **16b** were subjected to Mn-mediated addition of iodide **18**, the expected products **19a** and **19b** were obtained in moderate yield (ca. 40%). The fact that yields were similar with phenyl- and *p*-methoxyphenylacetaldehyde hydrazones indicated that the electron-donating methoxy substituent of the quinolinylacetaldehyde was not likely to be responsible for the failure of the coupling using hydrazone **12**. Hydrazone **16c**, bearing the pyridyl unit, failed to undergo the Mn-mediated coupling reaction; none of the desired coupling product **19c** was observed, consistent with observations on hydrazone **12**. The precipitation observed in attempted Mn-mediated coupling of **12**, taken together with

Scheme 8



the results of the control experiments using **16a**–**16c**, indicated that it was the heteroaromatic nitrogen of the quinoline substructure that interfered with the Mn-mediated coupling reaction.[51] The 6-methoxyquinoline would need to be introduced during a later stage in the synthesis.

Revised Strategy. Aware that an organolithium reagent had previously been prepared by metal–halogen exchange of 4-bromo-6-methoxyquinoline (**20**, X = Br),[52] we envisaged metal-mediated coupling of the aromatic subunit to the azabicyclo[2.2.2]octane (quinuclidine) ring system. For example, the 6-methoxyquinoline could be installed by nucleophilic addition of 6-methoxyquinolinyllithium (**20**, X = Li) to aldehyde **21a**.[52] Alternatively, a cuprate-mediated or transition-metal-catalyzed $C(sp^2)$–$C(sp^3)$ coupling of a structure at lower oxidation state, such as **21b** or its halogen analogues (e.g., **21b**, X = Br), could afford 9-deoxyquinine, and a known C–H oxidation of 9-deoxyquinine would install the C9 hydroxyl group.[3b] These considerations suggested an alternative plan focusing first on construction of the quinuclidine bearing an electrophilic one-carbon substituent destined to become C9.



Thus, the second iteration of the strategy focused on the two sets of coupling components suggested by structures **D** + **E** or **D′** + **E′**, forming bonds *a* or *b*, respectively (Scheme 9). Using enantiomeric ozazolidinones within the chiral *N*-acylhydrazone structures **E** and **D′**, the two alternative bond constructions would be stereoconvergent and would afford the same piperidine ring system **B**.

With iodide **6a** already available as a synthetic equivalent of structure **D**, it was necessary to prepare hydrazone corresponding to **E** in order to test bond construction of path *a*. For this purpose, chloroacetaldehyde dimethyl acetal (Scheme 10) was condensed with *N*-aminooxazolidinone **2**, affording hydrazone

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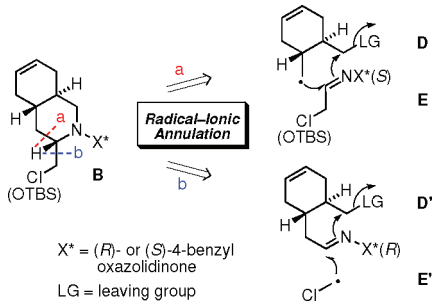
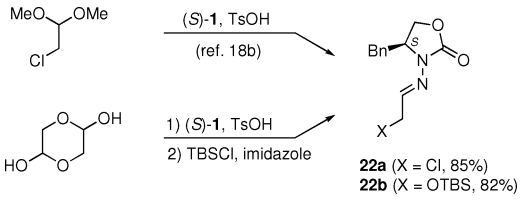
Scheme 9



Scheme 10



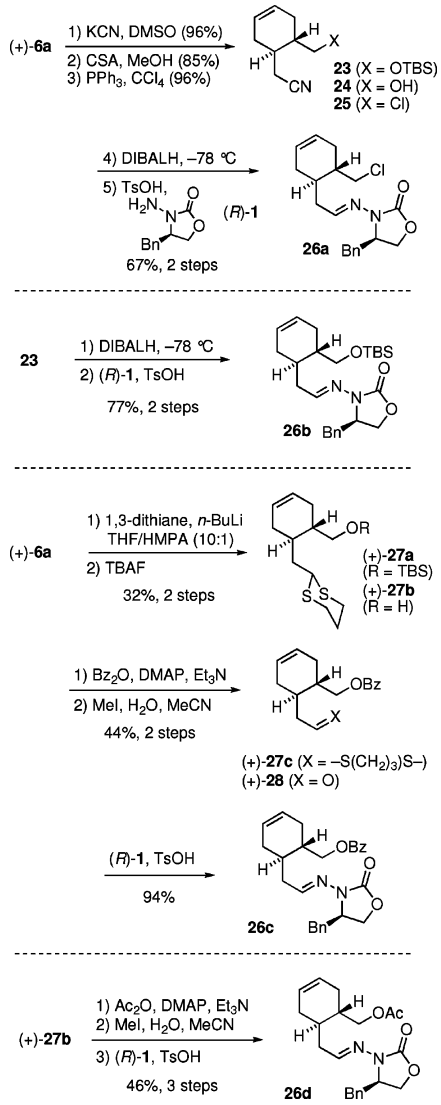
22a as previously reported.[18a,b] Similarly, hydrazone **22b** was prepared by condensation of glycolaldehyde dimer with (*S*)-**1**, followed by *O*-silylation.

To test the alternative C−C bond construction (path ***b***) it was also necessary to interchange the functionality from iodide to the homologous *N*-acylhydrazone. Therefore, four radical acceptors **26a−d** bearing different leaving groups were prepared (Scheme 11). From the iodide **6a**, both antipodes of which had already been prepared in enantiopure form for use as radical precursors, this was readily accomplished via a simple 5-step sequence. Some of the initial exploratory studies on these radical additions were carried out using materials prepared from antipode (+)-**6a** (Scheme 11). Homologation of (+)-**6a** by S_N2 reaction with potassium cyanide furnished nitrile **23**, which was subjected to acidic desilylation (CSA, MeOH) to afford alcohol **24**. Conversion of this alcohol to the corresponding chloride **25** was accomplished under standard conditions (PPh_3, CCl_4). Partial reduction of the nitrile to the corresponding aldehyde and condensation with *N*-amino-oxazolidinone (*R*)-**1** then furnished radical acceptor **26a** in an overall 56% yield. The related acceptor **26b** was prepared from (+)-**6a** in 3 steps via nitrile **23** with an overall yield of 74%.

Benzoate **26c** and acetate **26d** were synthesized by a dithiane homologation route. This began with treatment of iodide **6a** with 2-lithio-1,3-dithiane and desilylation to afford alcohol **27b** in modest yield.[53] After acylation with Bz_2O, dithiane hydrolysis afforded the corresponding aldehyde (+)-**28**,[54] which was condensed with *N*-aminooxazolidinone (*R*)-**1** to afford the *N*-acylhydrazone **26c** bearing benzoate functionality. The analogous acetate **26d** was prepared via the same synthetic sequence from **27b** in 46% yield for the three steps.

The sets of radical precursors **6a,b** and acceptors **26a−d** were subjected to Mn-mediated addition reactions with hydrazone **22a** and chloroiodomethane, respectively, in the presence of $InCl_3$ (Table 1). The desired adducts **29−30** were obtained in modest yields, generally as single diastereomers.[55] This series of Mn-mediated couplings (entries 1−6) showed no improvement despite changing the nature of remote functionality from Cl to various protected alcohols (TBS ether or benzoate or acetate) or changing the roles of the coupling component (radical or radical acceptor, entries 1, 2 vs 3−7).

Scheme 11



The yields in these couplings never exceeded ca. 50%, and a slight scaleup even decreased the yield from 49% to 31% (compare entries 3 and 7). Even more troubling was the poor mass balance; in contrast to our prior experience with these Mn-mediated coupling reactions, no starting material was recoverable from lower-yielding runs. Moreover, no tractable side products were found, which obscured any obvious corrections to the conditions.

The question remained of whether the remote alkene functionality of **6a,b** could interfere in some unanticipated manner.[56] This was easily tested by experiments employing a saturated analogue (±)-**6b**[**H**] (Scheme 12). This was readily accessible from racemic (±)-*trans*-cyclohexane-1,2-dicarboxylic acid ((±)-**4**[**H**]). After reduction to the corresponding diol according to the known procedure,[57] sequential monosilylation (*n*-BuLi, TBSCl) proceeded smoothly to (±)-**5**[**H**]. Conversion of the remaining hydroxyl to iodide and desilylation afforded (±)-**6b**[**H**].

Now absent the alkene functionality, the radical addition of (±)-**6b**[**H**] to **22a** (Table 1, entry 8) was significantly improved, furnishing 67% yield of a mixture of diastereomers **30e** and **30e′** (dr 1:1). The yield of this reaction, which was not subjected to any optimization, was notably improved from all

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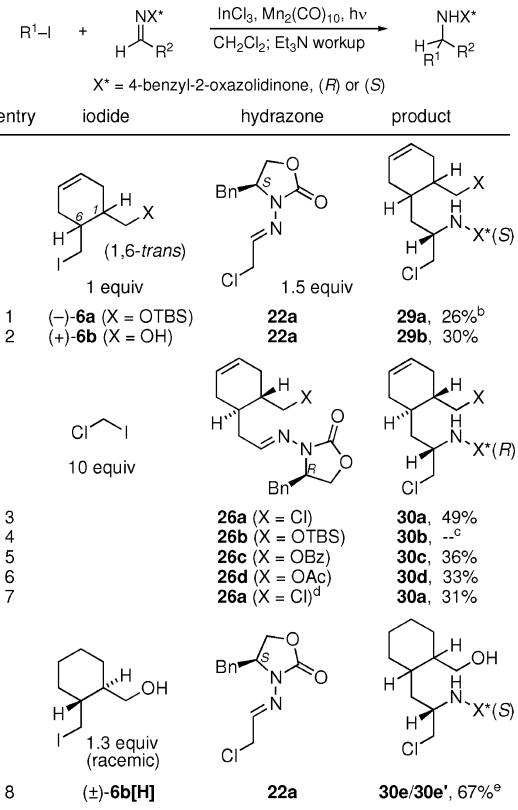
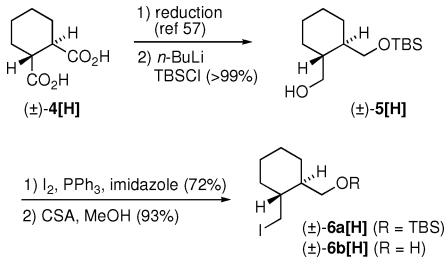
Table 1. Mn-Mediated Addition Studies[a]

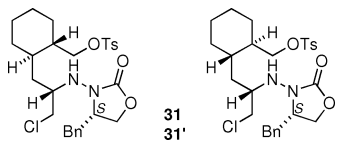


[a]Conditions: $InCl_3$ (2.2 equiv) and hydrazone (~0.2 mmol) in CH_2Cl_2 (0.02 M), 40 min at rt, then R–I and $Mn_2(CO)_{10}$ (1.2 equiv), irradiation (300 nm, Rayonet) for 10–20 h; Et_3N (5 equiv), then silica gel flash chromatography. [b]Solvent = 10:1 PhH/MeCN, DBU in place of Et_3N. [c]~25% yield, but inseparable impurities prevented characterization of **30b**. [d]0.65 mmol scale. [e]dr 1:1 (both *trans*).

Scheme 12



prior coupling combinations in Table 1. The two diastereomers obtained in this reaction were readily separated after conversion to the tosylates **31** and **31′** (TsCl, DMAP, Et_3N; 81% yield).



Comparison of entry 8 with the rest of Table 1 clearly shows the impact of removing the unsaturation from the reactant. The dramatically increased yield using saturated iodide (±)-**6b**[**H**] serves as a control experiment to confirm that the alkene was responsible for interference with the Mn-mediated coupling. In the absence of any tractable side products from entries 1–7, however, no further analysis was carried out on potential mechanisms by which the alkene functionality might interfere.

Role of Chiral Radical in Stereocontrol. Some fortuitous findings on the issue of stereocontrol by branched alkyl iodides, while not a focus of this study, are worth noting. First, two pseudoenantiomeric iodides (–)-**6a** and (+)-**6b** provided very high stereocontrol (94:6 and >95:5, Table 1, entries 1 and 2). One of these pairings with chiral hydrazone **22a** would give mismatched double stereoselection. Since there was little or no erosion of selectivity in either case, the extent of stereocontrol by the chiral radical appears to be insignificant relative to the effect of the chiral *N*-acylhydrazone. Second, in addition of the racemic iodide (±)-**6b**[**H**] to hydrazone **22a**, only two of the four possible diastereomers of **30e** were observed (Table 1, entry 8). This also suggests that neither enantiomeric iodide impacts the selectivity imparted by the chiral *N*-acylhydrazone. These observations are important for synthetic planning, as they offer confidence that the synthetic chemist can exert control of target chiral amine configuration simply by choosing the correct configuration of the stereocontrol element.

Second Revised Strategy. From the synthetic perspective, the alkene incompatibility provided another piece of guidance for improving the key C–C bond construction. The original C6–C7 bond cleavage (e.g., by alkene ozonolysis) was revised to a plan entailing oxidation of the C6–C7 alkene to a diol prior to the radical addition, with periodate cleavage to take place in a later stage. In the revised plan (Scheme 13), diastereoselective preparation of a C_2-symmetric *trans*-diol preserved the simplifying desymmetrization aspect of the strategy. The enantiopure diester (+)-**4** was treated with MCPBA, and the resulting epoxide **32** was subjected to acidic alcoholysis with benzyl alcohol to afford **33a**. Acid-catalyzed protection of the remaining free hydroxyl with benzyl trichloroacetimidate furnished bis-benzyl ether **33b**. Reduction to the C_2-symmetric diol **34a** and monosilylation furnished **34b** in 86% yield for the two steps. Conversion of the free hydroxyl to the corresponding iodide **6c** and desilylation smoothly provided multigram quantities of **6d** (95%, 2 steps). This route to **6d** followed procedures similar to our preliminary communication,[32b] but the $LiAlH_4$ reduction was improved by a modified workup, and the two-stage conversion of **34b** to **6d** was significantly more efficient upon scaleup.

In most intermolecular radical additions to imino compounds, large excesses (10–20 equiv or more) of radical precursors are required. Clearly this would be a prohibitive stoichiometric requirement for an iodide such as **6d**, prepared through several synthetic steps. In a preliminary examination of the reactivity of iodide **6d**, Mn-mediated coupling of **6d** (1.3 equiv) with hydrazone **22a** (1 equiv) was carried out under conditions as described in Table 1. A product with ^1H NMR data consistent with the desired adduct[58] was obtained in 59% and 65% yields in two runs (not shown). These preliminary tests suggested that the presence of vicinal benzyloxy substituents posed no problem for the Mn-mediated radical addition and could indeed be a satisfactory substitute for the alkene functionality in the revised strategy.

Even better results were obtained from the combination of **6d** with the alternative hydrazone **22b**, however (Scheme 13). We were delighted to find that the Mn-mediated coupling of **6d** with only 1.25 equiv of **22b** proceeded in 93% yield in 1 mmol scale, giving **35** as a single diastereomer.[59] This reaction highlights the potential for application of the Mn-mediated radical addition in complex target synthesis. Efficient addition

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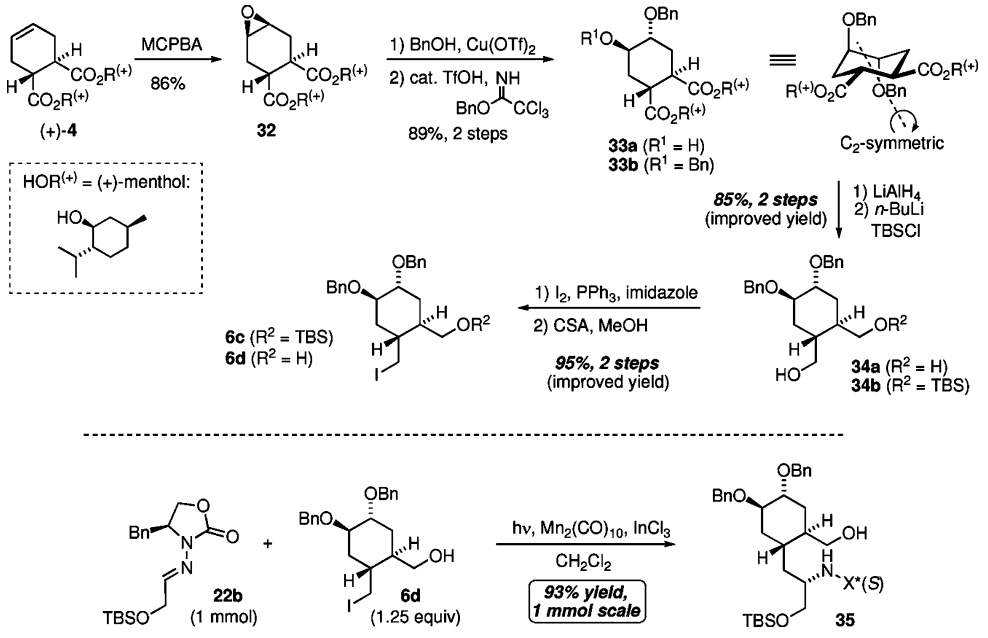
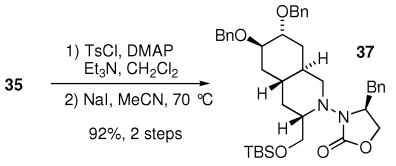
Scheme 13



of a multifunctional alkyl fragment such as **6d** to an imino compound by other existing methods is improbable.[60]

Completion of the hybrid radical–ionic annulation would ideally occur *in situ* during the Mn-mediated coupling, but this tandem process has not yet been reduced to practice. In stepwise fashion, the reactions proved efficient; treatment of **35** with TsCl afforded a tosylate (**36**, not shown), and cyclization occurred on exposure to NaI to provide decahydroisoquinoline **37** in 92% yield (eq 3).[61] Thus the hybrid radical–ionic



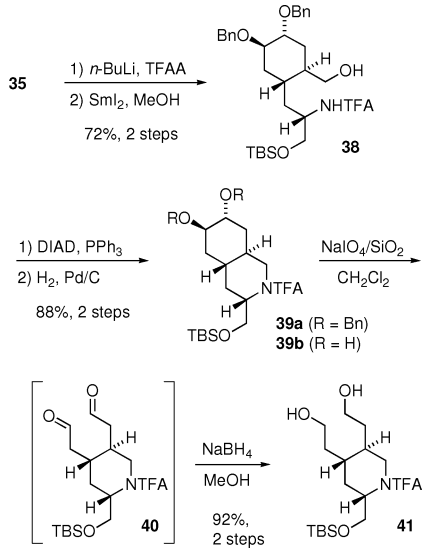
(3)

annulation sequence was accomplished in overall 85% yield for the three steps from **6d** and **22b**.

Cleavage of the N–N bond was required, and from piperidine **37** this proved disappointing. Although Enders' procedure, entailing heating with excess BH_3·THF, is often successful for such tasks, when applied to **37** it afforded a complex mixture. An extensive battery of catalytic hydrogenations on **37**, with and without added acid, with a variety of catalysts (PtO_2, $Pd(OH)_2$, Pd/C), and with pressures up to 950 psi, met with no success.

Fortunately, N–N bond cleavage could be addressed satisfactorily at a prior stage, before piperidine ring construction. Both the N–H and O–H bonds of **35** were functionalized by treatment with *n*-BuLi and TFAA (Scheme 14), resulting in a *N,O*-bis-trifluoroacetyl derivative that was subjected directly to reduction with SmI_2 in the presence of methanol. The trifluoroacetate ester hydrolyzed under these conditions to furnish trifluoroacetamide **38** in overall yield of 67% from **35** (1.7 mmol scale). Subjection of **38** to Mitsunobu conditions affected piperidine ring closure in efficient fashion, furnishing piperidine **39a** (R = Bn) in 95% yield (1.1 mmol scale). Hydrogenative debenzylation under Pd catalysis afforded corresponding diol **39b**.

Scheme 14



In preparation to forge the bicyclic quinuclidine ring system characteristic of the cinchona alkaloids, the vicinal diol **39b** (R = H) was exposed to sodium periodate, presumably forming an intermediate dialdehyde **40**. This labile material was not isolated but directly converted to diol **41** by borohydride reduction.

Quinuclidine Construction. Piperidine **41**, now possessing two nearly equivalent hydroxyethyl substituents, was next subjected to conditions expected to effect group-selective cyclization to furnish the azabicyclo[2.2.2]octane ring system required for quinine (Scheme 15). The diol functionality of **41** was quantitatively converted to the corresponding diiodide **42** via reaction with PPh_3 and I_2 in the presence of imidazole.[62] In methanolic ammonia, removal of the trifluoroacetyl group was accompanied by cyclization to **43a**; unfortunately, this was a mixture of bicyclic tertiary amines, the major component of which was assigned as azabicyclo[3.2.1]octane **43b**. Separation

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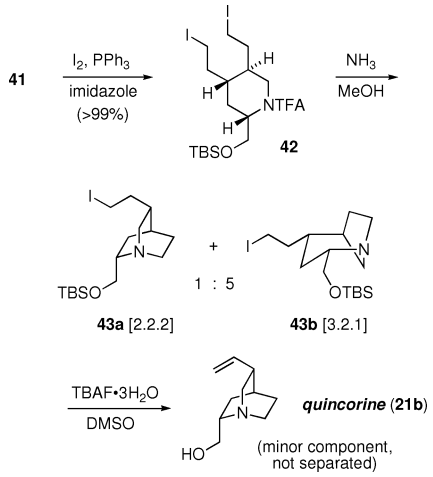
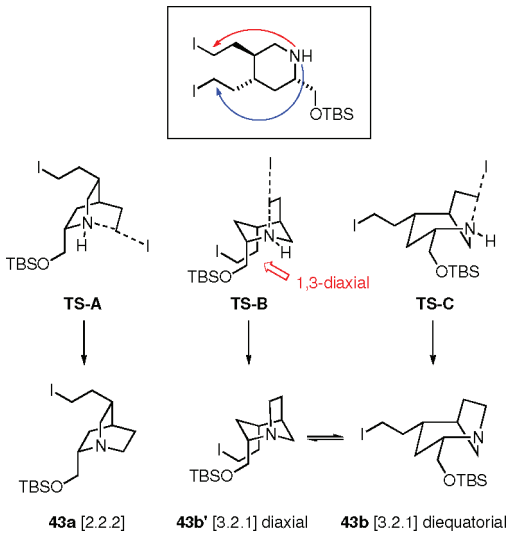
Scheme 15



of the desired azabicyclo[2.2.2]octane **43a** (minor) as a pure substance was not feasible at this point. However, treatment of the mixture with TBAF in DMSO afforded a product mixture containing a minor amount of quincorine (**21b**), the structure of which was confirmed by comparison of the ^{13}C NMR spectrum with an authentic sample.

Computational Study of Diiodide Cyclization. Though the cyclization of the diiodide served as a structural confirmation for its progenitors, the selectivity was disappointing and somewhat unexpected, as some preliminary modeling had suggested a preference for the desired azabicyclo[2.2.2]-octane ring system via **TS-A** (Scheme 16). In the transition

Scheme 16



state **TS-B** (Scheme 16), two substituents in a 1,3-diaxial relationship were expected to exhibit a significant van der Waals repulsion and therefore to kinetically disfavor the [3.2.1] cyclization product **42b**. The experiment clearly showed this is not the case. We suspected that another conformer of the [3.2.1] bicyclic system presents the two substituents in a pseudodiequatorial arrangement in a boatlike structure. Could this type of conformation offer a lower energy pathway via transition state **TS-C**, consistent with experimental observations? This question was investigated through computation.

Following a conformational search using a semiempirical PM3 method,[63,64] a series of low-energy conformers of the [2.2.2], [3.2.1] chair-diaxial, and [3.2.1] boat-diequatorial product isomers (**43a**, **43b′**, and **43b**, respectively; Scheme 16) were found. These were optimized in simulated methanol solution[65,66] using B3LYP functional[67] combined with 6-31G(d) basis set[68] on all atoms except iodine, for which the LANL2DZ basis set[69] was used. Results (Table 2) showed the

Table 2. Calculated Energies in Cyclizations of Diiodide 42 (Scheme 16)

entry	structure	Hartrees	E_{rel}, kcal/mol	population, %
1	**43a**, [2.2.2]	−1059.420813	0.00	95
2	**43b**, [3.2.1] diequatorial	−1059.417148	2.30	2
3	**43b′**, [3.2.1] diaxial	−1059.417546	2.05	3
4	**TS-A**, [2.2.2]	−1071.391446	1.80	3
5	**TS-C**, [3.2.1] diequatorial	−1071.394006	0.19	40
6	**TS-B**, [3.2.1] diaxial	−1071.394314	0.00	57

ground state (GS) of the [2.2.2] isomer was of significantly lower energy than either the [3.2.1] boat-diequatorial or [3.2.1] chair-diaxial structures; these three exhibited relative energies of 0.00, 2.30, and 2.05 kcal/mol, respectively. Boltzmann distributions were calculated to be 95%, 2%, and 3%, respectively, strongly favoring the [2.2.2] structure. This was not unexpected, considering the preliminary modeling considerations with which we had approached the experimental study.

Rather than simply refining the preliminary modeling, an examination of the transition states gave a quite different picture. From the calculated product structures, three transition state structures were found for the C−N bond construction via S_N2 displacement of iodide (Figure 2). Calculated relative energies showed a clear preference for the azabicyclo[3.2.1]-octane ring system; the transition state **TS-A** leading to the [2.2.2] system was 1.80 kcal/mol higher than the preferred transition state **TS-B** leading to **43b′**. The alternative transition state **TS-C**, leading to **43b**, was only 0.19 kcal/mol higher than **TS-B**. The calculated Boltzmann populations were 3%, 40%, and 57% for transition states leading to [2.2.2], [3.2.1] boat-diequatorial, and [3.2.1] chair-diaxial products, respectively. This distribution was quite different from that calculated from the ground state product structures and strongly favored the [3.2.1] product, consistent with the experimental results.

The concept of torsional steering was introduced by Houk to explain selectivities in additions to alkenes and carbonyl compounds: transition states that have a forming σ bond in a staggered conformation are stabilized relative to eclipsed transition states.[70] This concept has been used to rationalize unexpected selectivities in epoxidations[71] or cycloadditions[72] from more sterically hindered faces of alkenes. In the context of the cyclization of **42**, **TS-A** has a number of bonds eclipsed (Figure 2), while several of these same bonds are in staggered conformations in **TS-B** and **TS-C**. Although prior reports of torsional steering did not examine its impact on regioselectivity of S_N2 reactions, the concept appears to be consistent with our experimental and computational results.

These calculations suggested that a cyclization method employing thermodynamic control might invert the selectivity and efficiently access the [2.2.2] ring system based on its

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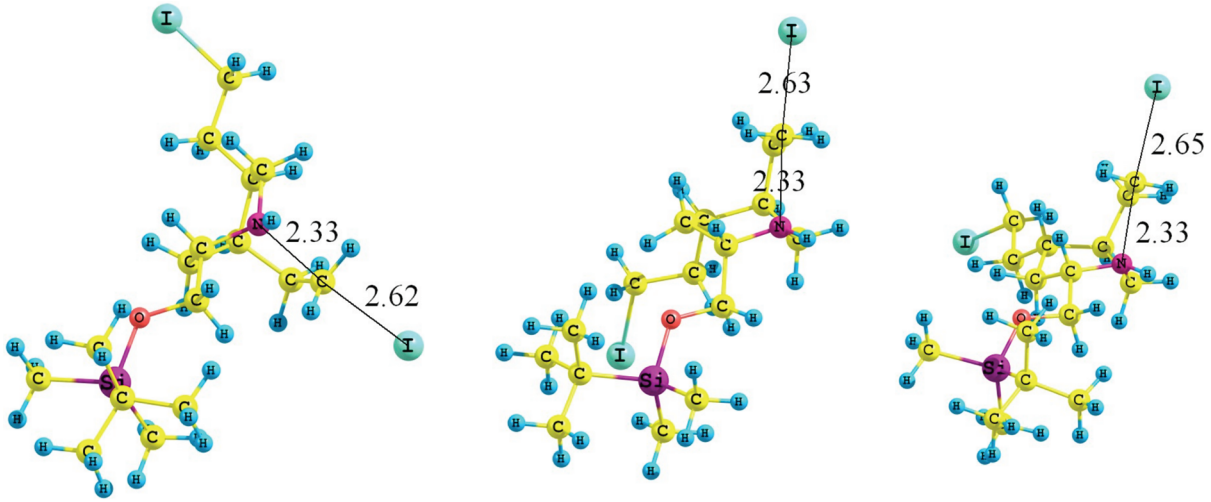


Figure 2. Calculated structures and relative energies of transition states **TS-A**, **TS-B**, and **TS-C** in the cyclization of diiodide **42** (Scheme 16). Bond lengths (in Å) at the site of reaction are shown.

ground-state stability. For example, a dialdehyde (i.e., **40**, Scheme 14) might be expected to cyclize reversibly to hemiaminal structures, from which the more stable [2.2.2] product isomer might be trapped via reduction. The potential of such a process could not be evaluated within the scope of this study; although dialdehyde **40** was an intermediate en route to diol **41** (Scheme 14), attempts to isolate the dialdehyde for further study were unsuccessful.

Regioconvergent Cyclization Pathways. A regio-convergent strategy was adopted as a practical alternative in order to complete the synthetic route. This strategy would simply differentiate the two hydroxyethyl groups at a prior stage, rendering moot the regioselectivity in the construction of the azabicyclic ring system.

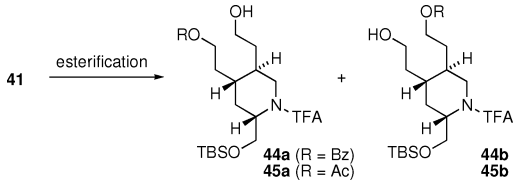
First, a simple monoesterification was examined as a means of differentiating the two hydroxyethyl groups of diol **41** (Scheme 17). Considering that these two primary alcohols are differentiated by their connectivity a full five bonds away from the oxygen, little regioselectivity was expected, but each of the regioisomeric esters **44a** and **44b** was envisioned to potentially converge to a single synthetic stream via two complementary sequences. Successive treatment with *n*-BuLi and benzoic anhydride afforded a moderate yield of the monobenzoates, and regioselectivity was observed to slightly favor **44b** (**b**/**a** = 1.6). Carrying out the reaction to partial conversion using Et_3N and BzCl gave low yield and low mass balance and was not further examined.

Attempted Enzymatic Group Differentiation. The potential of biocatalytic transformation of diol **41** to a single monoester also attracted our attention. We envisioned exploiting the substrate selectivity potential of enzymatic esterification to discriminate the two hydroxyethyl groups. To our knowledge there are no prior examples of reagent control in a regioselectivity problem of this type, in which the point of differentiation is so distant from the reactive site.[73] As an initial feasibility test, the diol was exposed to an excess of vinyl acetate in the presence of *Candida antarctica* lipase, with careful TLC monitoring to avoid significant amounts of bis-esterification. Under these conditions (Scheme 17), up to 64% yield of a mixture of monoesters **45a** and **45b** was obtained in a 1.2:1 ratio, along with 32% of starting material (94% yield based on conversion). Although the ratio was disappointing from a synthetic perspective, the experiment draws further attention to a more fundamental question regarding the sensitivity of lipase esterification to remote structural differences. The modest substrate regiocontrol observed with the achiral reagent system (*n*-BuLi/BzCl) was reversed by the enzyme-catalyzed acylation, showing some potential for remote regio- and/or stereocontrol in group-selectivity problems of this type.

Formal Synthesis. Both regioisomeric monoacetates **45a** and **45b** (R = Ac) were readily processed via standard transformations into the same bicyclic quinuclidine ring system, which served as additional confirmation of their structures.

The free hydroxyl of **45a** could be dehydrated under the Grieco conditions,[74] and the crude product was subjected to saponification and trifluoroacetamide hydrolysis to afford amino alcohol **46** (Scheme 18). Conditions expected to convert the hydroxyl group to bromide or iodide led to in situ cyclization of this material, affording a tertiary amine retaining one alcohol under silyl protection. This substance was presumed to contain the azabicyclo[2.2.2]octane ring system,

Scheme 17



Conditions	Product	Yield[a,b]	a:b
n-BuLi (1 equiv), Bz_2O	**44**	50% (69%)	39:61
Et_3N, BzCl (1 equiv)	**44**	13% (26%)[c]	--
Novozyme-435,[d] vinyl acetate	**45**	64% (94%)	55:45

[a]Combined isolated yield of mixture.

[b]In parentheses: yield based on conversion.

[c]The bis-benzoyl product was obtained in 11% yield along with 50% recovered diol.

[d]*Candida antarctica* lipase on acrylic resin.

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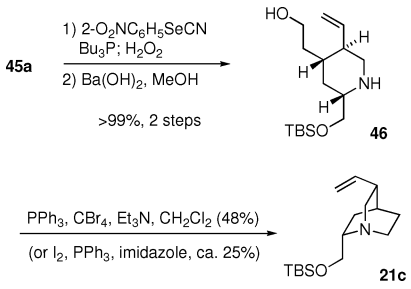
Scheme 18



and structure **21c** (*O*-TBS-quincorine) was eventually confirmed upon desilylation and comparison with an authentic sample of quincorine. Yields of these reactions were disappointing, however. The free amine was viewed as an impediment, perhaps by interfering at the stage of alcohol halogenation.

An alternative route was devised in order to install the halogen while the amine retained its trifluoroacetamide protection. For **45a**, such a sequence dramatically improved the efficiency (Scheme 19). First, the free hydroxyl was eliminated via the selenoxide,[74] affording the required vinyl group. Next, the acetate was hydrolyzed selectively upon exposure to sodium methoxide in methanol, with careful monitoring of the reaction progress. Under these conditions, the trifluoroacetamide was preserved, and alcohol **48** was obtained in excellent yield (92%, 2 steps). Conversion of the resulting alcohol to iodide (I_2, PPh_3) then facilitated an efficient cyclization in methanolic ammonia, affording *O*-silyl quincorine derivative **21c** in 83% yield.

The other regioisomeric acetate **45b** was submitted to a similar series of transformations, in a different order (Scheme 19). Conversion of the free hydroxyl group to the corresponding iodide (I_2, PPh_3, imidazole) and cyclization in methanolic ammonia established the azabicyclo[2.2.2]octane ring system, which was isolated as alcohol **47** after removal of the acetate ($Ba(OH)_2$, MeOH). Dehydration via the selenoxide elimination then provided **21c**.

After disilylation (TBAF), the material obtained from both sequences was found to match an authentic sample of quincorine (**21b**). The latter has previously been converted to quinine,[52,75] and thus this route constitutes a formal synthesis of quinine.

CONCLUSION

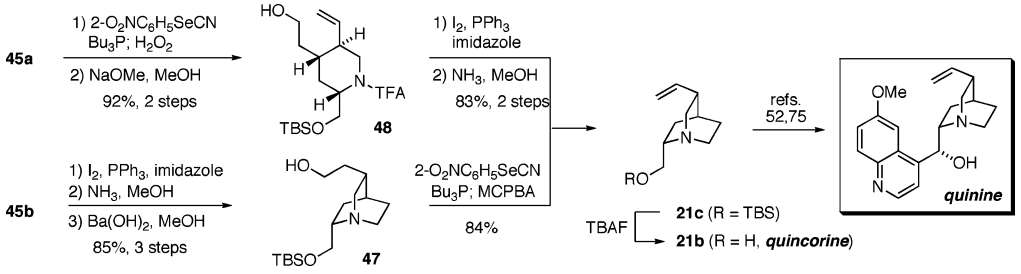
The Mn-mediated radical addition of alkyl iodides to chiral *N*-acylhydrazones was successfully applied in a formal synthesis of quinine, testing the limits of intermolecular radical addition to imino compounds as a strategic bond construction. Functional group incompatibilities were noted with pyridine and alkene moieties in the early efforts, which necessitated some revision to the original strategy for quinine. In the successful route, the Mn-mediated radical addition produced 93% yield of a single diastereomeric adduct, forging the key C−C bond at the chiral amine stereogenic center. Subsequent transformations raised interesting questions regarding an unusual case of group selectivity, and these were resolved by a combination of transition state calculations and strategic design of a regioconvergent synthetic route to efficiently produce quincorine and complete the formal synthesis.

There are very few applications of intermolecular radical additions to imino compounds as key strategic bond constructions in alkaloid synthesis.[76] As shown in this formal synthesis of quinine, our Mn-mediated additions to chiral *N*-acylhydrazones complement the functional group compatibilities of carbanion reagents. These Mn-mediated additions, applied in the most complex multifunctional setting to date, address an unmet need to demonstrate the power and broad reliability of intermolecular radical addition to imino compounds.

EXPERIMENTAL SECTION

Materials and Methods. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF, diethyl ether, benzene, and toluene were distilled from sodium/benzophenone ketyl under argon. CH_2Cl_2 was distilled from CaH_2 under argon or nitrogen. Alternatively, these solvents were purchased inhibitor-free and were sparged with argon and passed through columns of activated alumina prior to use (dropwise addition of blue benzophenone ketyl solution revealed the THF purified in this manner sustained the blue color more readily than the control sample purified by distillation). Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230−400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient from hexane to the indicated solvent. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed with a Chromatotron using commercially supplied rotors. Melting points are uncorrected. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies indicated in the text and are reported in units of ppm. Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission methods or by use of an attenuated total reflectance (ATR) probe. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low resolution mass spectra were obtained using sample introduction by dip, liquid chromatography, or gas chromatography.

Scheme 19



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High resolution mass spectra and combustion analyses were obtained from external commercial and institutional services. Chromatographic diastereomer ratio analyses employed GC–MS with 15 m × 0.25 mm × 0.25 μm (l × i.d. × f.t.) 5%-phenyl-95%-dimethylsiloxane column and helium as mobile phase or HPLC with Microsorb-MV Si 8 μm 100A or Chiralcel OD columns (2-propanol/hexane as mobile phase) or Chirex 3014 column (chloroform/hexane as mobile phase).

((1*R*,6*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)cyclohex-3-enyl)methanol ((−)-5). To a solution of ((1*R*,6*R*)-6-(hydroxymethyl)cyclohex-3-enyl)methanol[77] (891 mg, 6.28 mmol) in THF (40 mL) was added *n*-BuLi (2 M in hexane, 3.50 mL, 7.0 mmol) at 0 °C. After warming to room temperature for 80 min, TBSCl (947 mg, 6.28 mmol) was added, and the mixture was stirred overnight. The reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (hexane/EtOAc 7:1 to 1:1) to afford alcohol (−)-**5** (1.60 g, 99% yield) as a colorless oil. $[\alpha]^{30}_D$ −30.2 (*c* 4.6, $CHCl_3$); IR (film) 3371, 3024, 2955, 2929, 2899, 2857, 1472, 1436, 1361, 1256, 1102, 998 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75–5.55 (m, 2H), 3.80–3.43 (m, 4H), 3.42–2.87 (br s, 1H), 2.06–1.88 (m, 3H), 1.82–1.56 (m, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.6, 125.6, 67.0, 65.7, 40.5, 39.1, 28.7, 28.5, 25.8, 18.1, −5.6, −5.5; MS (CI) *m*/*z* (relative intensity) 257 ($[M + H]^+$, 66%), 107 (100%). The antipode (+)-**5** was prepared by the same procedure from ((1*S*,6*S*)-6-(hydroxymethyl)-cyclohex-3-enyl)methanol in 93% yield; $[\alpha]^{21}_D$ +31.6 (*c* 3.22, $CHCl_3$).

((1*R*,6*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)cyclohex-3-enyl)methanol ((−)-6a). To a solution of alcohol (−)-**5** (150 mg, 0.59 mmol) in CH_2Cl_2 (6 mL) were added imidazole (100 mg, 1.46 mmol) and PPh_3 (309 mg, 1.18 mmol). After 10 min, I_2 (300 mg, 1.18 mmol) was added in two portions over 10 min. After 15 min, the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $Na_2S_2O_3$. The organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (hexane/EtOAc 10:1 to 3:1) to afford iodide (−)-**6a** as a colorless liquid (186 mg, 86% yield). $[\alpha]^{27}_D$ −95.0 (*c* 4.4, $CHCl_3$); IR (film) 3025, 2954, 2928, 2897, 2856, 1471, 1462, 1256, 1107, 982 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68–5.54 (m, 2H), 3.67 (dd, *J* = 9.8, 4.1 Hz, 1H), 3.54 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.39 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.32 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.18–1.92 (m, 4H), 1.76–1.66 (m, 1H), 1.66–1.56 (m, 1H), 0.90 (s, 9H), 0.05 (d, *J* = 2.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.1, 125.0, 64.2, 39.6, 35.2, 31.1, 27.0, 25.9, 18.2, 14.9, −5.5; MS (CI) *m*/*z* (relative intensity) 367 ($[M + H]^+$, 26%), 239 (80%), 107 (100%). The antipode (+)-**6a** was prepared by the same procedure from (+)-**2** in 81% yield; $[\alpha]^{21}_D$ +54 (*c* 5.1, $CHCl_3$).

((1*S*,6*S*)-6-(Iodomethyl)cyclohex-3-enyl)methanol (6b). A solution of (+)-**6a** (160 mg, 0.43 mmol) and camphorsulfonic acid (9 mg, 0.04 mmol) in methanol (3 mL) was stirred for 4 h at room temperature. Concentration and flash chromatography (hexane/EtOAc 20:1 to 2:1) yielded **6b** (92 mg, 85% yield) as a colorless oil; $[\alpha]^{23}_D$ +48.28 (*c* 1.11, $CHCl_3$); 3553, 3022, 2895, 2837, 1432, 1182, 1061, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.55 (m, 2H), 3.74–3.62 (m, 2H), 3.45–3.35 (m, 2H), 2.87 (br s, 1H), 2.16–1.92 (m, 4H), 1.85–1.77 (m, 1H), 1.67–1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.6, 125.2, 64.9, 39.4, 35.4, 30.7, 26.5, 14.8; MS (EI) *m*/*z* (relative intensity) 252 (M^+, 1%), 234 ($[M - H_2O]^+$, 4%), 125 ($[M - I]^+$, 20%).

(±)-*trans*-(2-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexyl)-methanol ((±)-5[H]). To a solution of (±)-*trans*-2-(hydroxymethyl)-cyclohexylmethanol[57] (533 mg, 3.69 mmol) in THF (16 mL) was added *n*-BuLi (1.6 M in hexane, 2.4 mL, 3.87 mmol) at 0 °C. After warming to room temperature for 80 min under N_2, *tert*-butyldimethylsilyl chloride (556 mg, 3.69 mmol) was added. After ca. 12 h, the reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (hexane/EtOAc 10:1 to 2:1) afforded alcohol (±)-**5**[**H**][78] (955 mg, >99% yield) as a colorless oil; IR (film) 3362, 2927, 2856, 1471, 1388, 1255, 1110, 1066, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (br s, 1H), 3.51–3.35 (m, 4H), 1.69–1.65 (m, 2H), 1.59–1.51 (m, 2H), 1.26–0.90 (m, 6H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.6, 67.4, 45.5, 44.1, 30.2, 29.9, 26.28, 26.26, 25.9, 18.3, −5.3, −5.4. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.07; H, 11.80.

***tert*-Butyl((2-(iodomethyl)cyclohexyl)methoxy)-dimethylsilane ((±)-6a[H]).** To a solution of alcohol (±)-**5**[**H**] (955 mg, 3.69 mmol) in CH_2Cl_2 were added imidazole (628 mg, 9.22 mmol) and triphenylphosphine (1.94 g, 7.39 mmol). After 10 min, iodine (1.87 g, 7.39 mmol) was added in two portions over 10 min. After 15 min, the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $Na_2S_2O_3$. The organic phase was dried (Na_2SO_4), concentrated, and purified by gradient flash chromatography (hexane to 10:1 hexane/EtOAc) to afford iodide (±)-**6a**[**H**] (972 mg, 72% yield) as a colorless oil; IR (film) 2953, 2925, 2854, 1470, 1386, 1255, 1107, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.48 (dd, *J* = 10.1, 1.9, 1 H), 3.39 (dd, *J* = 9.8, 2.5, 1H), 3.29 (dd, *J* = 9.7, 5.4, 1H), 1.78–1.60 (m, 4H), 1.27–1.09 (m, 6H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.3, 44.0, 39.3, 33.4, 29.5, 26.3, 26.1, 25.9, 18.5, 17.1, −5.24, −5.25; MS (EI) *m*/*z* (relative intensity) 311 ($[M - t\text{-Bu}]^+$, 93%), 241 ($[M - I]^+$, 10%). Anal. Calcd for $C_{14}H_{29}IOSi$: C, 45.65; H, 7.94. Found: C, 45.91; H, 8.13.

(2-(Iodomethyl)cyclohexyl)methanol ((±)-6b[H]). A solution of (±)-**6a**[**H**] (410 mg, 1.12 mmol) and camphorsulfonic acid (30 mg, 0.1 mmol) in methanol (5 mL) was stirred for 4 h at room temperature. Concentration and flash chromatography (hexane/EtOAc 9:1 to 2:1) yielded (±)-**6b**[**H**] (265 mg, 93% yield) as a colorless oil; IR (film) 3338, 2921, 2852, 1446, 1292, 1240, 1183, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59–3.49 (m, 2H), 3.35–3.26 (m, 2H), 3.19 (s, 1H), 1.75–1.60 (m, 4H), 1.29–1.10 (m, 5H), 1.10–0.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.1, 43.6, 39.0, 33.2, 29.0, 25.9, 25.6, 16.9; MS (EI) *m*/*z* (relative intensity) 254 (M^+, 1%), 127 ($[M - I]^+$, 38%).

2-(6-Methoxyquinolin-4-yl)ethanol (8). A solution of LDA (0.87 mmol) was prepared by addition of *n*-BuLi (0.87 mmol, 2 M in hexane) to a solution of diisopropylamine (0.122 mL, 0.87 mmol) in THF (1 mL) at 0 °C. The LDA solution was cooled to −78 °C, and a solution of 6-methoxy-4-methylquinoline[47] (100 mg, 0.58 mmol) in THF/HMPA (5 mL/0.5 mL) was added. After 40 min, the reaction was warmed to 0 °C and stirred at this temperature for 4 h. The resulting solution was added slowly to a suspension of paraformaldehyde (190 mg, 6.3 mmol) in THF at −10 °C. After 40 min the mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4), concentrated, and purified by gradient flash chromatography (hexane/ethyl acetate) to afford alcohol **8** (71 mg, 0.35 mmol, 61% yield) as a colorless oil; IR (film) 3236, 2937, 2876, 2834, 1621, 1592, 1511, 1474, 1431, 1367, 1241, 1229, 1176, 1086, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.5 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.18 (dd, *J* = 9.4, 3.0 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 7.06 (d, *J* = 4.5 Hz, 1H), 4.97–4.85 (br s, 1H), 3.99 (dd, *J* = 6.8, 6.8 Hz, 2H), 3.77 (s, 3H), 3.16 (dd, *J* = 6.4, 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 146.9, 144.2, 143.6, 130.7, 128.6, 121.8, 121.4, 101.8, 61.3, 55.4, 35.6; MS (CI) *m*/*z* (relative intensity) 204 ($[M + H]^+$, 100%); HRMS (EI) calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0940.

Quininaldehyde (10). A mixture of 6-methoxy-4-methylquinoline[47] (3.19 g, 18.5 mmol), *tert*-butyl iodide (0.66 mL, 5.5 mmol), iodine (5.63 g, 22.15 mmol), $FeCl_2 \cdot 4H_2O$ (219 mg, 1.11 mmol), and trifluoroacetic acid (1.71 mL, 22.15 mmol) in DMSO (80 mL) was heated at 85–95 °C for 10 h. After cooling to ambient temperature, solvent was removed under vacuum. The residue was taken up in ether and washed with 20% aqueous $Na_2S_2O_3$ and 10% aqueous K_2CO_3. After each wash, aqueous phase was extracted with ether and CH_2Cl_2. Combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash chromatography (hexane/EtOAc 1:1 to 1:4) to give **10**[50] (2.5 g, 77% yield) as a light brown solid. A sample recrystallized from water gave fine yellow needles; mp 92–97 °C (lit. mp 92–97 °C[7]; 97–97.5 °C[79]); ^1H NMR ($CDCl_3$, 500 MHz) δ 10.42 (s, 1H), 9.03 (d, *J* = 4.3 Hz, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.09 (d, *J* = 9.3 Hz,

dx.doi.org/10.1021/jo2026349 | *J. Org. Chem.* 2012, 77, 3159–3180

1H), 7.73 (d, J = 4.3 Hz, 1H), 7.45 (dd, J = 9.2, 2.8 Hz, 1H), 4.00 (s, 3H).

(*S*)-3-(2-(6-Methoxyquinolin-4-yl)ethylideneamino)-4-benzyloxazolidin-2-one (12): Bredereck Homologation Method. A solution of 6-methoxy-4-methylquinoline (600 mg, 3.47 mmol) and *tert*-butoxybis(dimethylamino)methane (1.79 mL, 8.68 mmol) in DMF (5.5 mL) was heated at 130 °C under N_2 for 12 h. The solvent was removed by vacuum distillation. To the oily residue were added (*S*)-**1** (573 mg, 2.98 mmol) in EtOH (10 mL) and 5 N HCl (3.5 mL), and the mixture was heated at reflux for 4 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried with Na_2SO_4. Concentration and gradient flash chromatography (hexane/EtOAc 1:1 to 1:4) afforded **12** (800 mg, 2.13 mmol, 62%) as light brown oil. $[\alpha]^{23}_D$ +8.6 (c 1.0, $CHCl_3$); IR (film) 3007, 2930, 1769, 1620, 1591, 1508, 1403, 1365, 1241, 1216, 1081, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 4.9, 4.9 Hz, 1H), 8.05 (d, J = 9.8 Hz, 1H), 7.05 (d, J = 6.4 Hz, 2H), 7.43−7.16 (m, 7H), 4.37−4.27 (m, 1H), 4.22 (dd, J = 8.7, 8.7 Hz, 1H), 4.13−4.02 (m, 3H), 3.93 (s, 3H), 3.13 (dd, J = 13.9, 3.8 Hz, 1H), 2.77 (dd, J = 13.9, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 154.1, 151.2, 147.2, 147.0, 143.9, 141.1, 134.9, 131.2, 129.1, 128.9, 128.5, 127.3, 122.1, 121.9, 101.9, 65.8, 57.6, 55.6, 37.3, 36.9; MS (CI) m/z (relative intensity) 376 ($[M + H]^+$, 100%); HRMS (EI) calcd for $C_{22}H_{21}N_3O_3$ 375.1583; found 375.1587.

***N*-Acylhydrazone 12: Alternative Wittig Homologation Method.** A portion of **10** (494 mg, 2.64 mmol) in THF was added via cannula to a mixture of methoxymethyltriphenylphosphorane (2.26 g, 6.6 mmol) and *t*-BuOK (1.48 g, 13.2 mmol) in THF (20 mL) at 0 °C. After 30 min, the mixture was partitioned between water and ether. The organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (hexane/EtOAc 1:4) to furnish enol ether **11** as a colorless oil (400 mg, inseparable mixture of diastereomers). To a solution of **11** (46 mg, 0.214 mmol) in ethanol (3 mL) were added (*S*)-**1** (53 mg, 0.276 mmol) and aqueous HCl (5N, 0.2 mL, 1 mmol), and the mixture was stirred at reflux overnight. The mixture was partitioned between ether and saturated aqueous $NaHCO_3$, and the organic phase was dried (Na_2SO_4) and concentrated to afford an inseparable mixture of **12** and unreacted (*S*)-**1**. This mixture was taken up in CH_2Cl_2 and treated with propionaldehyde (15 μL) and $TsOH{\cdot}H_2O$ (5 mg) for 5 min, converting remaining (*S*)-**1** to the propionaldehyde hydrazone. After washing with water, drying (Na_2SO_4), and concentration, flash chromatography furnished **12** (25 mg, 31% yield).

Preparation of Hydrazones (General Procedure A). To a solution of 3-amino-4-phenylmethyl-2-oxazolidone in CH_2Cl_2 were added $TsOH{\cdot}H_2O$ (5 mol %) and the appropriate aldehyde at room temperature. When the reaction was complete (TLC), concentration and flash chromatography (e.g., hexane/EtOAc 4:1 to 1:1) furnished the hydrazone. Only the (*E*)-isomer was detected.

(*S*)-3-(2-Phenylethylideneamino)-4-benzyloxazolidin-2-one (16a). From (*S*)-**1** (120 mg, 0.625 mmol) and phenylacetaldehyde (74 μL, 0.625 mmol) by General Procedure A was obtained **16a** (150 mg, 0.51 mmol, 82% yield) as a colorless oil; $[\alpha]^{27}_D$ −3.3 (c 2.7, $CHCl_3$); IR (film) 3062, 3028, 2917, 1769, 1603, 1496, 1454, 1402, 1290, 1213, 1083, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, J = 6.0, 6.0 Hz, 1H), 7.44−7.21 (m, 8H), 7.15 (d, J = 6.8 Hz, 2H), 4.42−4.33 (m, 1H), 4.24 (dd, J = 8.3, 8.3 Hz, 1H), 4.10 (dd, J = 9.0, 5.3 Hz, 1H), 3.72 (d, J = 5.7 Hz, 2H), 3.23 (dd, J = 13.6, 3.8 Hz, 1H), 2.83 (dd, J = 13.6, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 153.9, 136.2, 135.2, 129.3, 128.9, 128.9, 128.8, 127.2, 126.9, 65.7, 57.6, 39.9, 37.2; MS (CI) m/z (relative intensity) 295 ($[M + H]^+$, 100%). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.19; N, 9.53.

(*S*)-3-(2-(Pyridin-4-yl)ethylideneamino)-4-benzyloxazolidin-2-one (16c). A solution of 4-picoline (0.5 mL, 5.16 mmol) and *tert*-butoxybis(dimethylamino)methane (2.14 mL, 10.32 mmol) in DMF (2 mL) was heated at 130 °C under N_2 for 12 h. Removal of solvent by vacuum distillation afforded enamine product (740 mg, 5 mmol, 93% yield) as a yellow solid. A solution of enamine product (72 mg, 0.49 mmol) and (*S*)-**1** (80 mg, 0.42 mmol) in EtOH (2 mL) and 5 N HCl (0.42 mL) was heated at reflux for 4 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried with Na_2SO_4. Concentration and gradient flash chromatography (EtOAc to EtOAc/MeOH 20:1) afforded **16c** (80 mg, 0.271 mmol, 65%) as a colorless oil; $[\alpha]^{25}_D$ +5.3 (c 6.0, $CHCl_3$); IR (film) 3028, 2921, 1768, 1600, 1497, 1403, 1216, 1091, 1069, 994 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 6.0 Hz, 2H), 8.15 (dd, J = 6.4, 6.4 Hz, 1H), 7.30−7.19 (m, 3H), 7.16 (d, J = 5.7 Hz, 2H), 7.10 (d, J = 6.8 Hz, 2H), 4.37−4.29 (m, 1H), 4.21 (dd, J = 7.9, 7.9 Hz, 1H), 4.05 (dd, J = 9.1, 5.3 Hz, 1H), 3.66 (d, J = 5.7 Hz, 2H), 3.17 (dd, J = 13.6, 4.1 Hz, 1H), 2.79 (dd, J = 13.94, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 151.7, 150.1, 149.9, 145.4, 135.1, 129.2, 128.8, 127.2, 124.2, 65.8, 57.8, 39.0, 37.4; MS (CI) m/z (relative intensity) 296 ($[M + H]^+$, 100%); HRMS (EI) calcd for $C_{17}H_{17}N_3O_2$ 295.1321; found 295.1327.

Radical Addition (General Procedure B). Using standard pyrex glassware, a solution of the hydrazone in CH_2Cl_2 (0.02 M) or in benzene/CH_3CN (10:1 v/v, 0.1 M) was deoxygenated (N_2 or Ar was bubbled through the solution via a syringe needle for ca. 30 min); then $InCl_3$ (dried for ca. 12 h at 0.1 mmHg prior to use, 2.2 equiv) was added. After 40 min at room temperature, the appropriate alkyl iodide (passed through basic alumina prior to use, 1.2−10 equiv) and $Mn_2(CO)_{10}$ (1.2 equiv) were added, and the mixture was irradiated (Rayonet photochemical reactor, 300 nm) for 10−20 h. Triethylamine (5 equiv) was added, and the mixture was stirred for 40 min and concentrated. Flash chromatography (hexane/EtOAc 9:1 to 1:1) afforded *N*-acylhydrazines. Unless otherwise noted, the minor diastereomers were not detected.

(*S*)-3-(6-(*tert*-Butyldimethylsilyloxy)-1-phenylhexan-2-ylamino)-4-benzyloxazolidin-2-one (19a). From phenylacetaldehyde hydrazone **16a** (97 mg, 0.33 mmol) and iodide **18** (0.13 mL, 0.50 mmol) according to General Procedure B in benzene/CH_3CN was obtained hydrazine **19a** (63 mg, 0.130 mmol, 40% yield, >98:2 dr, ^1H NMR analysis) as a colorless oil; $[\alpha]^{29}_D$ +18.5 (c 2.8, $CHCl_3$); IR (film) 3286, 3063, 3028, 2929, 2857, 1760, 1472, 1497, 1396, 1251, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.17 (m, 8H), 7.07 (d, J = 7.5 Hz, 2H), 4.05−3.99 (br s, 1H), 3.94 (d, J = 6.4 Hz, 2H), 3.70−3.56 (m, 3H), 3.41−3.32 (m, 1H), 3.11 (dd, J = 13.6, 3.8 Hz, 1H), 2.85−2.70 (m, 2H), 2.48 (dd, J = 13.2, 10.2 Hz, 1H), 1.61−1.39 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 139.3, 135.9, 129.2, 129.1, 128.9, 128.5, 127.0, 126.3, 65.7, 62.9, 60.6, 59.2, 39.9, 36.8, 33.0, 32.7, 26.0, 22.0, 18.3, −5.2; MS (CI) m/z (relative intensity) 484 ($[M + H]^+$, 100%). Anal. Calcd for $C_{28}H_{42}N_2O_3Si$: C, 69.67; H, 8.77; N, 5.80. Found: C, 69.69; H, 8.84; N, 5.81.

(*S*)-3-(6-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxyphenyl)-hexan-2-ylamino)-4-benzyloxazolidin-2-one (19b). From (*S*)-**1** (120 mg, 0.63 mmol) and *p*-methoxyphenylacetaldehyde (189 mg, 1.26 mmol) by General Procedure A, with rapid elution through silica gel, was obtained a partially purified sample of **16b** (204 mg, ca. 70% yield) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (t, J = 5.9 Hz, 1H), 7.33−7.13 (m, 7H), 6.87 (d, J = 8.6 Hz, 2H), 4.40−4.33 (m, 1H), 4.26−4.20 (m, 1H), 4.10−4.03 (m, 1H), 3.80 (s, 3H), 3.65 (d, J = 5.8 Hz, 2H), 3.23 (dd, J = 8.3, 3.5 Hz, 1H), 2.81 (dd, J = 8.2, 5.3 Hz, 1H). Despite numerous attempts, this material could not be further purified without extensive decomposition. From hydrazone **16b** (65 mg, 0.20 mmol) and iodide **18** (80 μL, 0.30 mmol) according to General Procedure B in benzene/CH_3CN was obtained hydrazine **19b** (40 mg, 0.078 mmol, 39% yield, 2.9:1 dr, ^1H NMR analysis) as a colorless oil; IR (film) 3492, 3028, 2932, 2857, 1758, 1612, 1513, 1410, 1248, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) major isomer δ 7.30 (dd, J = 8.3, 8.3 Hz, 2H), 7.24 (dd, J = 7.9, 7.9 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 7.2 Hz, 2H), 6.85 (dd, J = 8.7, 2.3 Hz, 2H), 4.03−3.92 (m, 2H), 3.80−3.55 (br s, 1H), 3.77 (s, 3H), 3.74−3.55 (m, 3H), 3.35−3.25 (m, 1H), 3.13 (dd, J = 13.6, 3.4 Hz, 1H), 2.80−2.64 (m, 2H), 2.49 (dd, J = 13.2, 10.2 Hz, 1H), 1.63−1.38 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H); minor isomer: 0.91 (s, 9H), 0.10 (s, 6H), some resonances not reported due to overlap with major isomer; ^{13}C NMR (125 MHz, $CDCl_3$) major isomer δ 158.5, 158.1, 135.9, 131.0, 130.0, 129.0, 128.8, 127.0, 113.9, 65.7, 62.9, 60.5, 59.0, 55.2, 38.8, 36.8, 32.9,

dx.doi.org/10.1021/jo2026349 | J. Org. Chem. 2012, 77, 3159−3180

32.5, 25.9, 21.9, 18.3, −5.3; minor isomer δ 135.8, 130.9, 62.4, 60.4, 58.8, 38.9, 36.7, 32.6, 32.3, 25.6, 21.5, −3.6, some resonances not reported due to overlap with major isomer; MS (CI) *m*/*z* (relative intensity) 514 ([M + H]$^+$, 100%). Anal. Calcd for $C_{29}H_{44}N_2O_4Si$: C, 67.93; H, 8.65; N, 5.46. Found: C, 67.81; H, 8.55; N, 5.39.

(*S*,*E*)-4-Benzyl-3-(2-(*tert*-butyldimethylsilyloxy)-ethylideneamino)oxazolidin-2-one (22b). From (*S*)-3-amino-4-phenylmethyl-2-oxazolidinone (760 mg, 3.95 mmol) and glycolaldehyde dimer (475 mg, 3.95 mmol) by General Procedure A was obtained the glycolaldehyde hydrazone (825 mg, 89%) as a colorless liquid. To this alcohol (825 mg, 3.52 mmol) and imidazole (480 mg, 7.04 mmol) in a solution of CH_2Cl_2 (16 mL) was added *tert*-butyldimethylsilyl chloride (530 mg, 3.52 mmol) at room temperature. After 4 h, the reaction mixture was diluted with CH_2Cl_2, washed successively with water and brine, and dried (Na_2SO_4). Concentration and flash chromatography (hexane/EtOAc 9:1 to 1:1) afforded **22b** (1.12 g, 92% yield) as a colorless liquid; $[\alpha]^{23}_D$ +8.76 (*c* 1.78, $CHCl_3$); IR (film) 3029, 2953, 2928, 2856, 1777, 1764, 1472, 1406, 1361, 1251, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (t, *J* = 4.7 Hz, 1H), 7.23−7.14 (m, 3H), 7.05−7.03 (m, 2H), 4.29 (d, *J* = 4.6 Hz, 2H), 4.26−4.23 (m, 1H), 4.12 (t, *J* = 8.8 Hz, 1H), 3.99 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.12 (dd, *J* = 13.8, 3.4 Hz, 1H), 2.68 (dd, *J* = 13.8, 8.8 Hz, 1H), 0.80 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 152.7, 135.2, 129.4, 129.1, 127.5, 65.9, 63.9, 57.4, 37.0, 26.0, 18.5, −5.0 (2C); MS (ESI) *m*/*z* (relative intensity) 348 (M$^+$, 34%).

2-((1*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)cyclohex-3-enyl)acetonitrile (23). A solution of (+)-**6a** (1.409 g, 3.85 mmol) and potassium cyanide (501 mg, 7.7 mmol) in dimethyl sulfoxide (25 mL) was heated at 40 °C for ca. 12 h. The reaction mixture was partitioned between water and diethyl ether. The organic phase was washed successively with brine and water, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc 20:1 to 9:1) furnished **23** (980 mg, 96% yield) as a colorless oil; $[\alpha]^{25}_D$ +60.5 (*c* 1.55, $CHCl_3$); IR (film) 3027, 2954, 2927, 2856, 2238, 1411, 1437, 1254 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67−5.58 (m, 2H), 3.65 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.51 (dd, *J* = 10.4, 5.1 Hz, 1H), 2.48 (d, *J* = 5.00 Hz, 2H), 2.28−2.21 (m, 1H), 2.10−1.95 (m, 4H), 1.80−1.71 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.3, 124.7, 119.1, 64.5, 38.7, 31.9, 29.9, 27.2, 25.9, 21.4, 18.3, −5.3, −5.4; MS (EI) *m*/*z* (relative intensity) 266 ([M + 1]$^+$, 1%). Anal. Calcd for $C_{15}H_{27}NOSi$; C, 67.87; H, 10.25; N, 5.28. Found: C, 67.83; H, 10.34; N, 5.38.

2-((1*R*,6*S*)-6-(Hydroxymethyl)cyclohex-3-enyl)acetonitrile (24). A solution of **23** (855 mg, 3.22 mmol) and camphorsulfonic acid (0.1 g, 0.5 mmol) in methanol (10 mL) was stirred for 4 h at room temperature. Concentration and flash chromatography (hexane/EtOAc 10:1 to 1:1) yielded **24** (420 mg, 85% yield) as a colorless oil; $[\alpha]^{25}_D$ +88.5 (*c* 3.19, $CHCl_3$); IR (film) 3423, 3023, 2904, 2251, 1426, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66−5.57 (m, 2H), 3.67−3.55 (m, 2H), 2.50−2.48 (m, 2H), 2.26−2.20 (m, 1H), 2.20−1.91 (m, 5H), 1.81−1.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.9, 124.6, 119.2, 64.5, 38.6, 31.9, 29.6, 26.7, 21.5; MS (EI) *m*/*z* (relative intensity) 151 (M$^+$, 1%); 133 ([M − H_2O]$^+$, 20%). Anal. Calcd for $C_9H_{13}NO$; C, 71.49; H, 8.67; N, 9.26. Found: C, 71.08; H, 8.77; N, 8.93.

2-((1*R*,6*S*)-6-(Chloromethyl)cyclohex-3-enyl)acetonitrile (25). A solution of **24** (378 mg, 2.47 mmol) and triphenylphosphine (1.29 g, 4.94 mmol) in carbon tetrachloride (10 mL) was heated under reflux for 10 h. Concentration and flash chromatography (hexane/EtOAc 20:1 to 5:1) yielded **25** (405 mg, 96% yield) as a colorless oil; $[\alpha]^{23}_D$ +83.7 (*c* 1.06, $CHCl_3$); IR (film) 3030, 2959, 2916, 2844, 2244, 1472, 1426, 1298, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70−5.58 (m, 2H), 3.66 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.56 (dd, *J* = 11.4, 4.1 Hz, 1H), 2.47 (ABX, $\Delta\nu_{AB}$ = 10.6, J_{AB} = 16.9, J_{AX} = 7.2, J_{BX} = 4.2 Hz, 2H), 2.30−1.99 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.1, 125.2, 118.9, 47.8, 38.3, 32.0, 29.7, 28.0, 21.6; MS (EI) *m*/*z* (relative intensity) 169 (M$^+$, ^{35}Cl, 11%), 171 (M$^+$, ^{37}Cl, 3%). Anal. Calcd for $C_9H_{12}ClN$: C, 63.72; H, 7.13; N, 8.26. Found: C, 63.95; H, 7.22; N, 8.09.

(*R*)-3-(2-((1*R*,6*S*)-6-(Chloromethyl)cyclohex-3-enyl)-ethylideneamino)-4-benzyloxazolidin-2-one (26a). To a solution of **25** (339 mg, 1.99 mmol) in toluene (16 mL) was added DIBALH (20% w/w solution in toluene, 1.63 g, 2.3 mmol) at −78 °C. After 30 min, the reaction was quenched with saturated aqueous sodium potassium tartrate, and the mixture was filtered through Celite. The filtrate was washed with brine, dried (Na_2SO_4), concentrated, and purified by gradient flash chromatography (hexane to hexane/EtOAc 20:1) to afford the corresponding aldehyde (253 mg, 74% yield) as a colorless oil; $[\alpha]^{23}_D$ +41.2 (*c* 0.58, $CHCl_3$); IR (film) 3027, 2922, 2847, 1723, 1425, 1295 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.83, 1H), 5.70−5.51 (m, 2H), 3.56 (ABX, $\Delta\nu_{AB}$ = 8.2, J_{AB} = 11.1, J_{AX} = 6.1, J_{BX} = 5.1 Hz, 2H), 2.59−2.52 (m, 1H), 2.42−2.37 (m, 2H), 2.25−2.10 (m, 3H), 1.94−1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 125.2, 125.0, 47.8, 47.4, 38.8, 29.3, 28.9, 27.2; MS (EI) *m*/*z* (relative intensity) 172 (M$^+$, <1%), 128 ([M − 44]$^+$, 30%).[80] From this aldehyde (245 mg, 1.41 mmol) and (*R*)-3-amino-4-phenylmethyl-2-oxazolidone (272 mg, 1.41 mmol) by General Procedure A was obtained **26a** (462 mg, 95%) as a colorless liquid; $[\alpha]^{24}_D$ +47.8 (*c* 1.45 $CHCl_3$); IR (film) 3012, 2905, 1775, 1764, 1755, 1432, 1402, 1207 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (t, *J* = 5.8 Hz, 1H), 7.38−7.29 (m, 3H), 7.21−7.18(m, 2H), 5.70−5.60 (m, 2H), 4.45−4.38 (m, 1H), 4.26 (dd, *J* = 8.7, 8.1 Hz, 1H), 4.11 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.68 (ABX, $\Delta\nu_{AB}$ = 25.1, J_{AB} = 11.0, J_{AX} = 6.1, J_{BX} = 4.6 Hz, 2H), 3.23 (dd, *J* = 13.8, 3.7 Hz, 1H), 2.85 (dd, *J* = 13.8, 8.6 Hz, 1H), 2.60 (ddd, *J* = 14.4, 5.3, 5.3, Hz 1H), 2.42 (ddd, *J* = 14.3, 7.6, 6.4 Hz, 1H), 2.26−2.15 (m, 4H), 1.99−1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 154.6, 135.4, 129.2, 129.3, 127.4, 125.30, 125.26, 65.9, 57.9, 48.2, 39.0, 37.5, 36.8, 32.4, 29.0, 27.4; MS (ESI) *m*/*z* (relative intensity) 347.09 ([M + H]$^+$, 100%), 369.08 ([M + Na]$^+$, 52%). Anal. Calcd for $C_{19}H_{23}ClN_2O_2$: C, 65.79; H, 6.68; N, 8.08. Found: C, 65.90; H, 6.65; N, 8.09.

(*R*)-3-(2-((1*R*,6*S*)-6-(*tert*-Butyldimethysilyloxymethyl)-cyclohex-3-enyl)ethylideneamino)-4-benzyloxazolidin-2-one (26b). To a solution of **23** (155 mg, 0.58 mmol) in toluene (2.5 mL) was added DIBALH (1 M in hexane, 0.8 mL, 0.8 mmol) at −78 °C. After 30 min, the reaction was quenched with saturated aqueous sodium potassium tartrate, and the mixture was filtered through Celite. The filtrate was washed with brine, dried (Na_2SO_4), concentrated, and purified by gradient flash chromatography (hexane to 20:1 hexane/EtOAc) to afford the corresponding aldehyde (120 mg, 77%) as a colorless oil. From this aldehyde (75 mg, 0.27 mmol) and (*R*)-3-amino-4-phenylmethyl-2-oxazolidinone (53 mg, 0.27 mmol) by General Procedure A was obtained **26b** (100 mg, 81% yield) as a colorless liquid; $[\alpha]^{23}_D$ +41.7 (*c* 2.46, $CHCl_3$); IR (film) 3025, 2953, 2899, 2855, 1776, 1755, 1471, 1399, 1250, 1207, 1099 cm^{-1}; ^{1}H NMR (300 M + Hz, $CDCl_3$) δ 8.03 (dd, *J* = 6.2, 5.6 Hz, 1H), 7.30−7.18 (m, 3H), 7.12−7.10 (m, 2H), 5.62−5.52 (m, 2H), 4.31−4.28 (m, 1H), 4.17 (dd, *J* = 8.7, 7.9 Hz, 1H), 4.02 (dd, *J* = 8.7, 5.7 Hz, 1H), 3.58 (ABX, $\Delta\nu_{AB}$ = 7.1, J_{AB} = 10.1, J_{AX} = 6.2, J_{BX} = 5.0 Hz, 2H), 3.17 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.74 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.55 (ddd, *J* = 14.3, 5.3, 5.3 Hz, 1H), 2.32 (ddd, *J* = 14.7, 8.5, 6.4 Hz, 1H), 2.20−1.75 (m, 5H), 1.70−1.60 (m, 1H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.7, 135.5, 129.4, 129.1, 127.4, 126.1, 125.3, 65.9, 64.9, 58.1, 39.5, 37.5, 37.2, 32.2, 29.4, 26.8, 26.1, 18.5, −5.20, −5.24; MS (ESI) *m*/*z* (relative intensity) 442.97 ([M + H]$^+$ 44%). Anal. Calcd for $C_{25}H_{38}N_2O_3Si$: C, 67.83; H, 8.65; N, 6.33. Found: C, 67.80; H, 8.76; N, 6.20.

(((1*R*,6*S*)-6-((1,3-Dithian-2-yl)methyl)cyclohex-3-enyl)-methoxy)(*tert*-butyl)dimethylsilane (27a). To a solution of 1,3-dithiane (409 mg, 3.41 mmol) in THF/HMPA (10:1 v/v, 8.8 mL) was added *n*-BuLi (1.6 M in hexane, 2.20 mL, 3.51 mmol) at −78 °C under N_2. After 1 h, iodide (−)-**6a** (220 mg, 0.60 mmol) was added, and the mixture was allowed to warm to room temperature over ca. 12 h. The reaction mixture was partitioned between water and EtOAc, and the organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexane/EtOAc) afforded dithiane (−)-**27a** as a light brown oil (210 mg, 97% yield); $[\alpha]^{28}_D$ −54.6 (*c* 4.5, $CHCl_3$); IR (film) 3022, 2952, 2927, 2855, 2897, 1597, 1471, 1422, 1251, 1105 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (ddd, *J* = 13.6, 13.6, 13.6

dx.doi.org/10.1021/jo2026349 | J. Org. Chem. 2012, 77, 3159−3180

Hz, 2H), 4.10 (dd, J = 9.0, 5.7 Hz, 1H), 3.56 (d, J = 6.0 Hz, 2H), 2.94−2.72 (m, 4H), 2.26−2.15 (m, 1H), 2.15−1.79 (m, 6H), 1.77−1.67 (m, 1H), 1.67−1.53 (m, 2H), 0.89 (s, 9H), 0.04 (d, J = 3.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.8, 124.9, 64.9, 45.3, 39.5, 39.0, 30.6, 30.5, 30.2, 28.8, 26.3, 26.1, 25.9, 18.2, −5.4, −5.5; MS (CI) m/z (relative intensity) 359 ([M + H]$^+$, 100%). Anal. Calcd for $C_{18}H_{34}OS_2Si$: C, 60.27; H, 9.55. Found: C, 60.53; H, 9.56. The antipode (+)-**27a** was prepared by silylation of (+)-**27b** (TBSCl, imidazole, CH_2Cl_2) in 94% yield; $[\alpha]^{25}_D$ +54.8 (c 0.95, $CHCl_3$).

((1*R*,6*S*)-6-((1,3-Dithian-2-yl)methyl)cyclohex-3-enyl)-methanol (27b). To a solution of dithiane (−)-**27a** (30 mg, 0.083 mmol) in THF (1.5 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 0.175 mL, 0.175 mmol). After 3 h, concentration and gradient flash chromatography (hexane/EtOAc 1:1) afforded alcohol (−)-**27b** (17 mg, 83% yield) as a colorless oil; $[\alpha]^{28}_D$ −59.8 (c 2.2, $CHCl_3$); IR (film) 3400, 3020, 2897, 1432, 1422, 1275, 1187, 1052, 1033, 908 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68−5.51 (m, 2H), 4.10 (dd, J = 9.0, 5.7 Hz, 1H), 3.68−3.56 (m, 2H), 2.98−2.72 (m, 4H), 2.31−1.59 (m, 10H), 1.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.0, 125.4, 65.0, 45.3, 39.1, 38.9, 30.5, 30.4, 30.3, 28.5, 26.0, 25.8; MS (CI) m/z (relative intensity) 245 ([M + H]$^+$, 8%), 137 (100%). The antipode (+)-**27b** was prepared by the same procedure in 32% yield over two steps from (+)-**6a**; $[\alpha]^{24}_D$ +53.3 (c 1.13, $CHCl_3$).

((1*R*,6*S*)-6-((1,3-Dithian-2-yl)methyl)cyclohex-3-enyl)methyl Benzoate 27c. A solution of alcohol (−)-**27b** (45 mg, 0.183 mmol), benzoic anhydride (83 mg, 0.366 mmol), 4-dimethylaminopyridine (DMAP) (10 mg, 0.08 mmol), and Et_3N (76 μL, 0.55 mmol) in CH_2Cl_2 (2.0 mL) was stirred for 1 d. Concentration and flash chromatography (3:1 hexane/EtOAc) afforded benzoate (−)-**27c** (56 mg, 87% yield) as a colorless oil; $[\alpha]^{30}_D$ −83.9 (c 2.0, $CHCl_3$); IR (film) 3063, 2899, 2842, 1789, 1718, 1451, 1314, 1274, 1175, 1026, 908 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H), 7.54 (dd, J = 7.2, 7.2 Hz, 1H), 7.43 (dd, J = 8.3, 8.3 Hz, 2H), 5.70−5.58 (m, 2H), 4.40−4.25 (m, 2H), 4.12 (dd, J = 9.4, 5.7 Hz, 1H), 2.94−2.74 (m, 4H), 2.37−2.27 (m, 1H), 2.26−1.96 (m, 6H), 1.92−1.76 (m, 2H), 1.76−1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 132.8, 130.4, 129.6, 128.3, 125.1, 125.1, 66.8, 45.1, 38.8, 36.4, 30.9, 30.4, 30.2, 28.6, 26.4, 26.0; MS (CI) m/z (relative intensity) 349 ([M + H]$^+$, 92%), 227 (100%). Anal. Calcd for $C_{19}H_{24}O_2S_2$: C, 65.48; H, 6.94. Found: C, 65.46; H, 7.04. The antipode (+)-**27c** was prepared by the same procedure from alcohol (+)-**27b** in 98% yield; $[\alpha]^{24}_D$ +80.9 (c 1.11, $CHCl_3$).

((1*R*,6*S*)-6-(Formylmethyl)cyclohex-3-enyl)methyl Benzoate 28. A solution of dithiane (−)-**27c** (44 mg, 0.130 mmol) and $Hg(ClO_4)_2$ (0.4 M in H_2O, 0.47 mL, 0.188 mmol) in THF (3.0 mL) was stirred for 3 h. Concentration and flash chromatography (1:1 hexane/EtOAc) afforded aldehyde (−)-**28** (30 mg, 89% yield) as a colorless oil; $[\alpha]^{31}_D$ −41.9 (c 1.6, $CHCl_3$); IR (film) 3027, 2901, 2839, 2722, 1720, 1451, 1389, 1314, 1273, 1115, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (dd, J = 1.5, 1.5 Hz, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.56 (m, J = 7.2, 1.1 Hz, 1H), 7.44 (dd, J = 7.9, 7.9 Hz, 2H), 5.72−5.60 (m, 2H), 4.37−4.26 (m, 2H), 2.64 (ddd, J = 16.2, 4.9, 1.5 Hz, 1H), 2.46 (ddd, J = 16.6, 8.3, 2.6 Hz, 1H), 2.43−2.35 (m, 1H), 2.33−2.17 (m, 2H), 2.12−1.99 (m, 2H), 1.93−1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 166.5, 133.0, 130.2, 129.5, 128.4, 125.2, 125.1, 66.7, 47.6, 36.4, 29.3, 29.2, 26.6; MS (CI) m/z (relative intensity) 258 (M, 2%), 256 (75%), 137 (100%). The antipode (+)-**28** was prepared from benzoate (+)-**27c** (MeI, acetonitrile/water) in 45% yield; $[\alpha]^{25}_D$ +44.5 (c 1.33, $CHCl_3$).

(*R*)-3-(2-((1*R*,6*S*)-6-(Benzoyloxymethyl)cyclohex-3-enyl)-ethylideneamino)-4-benzyloxazolidin-2-one (26c). From (*R*)-3-amino-4-phenylmethyl-2-oxazolidone (64 mg, 0.33 mmol), and aldehyde (+)-**28** (86 mg, 0.33 mmol) by General Procedure A was obtained **26c** (137 mg, 94% yield) as a colorless liquid; $[\alpha]^{23}_D$ +45.6 (c 1.97, $CHCl_3$); IR (film) 2904, 1776, 1755, 1720, 1402, 1273, 1209, 1113, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (t, J = 5.8, 1H), 8.03−8.00 (m, 2H), 7.55−7.50 (m, 1H), 7.43−7.38 (m, 2H), 7.30−7.22 (m, 3H), 7.13−7.11 (m, 2H), 5.70−5.60 (m, 2H), 4.41−4.26 (m, 3H), 4.18 (dd, J = 8.7, 8.7 Hz, 1H), 4.02 (dd, J = 8.74, 5.8 Hz, 1H), 3.18 (dd, J = 13.7, 3.6, 1H), 2.75 (dd, J = 13.7, 8.8 Hz, 1H), 2.61 (ddd, J = 14.5, 5.3, 5.3 Hz, 1H), 2.41 (ddd, J = 14.4, 7.8, 6.3 Hz, 1H), 2.28−1.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 156.1, 154.7, 135.4, 133.2, 130.4, 129.7, 129.4, 129.1, 128.6, 127.4, 125.5, 125.4, 67.0, 65.9, 58.2, 37.6, 37.1, 36.6, 32.6, 29.3, 26.9; MS (ESI) m/z (relative intensity) 433.05 ([M + 1]$^+$ 55%), 455.2 ([M + Na]$^+$, 100%). Anal. Calcd for $C_{26}H_{28}N_2O_4$; C, 72.20; H, 6.53; N, 6.48. Found: C, 72.14; H, 6.65; N, 6.20.

(*R*)-3-(2-((1*R*,6*S*)-6-(Acetoxymethyl)cyclohex-3-enyl)-ethylideneamino)-4-benzyloxazolidin-2-one (26d). A solution of alcohol (+)-**27b** (160 mg. 0.65 mmol), acetic anhydride (75 μL, 0.78 mmol), triethylamine (0.13 mL, 0.97 mmol), and DMAP (20 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 1 h and then partitioned between CH_2Cl_2 (10 mL) and water. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane to hexane EtOAc 9:1) afforded the acetate derivative (168 mg, 92%) as a colorless oil, which was immediately subjected to dithiane hydrolysis. To a solution of this dithiane in acetonitrile/water (4:1, 5 mL) was added methyl iodide (75 μL, 1.2 mmol). After 1 d, concentration and flash chromatography (hexane to hexane EtOAc 20:1) afforded the corresponding aldehyde (62 mg, 53%) as a colorless oil. From this aldehyde and (*R*)-3-amino-4-phenylmethyl-2-oxazolidinone (62 mg, 0.32 mmol) by General Procedure A was obtained **26d** (113 mg, 95% yield) as a colorless liquid. The overall yield was 46% for 3 steps from (+)-**27b**. $[\alpha]^{25}_D$ +47.4 (c, 1.45 $CHCl_3$); IR (film) 3026, 2903, 1776, 1754, 1742, 1730, 1401, 1241, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (t, J = 5.8 Hz, 1H), 7.43−7.34 (m, 3H), 7.26−7.23 (m, 2H), 5.75−5.68 (m, 2H), 4.48−4.40 (m, 1H), 4.31 (dd, J = 8.7, 8.0 Hz, 1H), 4.25−4.11 (m, 3H), 3.31 (dd, J = 13.7, 3.6 Hz, 1H), 2.89 (dd, J = 13.7, 8.7 Hz, 1H), 2.64 (ddd, J = 14.5, 5.4, 5.4 Hz, 1H), 2.47 (ddd, J = 14.4, 8.0, 6.2 Hz, 1H), 2.30−2.25 (m, 2H), 2.15 (s, 3H), 2.14−1.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 156.1, 154.6, 135.4, 129.4, 129.0, 127.3, 125.3, 125.2, 66.5, 65.9, 58.2, 37.6, 37.0, 36.2, 32.3, 28.9, 26.5, 21.1; MS (ESI) m/z (relative intensity) 371.07 ([M + 1]$^+$, 68%), 393.17 ([M + Na]$^+$, 100%).

(*S*)-4-Benzyl-3-((*S*)-3-chloro-1-((1*R*,6*S*)-6-(*tert*-butyldimethyl-silyloxy-methyl)cyclohex-3-enyl)propan-2-ylamino)-oxazolidin-2-one (29a). A mixture of hydrazone **22a**[18a] (75 mg, 0.297 mmol) and $InCl_3$ (106 mg, 0.476 mmol) in benzene/CH_3CN (10:1 v/v, 2.75 mL) was stirred at room temperature under N_2 for 40 min. Then $Mn_2(CO)_{10}$ (186 mg, 0.476 mmol) and iodide (−)-**6a** (87 mg, 0.238 mmol) were added, and the mixture was irradiated for 13 h. The reaction mixture was partitioned between CH_2Cl_2 and aqueous NH_4OH. The organic phase was dried (Na_2SO_4), concentrated, and filtered through a short column of silica gel to remove most of the Mn residues. A mixture of the crude product and DBU (50 μL) in EtOAc was stirred for 30 min. Concentration and flash chromatography (3:1 hexane/EtOAc) afforded hydrazine **29a** (30 mg, 26% yield) as a colorless oil; $[\alpha]^{31}_D$ −40.0 (c 1.2, $CHCl_3$); IR (film) 3301, 3026, 2954, 2928, 2856, 1760, 1471, 1401, 1361, 1252, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5H), 5.68−5.61 (m, 2H), 4.22−4.09 (m, 2H), 4.05 (dd, J = 8.7, 4.5 Hz, 1H), 4.02−3.92 (m, 1H), 3.74−3.52 (m, 4H), 3.52−3.42 (br s, 1H), 3.37 (dd, J = 13.2, 3.4 Hz, 1H), 2.58 (dd, J = 13.6, 9.8 Hz, 1H), 2.38 (m, apparent br d, J = 18.1 Hz, 1H), 2.14−1.90 (m, 3H), 1.85−1.71 (m, 2H), 1.68−1.57 (m, 1H), 1.56−1.44 (m, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 135.8, 129.1, 128.8, 127.0, 125.8, 125.1, 65.8, 64.6, 60.1, 57.9, 47.0, 39.9, 36.8, 34.4, 29.7, 29.1, 26.6, 25.9, 18.3, −5.5 (2C); MS (CI) m/z (relative intensity) 494 ([M + H]$^+$, 100%).

(*S*)-4-Benzyl-3-((*S*)-3-chloro-1-((1*R*,6*S*)-6-(hydroxymethyl)-cyclohex-3-enyl)propan-2-ylamino)oxazolidin-2-one (29b). From **22a** (47 mg, 0.18 mmol) and iodide (+)-**6b** (85 mg, 0.23 mmol) by General Procedure B was obtained **29b** (21 mg, 30% yield) as a colorless oil; $[\alpha]^{25}_D$ +26.2 (c 1.11, $CHCl_3$); IR (film) 3436, 3289, 3019, 2910, 1754, 1744, 1437, 1402, 1233, 1097, 1029 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 70 °C) δ 7.32−7.29 (m, 2H), 7.24−7.21 (m, 3H), 5.63−5.58 (m, 2H), 4.24−4.17 (m, 1H), 4.06−3.98 (m, 2H), 3.75−3.65 (m, 2H), 3.47 (dd, J = 10.4, 5.6 Hz, 1H), 3.40−3.33 (m, 2H), 3.18 (dd, J = 13.5, 3.1 Hz, 1H), 2.72 (dd, J = 13.6, 8.7 Hz, 1H), 2.18 (m, apparent br d, J = 18 Hz, 1H), 2.09 (m, apparent br d, J = 17.4 Hz,

dx.doi.org/10.1021/jo2026349 | J. Org. Chem. 2012, 77, 3159−3180

1H), 1.92−1.53 (m, 5H), 1.40−1.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO, 70 °C) δ 157.2, 136.1, 128.8, 128.1, 126.1, 125.3, 124.7, 65.1, 63.0, 58.3, 57.1, 46.6, 38.8, 36.1, 33.8, 29.7, 28.5, 25.3; MS (ESI) m/z (relative intensity) 379.08 ([M + H]$^+$ 66%); HRMS (ESI) m/z calcd for $C_{20}H_{27}N_2O_3NaCl$ 401.1608 ([M + Na]$^+$); found 401.1600.

(*R*)-4-Benzyl-3-((*S*)-3-chloro-1-((1*R*,6*S*)-6-(chloromethyl)-cyclohex-3-enyl)propan-2-ylamino)oxazolidin-2-one (30a). From hydrazone **26a** (46 mg, 0.13 mmol) and chloroiodomethane (0.09 mL, 1.3 mmol) by General Procedure B was obtained **30a** (26 mg, 49% yield) as a colorless oil; $[\alpha]^{23}_D$ +6.0 (*c* 0.9 $CHCl_3$); IR (film) 3286, 3026, 2916, 1754, 1432, 1401, 1218, 1092, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 3H), 7.18−7.16 (m, 2H), 5.67−5.59 (m, 2H), 4.15 (dd, *J* = 8.8, 7.5 Hz, 2H), 4.05 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.96−3.88 (m, 1H), 3.70−3.57 (m, 4H), 3.44 (dd, *J* = 13.5, 3.6 Hz, 1H), 3.41−3.34 (m, 1H), 2.61 (dd, *J* = 13.3, 10.1 Hz, 1H), 2.26−2.08 (m, 3H), 2.05−1.76 (m, 4H) 1.39 (ddd, *J* = 14.1, 7.7, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 135.9, 129.3, 129.2, 127.3, 125.23, 125.15, 66.4, 60.0, 58.5, 48.3, 46.2, 39.0, 37.2, 34.4, 30.7, 29.1, 27.0; MS (ESI) m/z (relative intensity) 397.05 ([M + H]$^+$ 100%); HRMS (ESI) m/z calcd for $C_{20}H_{26}N_2O_2NaCl_2$ ([M + Na]$^+$) 419.1269; found 419.1294.

((1*S*,6*R*)-6-((*S*)-2-((*R*)-4-Benzyl-2-oxazolidin-3-ylamino)-3-chloropropyl)-cyclohex-3-enyl)methyl Benzoate (30c). From **26c** (80 mg, 0.18 mmol) and chloroiodomethane (0.13 mL, 1.8 mmol) by General Procedure B was obtained **30c** (32 mg, 36% yield) as a colorless oil; $[\alpha]^{23}_D$ +9.8 (*c* 0.23 $CHCl_3$); IR (film) 3276, 2917, 2851, 1752, 1724, 1711, 1270, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08−8.02 (m, 2H) 7.57−7.51 (m, 1H), 7.44−7.38 (m, 2H), 7.32−7.15 (m, 3H), 7.15−7.13 (m, 2H), 5.72−5.63 (m, 2H), 4.38−4.35 (m, 2H), 4.16−4.09 (m, 2H), 4.02 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.93−3.85 (m, 1H), 3.64 (ABX, $\Delta\nu_{AB}$ = 18.9, J_{AB} = 11.5, J_{AX} = 4.4, J_{BX} = 4.4 Hz, 2H), 3.47−3.40 (m, 1H), 3.39 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.60 (dd, *J* = 13.3, 10.0, Hz, 1H), 2.34−2.21 (m, 2H), 2.09−1.80 (m, 5H), 1.50−1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.5, 135.8, 133.2, 129.8, 129.3, 129.22, 129.16, 128.6, 127.4, 125.5, 125.3, 67.0, 66.5, 60.0, 58.0, 46.0, 37.3, 36.7, 34.3, 31.0, 29.5, 26.6; MS (ESI) m/z (relative intensity) 483.09 ([M + H]$^+$ 57%); HRMS (ESI) m/z calcd for $C_{27}H_{31}N_2O_4NaCl$ 505.1870 ([M + Na]$^+$); found 505.1886.

((1*S*,6*R*)-6-((*S*)-2-((*R*)-4-Benzyl-2-oxazolidin-3-ylamino)-3-chloropropyl)-cyclohex-3-enyl)methyl Acetate (30d). From **26d** (85 mg, 0.23 mmol) and chloroiodomethane (0.16 mL, 2.3 mmol) by General Procedure B was obtained **30d** (32 mg, 33% yield) as a colorless oil; $[\alpha]^{23}_D$ +9.4 (*c* 0.16 $CHCl_3$); IR (film) 3285, 3227, 2916, 2848, 1755, 1737, 1729, 1453, 1365, 1240, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 3H), 7.18−7.15 (m, 2H), 5.68−5.58 (m, 2H), 4.18−4.02 (m, 5H), 3.95−3.86 (m, 1H), 3.65 (ABX, $\Delta\nu_{AB}$ = 17.9, J_{AB} = 11.4, J_{AX} = 4.4, J_{BX} = 4.2 Hz, 2H), 3.43 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.42−3.34 (m, 1H), 2.62 (dd, *J* = 13.2, 10.1 Hz, 1H), 2.24−2.09 (m, 2H), 2.08 (s, 3H), 2.08−1.75 (m, 5H), 1.46−1.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 159.5, 135.9, 129.3, 129.2, 127.4, 125.4, 125.2, 66.61, 66.55, 60.1, 57.9, 46.0, 37.4, 36.2, 34.1, 30.7, 29.3, 26.4, 21.2; MS (ESI) m/z (relative intensity) 421.07 ([M]$^+$, 53%); HRMS (ESI) m/z calcd for $C_{22}H_{29}N_2O_4NaCl$ 443.1714 ([M + Na]$^+$); found 443.1723.

(*S*)-4-Benzyl-3-((*S*)-3-chloro-1-((1*R*,2*S*)-2-(hydroxy-methyl)-cyclohexyl)propan-2-ylamino)oxazolidin-2-one and (*S*)-4-Benzyl-3-((*S*)-3-chloro-1-((1*S*,2*R*)-2-(hydroxymethyl)-cyclohexyl)-propan-2-ylamino)oxazolidin-2-one (30e and 30e′). From **22a** (95 mg, 0.37 mmol) and iodide (±)-**6b**[**H**] (125 mg, 0.49 mmol) by General Procedure B was obtained **30e** and **30e′** (95 mg, 67% yield, dr 1:1); the diastereomers were inseparable but were separated upon preparation of their *O*-tosylate derivatives (see below). Data for diastereomer mixture: IR (film) 3335, 3291, 2921, 2851, 1754, 1402, 1218, 1094 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 70 °C) δ 7.33−7.29 (m, 2H), 7.24−7.21 (m, 3H), 4.22−4.18 (m, 1H), 4.06−3.98 (m, 2H), 3.75−3.60 (m, 2H), 3.54−3.31 (m, 4H), 3.19−3.14 (m, 1H), 2.75−2.68 (m, 1H), 1.94−1.89 (m, 0.5H), 1.83−1.71 (m, 2H), 1.69−1.60 (m, 2H), 1.60−1.48 (m, 0.5H), 1.33−1.10 (m, 6H), 1.03−0.94 (m, 1H); ^{13}C NMR (100 MHz, DMSO, 70 °C) δ 157.2, 157.1, 136.11, 136.09, 128.8, 128.10, 128.09, 126.1 (2C), 65.1, 65.0, 63.4, 63.2, 58.5, 58.1, 57.3, 57.1, 47.4, 46.5, 44.2, 44.1, 36.1, 36.0, 34.6, 34.1, 34.0, 33.8, 31.5, 31.2, 28.8, 28.6, 25.0, 24.9 (2C), 24.7; MS (ESI) m/z (relative intensity) 381.10 ([M + H]$^+$ 81%), 403.16 ([M + Na]$^+$, 100%). Anal. Calcd for $C_{20}H_{29}ClN_2O_3$; C, 63.06; H, 7.67; N, 7.35. Found: C, 62.87; H, 7.70; N, 7.33.

((1*S*,2*R*)-2-((*S*)-2-((*S*)-4-Benzyl-2-oxazolidin-3-ylamino)-3-chloropropyl)cyclohexyl)methyl 4-Methylbenzenesulfonate and ((1*R*,2*S*)-2-((*S*)-2-((*S*)-4-Benzyl-2-oxazolidin-3-ylamino)-3-chloropropyl)cyclohexyl)methyl 4-Methylbenzenesulfonate (31 and 31′). To a solution of **30e** and **30e′** (dr 1:1, 70 mg, 0.18 mmol), triethylamine (0.1 mL, 0.27 mmol), and DMAP (2 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was added *p*-toluenesulfonyl chloride (42 mg, 0.22 mmol) at room temperature. After 4 h, the reaction mixture was partitioned between CH_2Cl_2 and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc (9:1 to 2:1) afforded the separate diastereomers **31** and **31′** (1:1 ratio, 80 mg, 81% yield). Relative configuration was not determined. More polar diastereomer **31**: R_f 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]^{25}_D$ +24.4 (*c* 1.60 $CHCl_3$); IR (film) 3295, 2925, 2855, 1755, 1598, 1448, 1400, 1358, 1175, 1096, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34−7.23(m, 5H), 7.19−7.16 (m, 2H), 4.18−3.93 (m, 5H), 3.65 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.49 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.37−3.32 (m, 2H), 2.58 (dd, *J* = 13.3, 10.2 Hz, 1H), 2.43 (s, 3H), 1.83−1.68 (m, 4H), 1.38−1.11 (m, 8H), 1.10−0.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 145.0, 135.9, 133.1, 130.0, 129.5, 129.1, 128.1, 127.3, 73.0, 68.2, 59.9, 58.0, 45.9, 42.1, 37.1, 35.1, 34.3, 32.2, 29.5, 25.6, 25.5, 21.9; MS (ESI) m/z (relative intensity) 557.10 ([M + Na]$^+$ 100%), 535.06 ([M + H]$^+$, 47%). Less polar diastereomer **31′**: R_f 0.6 (SiO_2, 30% EtOAc/hexanes); $[\alpha]^{25}_D$ −25.3 (*c* 1.62 $CHCl_3$); IR (film) 3318, 2924, 2854, 1755, 1598, 1448, 1400, 1358, 1188, 1175, 1097, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.36−7.23(m, 5H), 7.20−7.17 (m, 2H), 4.15−3.94 (m, 6H), 3.61 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.49 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.34 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.36−3.25 (m, 1H), 2.60 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.44 (s, 3H), 2.04−1.98 (m, 1H), 1.75−1.49 (m, 5H), 1.36−1.18 (m, 6H), 1.03−0.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 145.1, 135.9, 133.0, 130.1, 129.3, 129.2, 128.1, 127.3, 72.8, 66.2, 60.5, 58.5, 47.4, 42.3, 37.2, 34.6, 34.5, 31.6, 29.6, 25.7, 25.6, 21.9; MS (ESI) m/z (relative intensity) 557.11 ([M + Na]$^+$ 100%), 535.06 ([M + H]$^+$, 51%).

(1*S*,3*R*,4*R*,6*R*)-Di((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) 7-Oxa-bicyclo[4.1.0]-heptane-3,4-dicarboxylate (32). To a solution of (+)-**4** (13.4 g, 30.2 mmol) in CH_2Cl_2 (200 mL) was added *m*-chloroperbenzoic acid (50−60%, 15.6 g, 45.3 mmol). After 3 h, the reaction mixture was diluted with CH_2Cl_2, washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc 20:1 to 4:1) afforded **32** (12 g, 86% yield) as a colorless oil; $[\alpha]^{24}_D$ +41.6 (*c* 2.88 $CHCl_3$); IR (film) 2954, 2869, 1937, 1726, 1453, 1387, 1370, 1307, 1242, 1171, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67−4.57 (m, 2H), 3.22−3.17 (m, 1H), 3.16 (dd, *J* = 4.5, 3.9 Hz, 1H), 2.80 (ddd, *J* = 10.4, 10.4, 4.9 Hz, 1H), 2.59 (ddd, *J* = 10.4, 10.4, 6.7, 1H), 2.45 (ddd, *J* = 14.7, 4.8, 1.7 Hz, 1H), 2.29 (ddd, *J* = 15.4, 6.6, 4.7 Hz, 1H,), 2.06−1.79 (m, 6H), 1.66−1.62 (m, 4H), 1.52−1.31 (m, 4H), 1.08−0.81 (m, 18H), 0.73−0.69 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 173.5, 74.7 (2C), 52.0, 50.5, 47.1, 47.1, 40.8 (2C), 40.3, 37.9, 34.4, 34.4, 31.6, 31.5, 27.4, 26.6, 26.2, 26.1, 23.3 (2C), 22.2 (2C), 21.0, 21.0, 16.10, 16.08; MS (ESI) m/z (relative intensity) 485.25 ([M + Na]$^+$ 100%), 947.3 ([2M + Na]$^+$, 68%). Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.91; H, 10.12.

(1*R*,2*R*,4*R*,5*R*)-Di((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) 4-(Benzyloxy)-5-hydroxycyclohexane-1,2-dicarboxylate (33a). To a solution of **32** (11 g, 23.8 mmol) and benzyl alcohol (12.8 g, 119 mmol) was added $Cu(OTf)_2$ (1.72 g, 4.76 mmol). After 1 d, the reaction mixture was diluted with CH_2Cl_2, washed successively with water and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc 9:1 to 4:1) provided **33a** (12.1 g, 89% yield) as a colorless solid; mp 103−104 °C; $[\alpha]^{26}_D$ +48.7 (*c* 1.5, $CHCl_3$); IR (film) 3491, 2955, 2927, 2869, 1736, 1726, 1710, 1452, 1369, 1241,

dx.doi.org/10.1021/jo2026349 | J. Org. Chem. 2012, 77, 3159−3180

1165, 1071, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.72−4.62 (m, 3H), 4.50 (d, J = 11.8 Hz, 1H), 3.89−3.82 (m, 1H), 3.51−3.46 (m, 1H), 3.12−3.05 (m, 2H), 2.20−1.80 (9H), 1.69−1.65 (m, 2H), 1.55−1.39 (m, 4H), 1.10−0.84 (m, 20H), 0.75−0.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 174.0, 138.5, 128.7, 128.0, 127.8, 77.2, 74.69, 74.68, 71.2, 68.3, 47.1, 47.1, 40.90, 40.88, 40.0, 39.6, 34.4 (2C), 31.6 (2C), 30.9, 27.4, 26.2, 26.1, 23.3, 23.2, 22.2 (2C), 21.09, 21.07, 16.2, 16.1; MS (EI) m/z (relative intensity) 570.47 ($[M]^+$ 2%) . Anal. Calcd for $C_{35}H_{54}O_6$; C, 73.65; H, 9.54. Found: C, 73.46; H, 9.45. Crystallography confirmed the structure.

(1*R*,2*R*,4*R*,5*R*)-Di((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) 4,5-Bis(benzyloxy)cyclohexane-1,2-dicarboxylate (33b). To a solution of **33a** (12.1 g, 21.12 mmol) and benzyl trichloroacetamidate (8.45 g, 42.2 mmol) in CH_2Cl_2 (30 mL) and cyclohexane (60 mL) was added trifluoromethanesulfonic acid (0.17 mL, 2 mmol) at room temperature. After 1 d, the reaction mixture was diluted with CH_2Cl_2, washed successively with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc 30:1 to 9:1) afforded **33b** (14 g, >99% yield) as a colorless liquid; $[\alpha]^{24}_D$ +44.4 (c 1.83, $CHCl_3$); IR (film) 2954, 2925, 2864, 1726, 1450, 1368, 1249, 1155, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.18 (m, 10H), 4.63−4.41 (m, 6H), 3.60 (s, 2H), 3.08−2.86 (m, 2H), 2.05−1.75 (m, 8H), 1.62−1.57 (m, 4H), 1.47−1.28 (m, 4H), 1.04−0.78 (m, 18H), 0.69−0.65 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 138.6, 128.6, 127.8, 127.7, 74.4, 73.9, 71.1, 47.1, 40.9, 39.5, 34.5, 31.6, 28.0, 26.2, 23.3, 22.2, 21.1, 16.2; MS (ESI) m/z (relative intensity) 661.11 ($[M + H]^+$ 17%), 683.41 ($[M + Na]^+$, 100%). Anal. Calcd for $C_{42}H_{60}O_6$; C, 76.33; H, 9.15. Found: C, 76.16; H, 9.20.

((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)-cyclohexyl)methanol (34a). A solution of the diester **33b** (14 g, 21 mmol) in ether (40 mL) was added dropwise to a mixture of lithium aluminum hydride (1.66 g, 45 mmol) in ether (60 mL) at −78 °C. The mixture was allowed to warm to room temperature over 12 h, then was cooled to −20 °C, and quenched by successive addition of water (3 mL), aqueous NaOH (3 M, 3 mL), and water (6 mL). Filtration through Celite, concentration, and flash chromatography (hexane/EtOAc 3:1 to 1:2) furnished **34a** (6.43 g, 85% yield) as a colorless liquid; $[\alpha]^{23}_D$ −20.7 (c 1.14, $CHCl_3$); IR (film) 3353, 3029, 2911, 2877, 1452, 1432, 1394, 1352, 1091, 1065, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.18 (m, 10H), 4.45 (ABq, $\Delta\nu_{AB}$ = 24.5, J_{AB} = 12.0, 4H), 3.99 (br s, 2H), 3.64−3.60 (m, 2H), 3.49−3.39 (m, 4H), 1.70−1.42 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.5, 127.7, 127.6, 74.5, 70.8, 67.4, 38.5, 28.8; MS (ESI) m/z (relative intensity) 356.85 ($[M]^+$ 84%). Anal. Calcd for $C_{22}H_{28}O_4$; C, 74.13; H, 7.92. Found: C, 74.34; H, 8.10.

Modified Procedure for Alcohol 34a. To a solution of diester **33b** (7.59 g, 11.5 mmol) in ether (37 mL) at 0 °C was added lithium aluminum hydride (0.89 g, 23.5 mmol) with stirring over a period of 2 h. The mixture was allowed to warm to room temperature. After 12 h, the reaction mixture was quenched by careful dropwise addition of saturated aqueous sodium sulfate. Filtration, concentration, and flash chromatography (hexane/EtOAc 3:1 to 1:2) furnished **34a** (3.74 g, 91% yield).

((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-((*tert*-butyldimethylsilyloxy)-methyl)cyclohexyl)methanol (34b). To a solution of diol **34a** (6.35 g, 17.83 mmol) in THF (120 mL) was added *n*-BuLi (1.5 M in hexane, 14.2 mL, 21.4 mmol) at 0 °C. After warming to room temperature for 80 min, *tert*-butyldimethylsilyl chloride (2.68 g, 17.83 mmol) was added. After ca. 12 h, the reaction mixture was partitioned between ethyl acetate and saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (hexane/EtOAc 9:1 to 4:1) afforded alcohol **34b** (7.86 g, 93% yield) as a colorless liquid; $[\alpha]^{25}_D$ −14.4 (c 1.55, $CHCl_3$); IR (film) 3437, 3029, 2952, 2927, 2856, 1461, 1389, 1360, 1253, 1094, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.18 (m, 10H), 4.54−4.37 (m, 4H), 3.65−3.61 (m, 2H), 3.53−3.44 (m, 5H), 1.75−1.48 (m, 6H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.92, 138.91, 128.51, 128.48, 127.7, 127.61, 127.55, 127.5, 74.8, 74.7, 70.8, 70.7, 68.3, 67.2, 38.9, 37.8, 28.9 (2C), 26.0, 18.3, −5.2, −5.4; MS (ESI) m/z (relative intensity) 470.99 (M^+, 91%). Anal. Calcd for $C_{28}H_{42}O_4Si$; C, 71.44; H, 8.99. Found: C, 71.70; H, 9.12.

((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(iodomethyl)-cyclohexyl)meth-oxy)(*tert*-butyl)dimethylsilane (6c). To a solution of alcohol **34b** (575 mg, 1.22 mmol) in THF (6 mL) were added imidazole (210 mg, 3.05 mmol) and triphenylphosphine (640 mg, 2.44 mmol). After 10 min, iodine (620 mg, 2.44 mmol) was added in two portions over 10 min. After 15 min, the reaction mixture was partitioned between EtOAc and saturated aqueous $Na_2S_2O_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (hexane to hexane/EtOAc 9:1) gave iodide **6c** (580 mg, 82.4% yield) as a colorless oil; $[\alpha]^{23}_D$ −38.5 (c 1.57, $CHCl_3$); IR (film) 3024, 2952, 2926, 2884, 2885, 1469, 1462, 1252, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.16 (m, 10H), 4.52 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 3.65−3.60 (m, 2H), 3.57 (dd, J = 10.2, 4.4 Hz, 1H), 3.41 (dd, J = 10.2, 3.2 Hz, 1H), 3.33 (dd, J = 9.9, 2.7 Hz, 1H), 3.22 (dd, J = 9.8, 5.8 Hz, 1H), 1.83−1.50 (m, 6H), 0.83 (s, 9H), 0.0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.03, 138.96, 128.53, 128.51, 127.6, 127.53, 127.52 (2C), 74.8 (2C), 70.7, 70.6, 64.8, 38.0, 33.3, 32.2, 28.4, 26.1, 18.4, 16.5, −5.2, −5.3; MS (EI) m/z (relative intensity); 523 ($[M - t\text{-Bu}]^+$, <1%).

((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(iodomethyl)-cyclohexyl)methanol (6d). A solution of **6c** (580 mg, 1 mmol) and camphorsulfonic acid (20 mg, 0.1 mmol) in methanol (6 mL) was stirred for 4 h at room temperature. Concentration and flash chromatography (hexane/EtOAc 9:1 to 2:1) afforded **6d** (400 mg, 85% yield) as a colorless oil; $[\alpha]^{24}_D$ −32.2 (c 0.62, $CHCl_3$); IR (film) 3425, 3028, 2917, 2874, 1452, 1325, 1179, 1090, 1072, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.16 (m, 10H), 4.50 (d, J = 11.8 Hz, 2H), 4.42 (d, J = 12.3 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.65−3.61 (m, 2H), 3.57−3.47 (m, 2H), 3.34−3.24 (m, 2H), 1.82−1.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.8, 128.6, 128.5, 127.8, 127.7 (2C), 127.5, 74.60, 74.57, 70.9, 70.8, 65.2, 38.0, 33.6, 32.4, 28.2, 16.4; MS (EI) m/z (relative intensity); 338 ($[M - I]^+$, <1%), 247 ($[M - I - Bn]^+$, 92%).

Modified Procedure for Iodide 6d. To a solution of alcohol **34b** (2.468 g, 5.24 mmol), imidazole (0.891 g, 13.1 mmol) and triphenylphosphine (2.75 g, 10.5 mmol) in THF (50 mL) at 0 °C was added iodine (2.66 g, 10.5 mmol) in two portions over 10 min. After 30 min, the reaction mixture was partitioned between EtOAc and saturated aqueous $Na_2S_2O_3$. The organic phase was dried (Na_2SO_4) and concentrated to a crude product containing **6c**. This material was taken up in methanol (52 mL) and dichloromethane (13 mL) and then cooled to 0 °C. Camphorsulfonic acid (61 mg, 0.26 mmol) was added, and the mixture was allowed to warm to room temperature. After 12 h, concentration and flash chromatography (hexane/EtOAc 9:1 to 2:1) afforded **6d** (2.33 g, 95% yield from alcohol **34b**).

(*S*)-3-((*S*)-1-((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)-cyclohexyl)-3-(*tert*-butyldimethylsilyloxy)propan-2-ylamino)-4-benzyloxa-zolidin-2-one (35). From *N*-acylhydrazone **22b** (356 mg, 1.02 mmol) and iodide **6d** (600 mg, 1.28 mmol) by General Procedure B was obtained **35** (658 mg, 93% yield) as a colorless oil; $[\alpha]^{24}_D$ −13.4 (c 0.29, $CHCl_3$); IR (film) 3474, 3028, 2926, 2856, 1775, 1764, 1452, 1251, 1094, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.02 (m, 15H), 4.54−4.34 (m, 5H), 3.98−3.74 (m, 4H), 3.67−3.45 (m, 5H), 3.26 (dd, J = 12.9, 1.9 Hz, 1H), 3.15−3.05 (m, 1H), 2.55−2.40 (m, 1H), 2.00−1.69 (m, 5H), 1.55−1.47 (m, 2H), 1.21−1.06 (m, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 139.02, 138.95, 135.8, 129.2, 129.2, 129.1, 128.4, 127.62, 127.55, 127.53, 127.49, 127.2, 74.9 (2C), 70.90, 70.87, 66.1, 65.4, 64.7, 59.0, 58.9, 39.3, 37.3, 34.6, 32.1, 29.4, 28.9, 27.1, 18.5, −5.1, −5.2; MS (ESI) m/z (relative intensity) 689.25 ($[M + 1]^+$ 100%). Anal. Calcd for $C_{40}H_{56}N_2O_6Si$; C, 69.73; H, 8.19; N, 4.07. Found: C, 69.99; H, 8.13; N, 3.97.

((1*R*,2*R*,4*R*,5*R*)-2-((*S*)-2-((*S*)-4-Benzyl-2-oxooxazolidin-3-ylamino)-3-(*tert*-butyldimethylsilyloxy)propyl)-4,5-bis-(benzyloxy)cyclohexyl)methyl 4-methylbenzenesulfonate

dx.doi.org/10.1021/jo2026349 | *J. Org. Chem.* 2012, 77, 3159−3180

(36). To a solution of **35** (195 mg, 0.28 mmol), triethylamine (0.1 mL, 0.52 mmol), and 4-dimethylaminopyridine (7 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added *p*-toluenesulfonyl chloride (64 mg, 0.33 mmol) at room temperature. After 4 h, the reaction mixture was diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc 9:1 to 2:1) gave **36** (223 mg, 94% yield) as a colorless oil; $[\alpha]^{23}_D$ −17.5 (*c* 3.8, $CHCl_3$); IR (film) 3295, 3062, 3029, 2927, 2856, 1775, 1764, 1758, 1755, 1494, 1452, 1399, 1358, 1250, 1176, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.31−7.23 (m, 15H), 7.16−7.13 (m, 2H), 4.60 (d, *J* = 12.3 Hz, 1H), 4.53−4.41 (m, 3H), 4.12−3.94 (m, 6H), 3.67−3.63 (m, 3H), 3.53 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.31 (dd, *J* = 13.2, 2.5 Hz, 1H), 3.25−3.15 (m, 1H), 2.60 (dd, *J* = 13.2, 9.1 Hz, 1H), 2.42 (s, 3H), 2.10 (br d, 13.5 Hz, 1H), 1.89−1.69 (m, 4H), 1.61−1.43 (m, 2H), 1.29−1.20 (m, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 144.8, 138.8, 138.7, 135.9, 133.1, 130.0, 129.2, 129.0, 128.9, 128.5, 128.4, 128.0, 127.7, 127.6, 127.5, 127.1, 74.3, 74.0, 72.7, 70.8, 70.7, 65.9, 65.3, 59.5, 58.4, 37.0, 36.9, 33.7, 30.7, 28.9, 28.8, 26.1, 21.7, 18.4, −5.22, −5.24; MS (ESI) *m*/*z* (relative intensity) 843.28 ([M]$^+$ 100%). Anal. Calcd for $C_{47}H_{62}N_2O_8SSi$; C, 66.95; H, 7.41; N, 3.32. Found: C, 67.09; H, 7.29; N, 3.34.

(*S*)-3-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-6,7-Bis(benzyloxy)-3-((*tert*-butyldimethyl-silyloxy)methyl)-octahydroisoquinolin-2(1*H*)-yl)-4-benzyloxazolidin-2-one (37). To a solution of **36** (42 mg, 0.049 mmol) in acetonitrile were added K_2CO_3 (67 mg, 0.49 mmol) and NaI (15 mg, 0.1 mmol), and the mixture was heated under reflux for 6 h. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/EtOAc 20:1 to 9:1) afforded **37** (27 mg, 82% yield) as a colorless oil; $[\alpha]^{23}_D$ −21.6 (*c* 0.97, $CHCl_3$); IR (film) 2926, 2855, 1755, 1453, 1399, 1251, 1091, 1071, 1027 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.36−7.19 (m, 15H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.18 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.12−4.06 (m, 1H), 4.01 (dd, *J* = 8.5, 6.9 Hz, 1H), 3.77−3.75 (m, 2H), 3.74 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.66 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.58 (dddd, *J* = 11.5, 4.4, 4.4, 2.8 Hz, 1H), 3.35 (dd, *J* = 13.4, 4.2 Hz, 1H), 3.28 (dd, *J* = 10.9, 10.9 Hz, 1H), 2.85 (dd, *J* = 10.45, 3.76 Hz, 1H), 2.74 (dd, *J* = 13.37, 9.77 Hz, 1H), 1.85−1.77 (m, apparent br q, *J* = ca. 10 Hz, 1H), 1.74−1.70 (m, apparent br d, *J* = ca. 13 Hz, 1H), 1.68−1.61 (m, 1H), 1.63 (ddd, *J* = 12.7, 2.8, 2.8 Hz, 1H), 1.50−1.42 (m, 3H), 1.10 (ddd, apparent q, *J* = ca. 12 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 139.0, 138.9, 136.6, 129.2, 129.0, 128.57, 128.56, 127.73, 127.66, 127.6, 127.5, 127.0, 76.8, 74.6, 74.4, 71.0, 70.8, 67.2, 65.8, 61.1, 60.1, 59.1, 39.2, 36.0, 35.7, 33.8, 31.7, 29.9, 29.3, 26.2, 18.7, −5.2 (2C); MS (ESI) *m*/*z* (relative intensity) 671.33 ([M + 1]$^+$ 100%); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{54}N_2O_5NaSi$ 693.3700 ([M + Na]$^+$); found 693.3712.

***N*-((*S*)-1-((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)cyclohexyl)-3-(*tert*-butyldimethylsilyloxy)-propan-2-yl)-2,2,2-trifluoroacetamide (38).** To a solution of **35** (104 mg, 0.17 mmol) in THF (1.7 mL) was added *n*-BuLi (1.7 M in hexanes, 0.22 mL, 0.38 mmol) at −78 °C. After 1 h, trifluoroacetic anhydride (0.21 mL, 1.51 mmol) was added at −78 °C, and the mixture was allowed to warm to ambient temperature overnight. The reaction was quenched by saturated NH_4Cl solution, and the organic phase was washed with water, saturated $NaHCO_3$ solution, and brine, then dried (Na_2SO_4), and concentrated to afford the trifluoroacetohydrazide. This material was taken up in MeOH (1 mL, and a solution of SmI_2 in THF (0.3 M, 4.33 mL) was added dropwise until the blue color remained. After 1 h, the reaction mixture was opened to the air. Concentration and flash chromatography (hexane/EtOAc 10:1 to 3:1) afforded **38** (66 mg, 72% yield) as a pale yellow oil; $[\alpha]^{24.1}_D$ −50.1 (*c* 0.9, $CHCl_3$); IR (film) 3424, 3317, 3088, 3063, 3030, 2925, 2855, 1711, 1551, 1462, 1253, 1182, 1161, 1095, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10H), 6.94 (d, *J* = 8.4 Hz, 1H), 4.50 (ABq, $\Delta\nu$ = 19.6 Hz, J_{AB} = 12.0 Hz, 2H), 4.48 (ABq, $\Delta\nu$ = 54.2 Hz, J_{AB} = 12.0 Hz, 2H), 4.16−4.08 (m, 1H), 3.75 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.68 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.68−3.62 (m, 2H), 3.61 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.51 (dd, *J* = 11.0, 3.0 Hz, 1H), 2.03−1.94 (m, 2H), 1.85−1.78 (m, 2H), 1.76−1.57 (m, 3H), 1.47 (ddd, *J* = 13.9, 11.7, 2.5 Hz, 1H), 1.29 (ddd, *J* = 13.9, 9.2, 4.3 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.1 ($^2J_{CF}$ = 36.4 Hz), 138.7, 138.6, 128.33, 128.27, 127.49, 127.46, 127.41, 127.36, 116.0 ($^1J_{CF}$ = 286.3 Hz), 75.0, 74.1, 70.8, 70.5, 64.9, 64.7, 49.5, 38.4, 33.9, 30.3, 28.9, 28.1, 25.8, 18.2, −5.5, −5.6; MS (ESI) *m*/*z* (relative intensity) 610.01 ([M + H]$^+$, 13%), 632.29 ([M + Na]$^+$, 100%); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{47}F_3NO_5Si$ ([M + H]$^+$) 610.3176; found 610.3180.

1-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-6,7-Bis(benzyloxy)-3-((*tert*-butyldimethylsilyloxy)-methyl)octahydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (39a). To a solution of trifluoroacetamide **38** (53 mg, 0.087 mmol) and PPh_3 (47 mg, 0.18 mmol) in THF (4.5 mL) at 0 °C was added diisopropyl azodicarboxylate (0.036 mL, 0.18 mmol). The mixture was allowed to warm to ambient temperature and stirred overnight. Concentration and flash chromatography (hexane to 5:1 hexane/EtOAc) afforded **39a** (49 mg, 95% yield) as a pale yellow oil; $[\alpha]^{23.3}_D$ −52.0 (*c* 1.0, $CHCl_3$); IR (film) 3064, 3031, 2928, 2857, 1685, 1454, 1253, 1205, 1171, 1141, 1090, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 10H), 4.51 (ABq, $\Delta\nu$ = 23.7 Hz, J_{AB} = 12.0 Hz, 2H), 4.50 (ABq, $\Delta\nu$ = 24.9 Hz, J_{AB} = 12.0 Hz, 2H), 4.02−3.65 (br m, 6H), 3.17 (br s, 1H), 1.90−1.77 (m, 4H), 1.64−1.48 (m, 3H), 1.40−1.25 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.0, 138.5, 138.4, 128.4 (2C), 127.6, 127.41, 127.39 (2C), 116.6 ($^1J_{CF}$ = 286.6 Hz), 74.2, 74.1, 70.8 (2C), 64.0, 31.9, 30.4, 25.8, 18.2, −5.51, −5.53, some peaks not observed due to line broadening related to TFA rotamers; MS (ESI) *m*/*z* (relative intensity) 592.00 ([M + H]$^+$, 52%), 614.19 ([M + Na]$^+$, 100%); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{45}F_3NO_4Si$ ([M + H]$^+$) 592.3070; found 592.3073.

1-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-3-((*tert*-Butyldimethylsilyloxy)-methyl)-6,7-dihydroxy-octahydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (39b). To a solution of bis-benzyl ether **39a** (49 mg, 0.083 mmol) in EtOAc (2 mL) was added Pd/C (10% *w*/*w*, 0.21 mmol). The mixture was stirred under H_2 (balloon) for 2 days. Filtration, concentration, and flash chromatography (hexane/EtOAc 3:1 to 1:1) afforded **39b** (32 mg, 93% yield) as a colorless oil; $[\alpha]^{24.0}_D$ −53.3 (*c* 0.7, $CHCl_3$); IR (film) 3429, 2930, 2859, 1683, 1464, 1255, 1205, 1147, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94−3.80 (m, 6H), 3.20 (br s, 1H), 1.92−1.53 (m, 9H), 1.29 (br s, 1H), 0.87 (s, 9H), 0.039 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 116.5 ($^1J_{CF}$ = 286.6 Hz), 69.5, 63.9, 34.1, 32.9, 31.6, 25.8, 18.1, −5.5, −5.6, some peaks exhibited line broadening related to TFA rotamers; MS (ESI) *m*/*z* (relative intensity) 411.92 ([M + H]$^+$, 100%), 280.20 ([M − OTBS]$^+$, 58%); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{33}F_3NO_4Si$ ([M + H]$^+$) 412.2131; found 412.2138.

1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4,5-bis-(2-hydroxyethyl)-piperidin-1-yl)-2,2,2-trifluoroethanone (41). To a solution of vicinal diol **39b** (144 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) was added silica gel-supported $NaIO_4$ (0.667 mmol/g, 577 mg, 0.385 mmol). After the mixture was stirred overnight, filtration and concentration afforded an unstable dialdehyde (**40**). This material was taken up in MeOH (35 mL), and to this solution was added $NaBH_4$ (26 mg, 0.69 mmol) at 0 °C. After 1 h the solution was concentrated and partitioned between CH_2Cl_2 and water, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography (hexane/EtOAc 1:1 to EtOAc) afforded diol **41** (133 mg, 92% yield) as a colorless oil; $[\alpha]^{25.0}_D$ −54.9 (*c* 0.5, $CHCl_3$); IR (film) 3366, 2930, 2859, 1683, 1472, 1451, 1256, 1202, 1143, 1114, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13−4.05 (m, 1H), 3.98 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.78−3.53 (m, 7H), 1.80−1.77 (m, 6H), 1.66−1.52 (m, 3H), 1.39−1.33 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.6 ($^2J_{CF}$ = 34.9 Hz), 116.4 ($^1J_{CF}$ = 288.5 Hz), 62.1, 60.6, 60.0, 55.4, 43.9, 38.0, 36.1, 34.9, 33.8, 27.8, 25.8, 18.1, −5.7 (2C); MS (ESI) *m*/*z* (relative intensity) 414.02 ([M + H]$^+$, 100%), 436.15 ([M + Na]$^+$, 30%); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{35}F_3NO_4Si$ ([M + H]$^+$) 414.2287; found 414.2287.

1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4,5-bis-(2-iodoethyl)-piperidin-1-yl)-2,2,2-trifluoroethanone (42). To a

dx.doi.org/10.1021/jo2026349 | *J. Org. Chem.* 2012, 77, 3159−3180

solution of diol **41** (68 mg, 0.16 mmol), PPh_3 (173 mg, 0.66 mmol, and imidazole (56 mg, 0.82 mmol) in THF (10 mL) at 0 °C was added I_2 (168 mg, 0.66 mmol) in two portions over 15 min. After 1 h the mixture was quenched with satd $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the diiodide **42** (105 mg, quantitative) as a colorless oil; $[\alpha]^{24.2}_D$ −5.3 (*c* 0.4, $CHCl_3$); IR (film) 2953, 2928, 2857, 1679, 1449, 1198, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13−4.07 (m, 1H), 4.02 (br d, *J* = 8.5 Hz, 1H), 3.67 (br, 1H), 3.58−3.52 (m, 2H), 3.38−3.30 (m, 2H), 3.18−3.05 (m, 2H), 2.14−2.06 (m, 1H), 1.88−1.72 (m, 5H), 1.66−1.58 (m, 1H), 1.34−1.25 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.1, 55.3, 42.9, 40.1, 38.4, 37.4, 35.5, 26.5, 25.8, 18.2, 3.9, 3.6, −5.6 (2C); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{33}F_3I_2NO_2Si$ ($[M + H]^+$) 634.0322; found 634.0336.

(2*S*,4*S*,8*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-8-(2-iodoethyl)-quinuclidine (43a) and (2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)-methyl)-4-(2-iodoethyl)-1-azabicyclo[3.2.1]octane (43b). To a solution of diiodide **42** (32 mg, 0.051 mmol) in MeOH (2 mL) was added NH_3/MeOH (7 N, 2 mL). After ca. 12 h, the mixture was concentrated and purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) to provide the tertiary amines **43a** and **43b** as an inseparable mixture of isomers (21 mg, quantitative, ratio 5:1) as a colorless oil; IR (film) 2952, 2927, 2855, 1467, 1255, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major isomer δ 4.08 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.99−3.92 (m, 2H), 3.50−3.53 (m, 2H), 3.48−3.40 (m, 1H), 3.22−3.10 (m, 2H), 3.08 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.55−2.50 (m, 1H), 2.36 (dddd, *J* = 13.2, 12.4, 6.8, 5.2 Hz, 1H), 2.11 (ddd, *J* = 15.6, 7.6. 7.2 Hz, 1H), 2.02−1.88 (m, 4H), 1.61 (ddd, *J* = 15.6, 3.6, 2.8 Hz, 1H), 0.91 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 63.8, 62.8, 53.8, 48.9, 38.4, 38.0, 36.3, 28.3, 26.1, 21.6, 18.4, 3.2, −5.0, −5.2; minor isomer δ 62.1, 58.5, 54.7, 43.0, 36.5, 33.8, 25.8, 24.5, 24.3, 21.0, 18.1, 2.4, −5.3, −5.5; MS (ESI) *m*/*z* (relative intensity) 410.10 ($[M + H]^+$, 100%); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{33}NOISi$ ($[M + H]^+$) 410.1376; found 410.1386.

2-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-5-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ethyl Benzoate (44a) and 2-((3*R*,4*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)-methyl)-4-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)ethyl Benzoate (44b). To a solution of diol **41** (16 mg, 0.039 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (2.2 M, 19 μL, 0.043 mmol). After 1 h, $(PhCO)_2O$ (9 mg, 0.041 mmol) was added, and the mixture was allowed to warm to ambient temperature overnight. The mixture was partitioned between water and CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded **44a** (4.8 mg, 24%) and **44b** (5.9 mg, 29%) as colorless oils. **44a**: $[\alpha]^{23}_D$ −31.2 (*c* 0.2, $CHCl_3$); IR (film) 3435, 2955, 2927, 2855, 1722, 1680, 1462, 1275, 1203, 1144, 1113, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.99 (m, 2H), 7.59−7.53 (m, 1H), 7.47−7.41 (m, 2H), 4.49−4.35 (m, 2H), 4.15−3.99 (m, 2H), 3.77−3.50 (m, 4H), 2.10−1.98 (m, 1H), 1.90−1.80 (m, 3H), 1.80−1.68 (m, 2H), 1.68−1.56 (m, 2H), 1.43−1.26 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 133.1, 130.1, 129.5, 128.4, 62.7, 62.2, 60.0, 55.6, 43.9, 36.4, 35.0, 34.4, 34.0, 27.6, 25.8, 18.1, −5.7 (2C); MS (ESI) *m*/*z* (relative intensity) 540 ($[M + Na]^+$, 26%), 518 ($[M + H]^+$, 100%), 386 ($[M - OBz]^+$, 80%); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{39}F_3NO_5Si$ ($[M + H]^+$) 518.2550; found 518.2570. **44b**: $[\alpha]^{23}_D$ −18.3 (*c* 0.3, $CHCl_3$); IR (film) 3434, 2949, 2927, 2856, 1722, 1679, 1451, 1275, 1203, 1142, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.99 (m, 2H), 7.58−7.53 (m, 1H), 7.48−7.41 (m, 2H), 4.42−4.32 (m, 2H), 4.16−4.08 (m, 1H), 4.05−3.97 (m, 1H), 3.77−3.55 (m, 4H), 2.03−1.54 (m, 8H), 1.43−1.25 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 133.0, 130.1, 129.5, 128.4, 62.5, 62.2, 60.5, 55.6, 43.8, 37.9, 37.1, 33.9, 31.2, 27.7, 25.8, 18.2, −5.6 (2C); MS (ESI) *m*/*z* (relative intensity) 540.24 ($[M + Na]^+$, 40%), 518 ($[M + H]^+$, 100%), 386 ($[M - OBz]^+$, 10%), 308 (60%); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{39}F_3NO_5Si$ ($[M + H]^+$) 518.2550; found 518.2558.

2-((3*R*,4*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)ethyl Acetate (45a) and 2-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)-methyl)-5-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ethyl Acetate (45b). To a solution of diol **41** (155 mg, 0.38 mmol) in CH_2Cl_2 (16 mL) were added vinyl acetate (0.038 mL, 0.41 mmol) and lipase acrylic resin (*Candida antarctica*, 31 mg, 0.012 mmol). After 7 days, filtration, concentration, and radial chromatography (hexane/EtOAc 10:1 to 1:1) afforded starting material (49 mg, 32%), which can be reused, **45a** (60 mg, 35%), and **45b** (50 mg, 29%) as colorless oils. **45a**: $[\alpha]^{24.0}_D$ −50.7 (c 0.6, $CHCl_3$); IR (film) 3466, 2955, 2929, 2861, 1739, 1683, 1471, 1367, 1252, 1193, 1143, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19−4.01 (m, 3H), 3.99 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.73 (ddd, *J* = 10.8, 5.5, 5.5 Hz, 1H), 3.69−3.53 (m, 4H), 2.05 (s, 3H), 1.92−1.86 (m, 1H), 1.82−1.76 (m, 1H), 1.70−1.45 (m, 6H), 1.28−1.20 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.1, 56.7 ($^2J_{CF}$ = 35.2 Hz), 116.4 ($^1J_{CF}$ = 286.0 Hz), 62.2, 62.1, 59.9, 55.5, 43.8, 36.2, 34.8, 34.1, 33.7, 27.4, 25.8, 21.0, 18.1, −5.7 (2C); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{37}F_3NO_5Si$ ($[M + H]^+$) 456.2393; found 456.2396. **45b**: $[\alpha]^{23.1}_D$ −42.4 (c 0.5, $CHCl_3$); IR (film) 3469, 2949, 2928, 2857, 1741, 1678, 1462, 1366, 1249, 1202, 1142, 1110, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15−4.02 (m, 3H), 3.99 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.77−3.51 (m, 5H), 2.05 (s, 3H), 1.81−1.45 (m, 8H), 1.33−1.27 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.1,156.5 ($^2J_{CF}$ = 34.0 Hz), 116.4 ($^1J_{CF}$ = 285.9 Hz), 62.1, 60.5, 55.5, 43.7, 37.9, 37.2, 33.9, 30.9, 27.6, 25.8, 20.9, 18.1, −5.7 (2C); MS (ESI) *m*/*z* (relative intensity) 456.05 ($[M + H]^+$, 41%), 478.26 ($[M + Na]^+$, 100%); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{37}F_3NO_5Si$ ($[M + H]^+$) 456.2393; found 456.2402.

2-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-5-vinylpiperidin-4-yl)ethanol (46). To a solution of alcohol **45a** (22 mg, 0.048 mmol) in THF (0.48 mL) were added 2-$O_2NC_6H_5SeCN$ (22 mg, 0.096 mmol) and Bu_3P (24 μL, 0.096 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated, and the residue was dissolved in THF (1 mL). To this solution was added aqueous H_2O_2 (30% w/w, 0.09 mL, 0.082 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography afforded the product (21 mg). To a portion (5.8 mg, 0.013 mmol) of the material thus obtained in MeOH/H_2O (5:1, 0.6 mL) at 0 °C was added $Ba(OH)_2 \cdot 8H_2O$ (33 mg, 0.10 mmol), and the mixture was allowed to warm to ambient temperature. After 2 h, the mixture was diluted with CH_2Cl_2, filtered, and concentrated to afford **46** (4.0 mg, quantitative) as a colorless oil; $[\alpha]^{24}_D$ +28.2 (*c* 0.4, $CHCl_3$); IR (film) 3318, 3076, 2954, 2928, 2856, 1462, 1256, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 17, 10, 10 Hz, 1H), 5.10−5.04 (m, 2H), 3.73−3.60 (m, 2H), 3.58 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.42 (dd, *J* = 9.6 Hz, 7.8 Hz, 1H), 3.02 (dd, *J* = 11.8, 4.2 Hz, 1H), 2.67−2.60 (m, 1H), 2.50 (dd, *J* = 11.6, 11.3 Hz, 1H), 1.92−1.82 (m, 2H), 1.72−1.65 (m, 3H), 1.45−1.35 (m, 1H), 1.32−1.25 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 116.5, 67.6, 60.3, 57.8, 52.3, 48.3, 37.0, 36.7, 33.5, 25.9, 18.3, −5.4 (2C); MS (ESI) *m*/*z* (relative intensity) 300.20 ($[M + H]^+$, 100%); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{34}NO_2Si$ ($[M + H]^+$) 300.2359; found 300.2364.

1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-5-vinylpiperidin-1-yl)-2,2,2-trifluoroethanone (48). To a solution of monoester alcohol **45a** (22 mg, 0.048 mmol) in THF (0.48 mL) were added 2-$O_2NC_6H_5SeCN$ (22 mg, 0.096 mmol) and Bu_3P (24 μL, 0.096 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated, and the residue was dissolved in THF (1 mL). To this solution was added aqueous H_2O_2 (30% *w*/*w*, 0.09 mL, 0.82 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography afforded the product (21 mg). To a portion (10 mg, 0.023 mmol) of the material thus obtained in MeOH (1 mL) was added NaOMe/MeOH solution (0.1 M, 0.23 mL, 0.023 mmol) in five portions over 5 h with TLC monitoring. Concentration and flash chromatography (hexane/EtOAc 10:1 to 3:1) afforded **48** (8.3 mg, 92%) as a colorless oil; $[\alpha]^{25.5}_D$ −60.3 (c 0.4, $CHCl_3$); IR (film) 3448, 2954, 2929, 2858, 1685, 1463, 1255, 1204, 1145, 1117, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

dx.doi.org/10.1021/jo2026349 | *J. Org. Chem.* 2012, 77, 3159−3180

5.74 (ddd, J = 17.1, 9.7, 9.2 Hz, 1H), 5.09−5.04 (m, 2H), 4.13−4.08 (m, 1H), 3.99−3.91 (m, 1H), 3.76−3.60 (m, 5H), 2.10 (m, apparent q, J = 8.2 Hz, 1H), 1.89 (dd, J = 11.4, 4.0 Hz, 1H), 1.83−1.67 (m, 2H), 1.53−1.46 (m, 2H), 1.26−1.20 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ139.6, 116.5 ($^1J_{CF}$ = 286.6 Hz), 116.1, 63.0 (br), 60.9, 56.1, 46.3 (br), 46.0, 37.2, 33.1, 28.0, 26.1, 18.3, −5.5 (2C); HRMS (ESI) m/z calcd for $C_{18}H_{33}F_3NO_3Si$ ($[M + H]^+$) 396.2182; found 396.2188.

***O*-(*tert*-Butyldimethylsilyl)quincorine (21c).** To a solution of alcohol **48** (5.2 mg, 0.013 mmol), PPh_3 (6.8 mg, 0.026 mmol), and imidazole (2.2 mg, 0.032 mmol) in THF (0.5 mL) at 0 °C was added I_2 (7 mg, 0.028 mmol) in two portions over 15 min. The mixture was stirred for 1 h, quenched with satd $Na_2S_2O_3$, and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the iodide, which was dissolved in MeOH (0.4 mL). To this solution was added NH_3/MeOH (7N, 0.4 mL). After ca. 12 h, concentration and flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) afforded *O*-TBS-quincorine (**21c**, 3 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.24 (d, J = 10.8 Hz, 1H), 5.19 (d, J = 17.2 Hz, 1H), 4.37 (br d, J = 10.4 Hz, 1H), 3.76 (dd, J = 12.0, 4.5 Hz, 1H), 3.72−3.62 (m, 1H), 3.45 (dd, J = 13.3, 10.8 Hz, 1H), 3.36−3.28 (m, 1H), 3.18−3.03 (m, 2H), 2.72−2.64 (m, 1H), 2.13−2.09 (m, 1H), 2.03−1.90 (m, 2H), 1.90−1.79 (m, 1H), 0.92 (s, 9H), 0.90−0.84 (m, 1H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ137.5, 117.3, 62.3, 58.3, 53.9, 43.1, 36.9, 27.1, 25.9, 24.5, 21.0, 18.2, −5.3, −5.6; HRMS (ESI) m/z calcd for $C_{16}H_{32}NOSi$ ($[M + H]^+$) 282.2253; found 282.2266.

Quincorine (21b). To a solution of **21c** (8 mg, 0.028 mmol) in THF (1 mL) was added TBAF (1 M in THF, 37 μL, 0.037 mmol) at 0 °C. The solution was allowed to warm to ambient temperature. After ca. 12 h, concentration and preparative TLC (CH_2Cl_2/MeOH 2:1) afforded quincorine (**21b**, 5.1 mg, 78%) as a colorless oil; $[\alpha]^{22.5}_D$ +38 (c 0.3, MeOH) [lit. $[\alpha]^{20}_D$ +39 (c 1.0, MeOH)[81]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, J = 17.3, 10.4, 7.6 Hz, 1H), 5.07−5.01 (m, 2H), 3.46−3.43 (m, 2H), 3.17 (dd, J = 14.0 Hz, J = 6.0 Hz, 1H), 2.98−2.90 (m, 3H), 2.70−2.57 (m, 2H), 2.34−2.29 (m, 1H), 1.85−1.79 (m, 1H), 1.75−1.71 (m, 1H), 1.57−1.41 (m, 2H), 0.80−0.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ141.9,1144, 63.0, 57.2, 55.7, 40.3, 40.1, 28.0, 27.3, 24.7; HRMS (ESI) m/z calcd for $C_{10}H_{18}NO$ ($[M + H]^+$) 168.1388; found 168.1388.

Quinuclidine 47: Alternate Route to *O*-TBS-Quincorine. To a solution of alcohol **45b** (18 mg, 0.053 mmol), PPh_3 (28 mg, 0.11 mmol, and imidazole (9 mg, 0.13 mmol) in THF (0.5 mL) at 0 °C was added I_2 (27 mg, 0.11 mmol) in two portions over 15 min. After 1 h the mixture was quenched with satd $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the iodide. This material was dissolved in MeOH (1.5 mL). To this solution was added NH_3/MeOH (7N, 1.5 mL). After ca. 12 h, the mixture was concentrated to provide the tertiary amine (18 mg). To a solution of the tertiary amine (13 mg) in MeOH/H_2O (5:1, 0.6 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (60 mg, 0.19 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature. After 2 h, the mixture was diluted with CH_2Cl_2, filtered, and purified by flash chromatography (CH_2Cl_2/MeOH 3:1 to 1:1) to afford **47** (11 mg, 85% over 3 steps) as a colorless oil; $[\alpha]^{25.4}_D$ +5.8 (c 0.3, $CHCl_3$); IR (film) 3352, 2950, 2927, 2857, 1463, 1254, 1117, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, J = 10.8, 6.0, 1H), 3.72−3.66 (m, 3H), 3.33 (dd, J = 13.6, 10.8 Hz, 1H), 3.27−3.17 (m, 1H), 3.12−3.04 (m, 1H), 2.88−2.78 (m, 1H), 2.68 (ddd, J = 13.2, 5.2, 2.4 Hz, 1H), 2.5 (br, 1H), 1.93−1.81 (m, 2H), 1.69 (m, apparent q, J = 6.8 Hz, 2H), 1.66−1.53 (m, 1H), 1.40 (br dd, J = 13.2, 6.8 Hz, 1H), 1.33−1.28 (br, 1H), 0.93−0.88 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ64.7, 60.8, 57.7, 57.1, 42.3, 37.3, 31.5, 27.0, 26.0, 23.5, 18.4, −5.2, −5.3, one carbon is not resolved; ^{13}C NMR (100 MHz, C_6D_6) δ65.5, 61.0, 57.6, 57.4, 42.2, 37.1, 32.2, 30.2, 26.7, 26.2, 24.4, 18.6, −5.1, −5.3; MS (ESI) m/z (relative intensity) 300.30 ($[M + H]^+$, 100%); HRMS (ESI) m/z calcd for $C_{16}H_{34}NO_2Si$ ($[M + H]^+$) 300.2359; found 300.2369.

***O*-TBS-Quincorine, Alternate Method.** To a solution of alcohol **47** (10 mg, 0.034 mmol) in THF (0.34 mL) were added 2-$O_2NC_6H_5SeCN$ (15 mg, 0.068 mmol) and Bu_3P (16 μL, 0.068 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated, and the residue (11 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (0.6 mL). To this solution were added aq K_2HPO_4 (2.4 M, 30 μL) and mCPBA (6 mg, 0.024 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) afforded *O*-TBS-quincorine (**21b**, 5.4 mg, 84%) as a colorless oil. This material was identical to that produced as described above.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NIH (R01-GM67187), NSF (CHE-0749850) and the University of Iowa for generous support of this work.

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