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A Diastereoselective Radical Cyclization Approach to Substituted Quinuclidines

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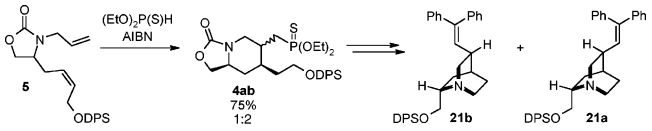

A new, concise, and flexible approach to novel quinuclidines has been developed, which employs a phosphorus hydride mediated radical addition/cyclization reaction in the key step. 1,7-Diene **5** reacts with diethyl thiophosphite in an efficient and diastereoselective radical addition/cyclization reaction to give trisubstituted piperidines **4ab**. Piperidines **4ab** are subsequently converted into 2,5-disubstituted quinuclidines using S_N2-type cyclizations. Finally, the resulting quinuclidines are shown to undergo novel Horner−Wadsworth−Emmons-type (HWE-type) reactions to give unsaturated quinuclidines **21a** and **21b**, which have structures similar to that of (−)-quinine **1**.

Quinuclidines are an important class of molecules found in many natural products[1,2] including (−)-quinine **1**, which is one of the most important naturally occurring alkaloids because of its role in treating malaria.[3] (−)-Quinine **1** is a member of the cinchona family of alkaloids, and these compounds and their derivatives have been used in a wide range of synthetic applications.[4] Various quinuclidines have also been shown to be inhibitors of the muscarinic (M_1),[5] serotonin-3 (5-HT_3),[6] and neurokinin (NK_1)[7] receptors and also as squalene synthase inhibitors.[8] The inhibition of these targets is important in the treatment of Alzheimer's dementia,[5] eating disorders, sexual behavior and stress,[9] depression,[10] and cholesterol blood levels.[8] Recently, 2,5-disubstituted quinuclidines[11] have been used as chiral ligands in asymmetric reactions.[12] The development of a new, general, and convergent method for the synthesis of substituted quinuclidines is therefore important to further exploit the important properties of this class of molecules.

Building on our earlier research into the phosphorus hydride mediated radical cyclization of dienes,[13] we embarked on a diastereoselective synthesis of 2,5-disubstituted quinuclidines, of type **2**, that would be amenable to a synthesis of (−)-quinine **1** (Scheme 1).[14] It is envisaged that the HWE-type reaction of unstabilized phosphonothioate **3** with ketones would give access to a diverse library of quinuclidines. Construction of phosphonothioate **3** is to be achieved by an S_N2-type cyclization of phosphonothioate **4**, which is to be synthesized by a diastereoselective phosphorus hydride mediated radical cyclization of diene **5**. Known iodide **6**[15] will be used to construct diene **5** and the oxazolidinone ring will act as a N- and O-protecting group.

Elaboration of substrates such as iodide **6** can be difficult due to the presence of a β-heteroatom.[16] However, it has been shown that iodide **6** readily forms an organozinc reagent, which reacts with a range of electrophiles.[17] The synthesis of diene **5** began with an organozinc/copper coupling reaction of iodide **6** (Scheme 2). Insertion of activated zinc (Zn*)[18] into the C−I bond in **6**, followed by transmetalation to copper, gave an

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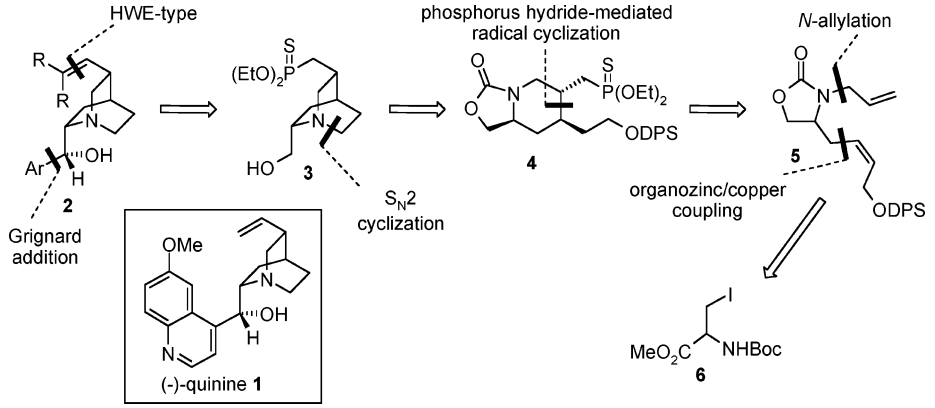
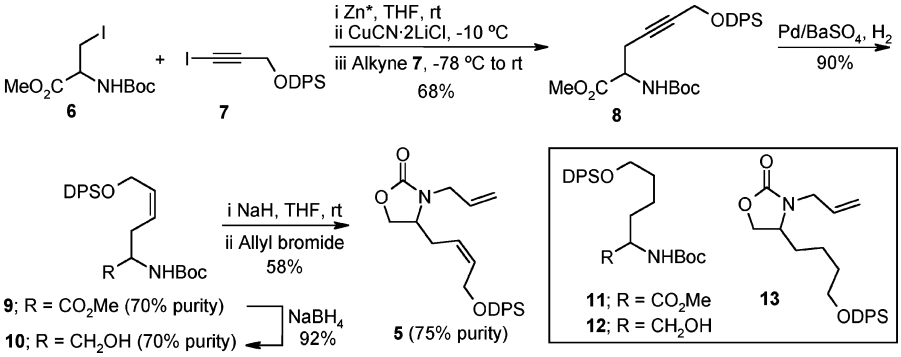
SCHEME 1. Retrosynthetic Analysis of Substituted Quinuclidine 2



SCHEME 2. Synthesis of Diene 5

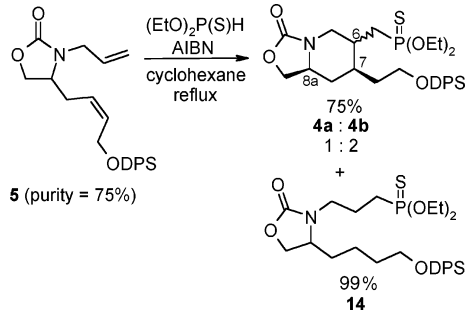


organozinc/copper reagent.[19] This reagent reacted with alkynyl iodide **7** (formed in 96% yield in one step from the previously reported *tert*-butyl(diphenyl)(2-propynyloxy)silane)[20,21] to give alkyne **8** in good yield on a multigram scale. Reduction of alkyne **8** with Pd/$BaSO_4$ (Rosenmund's catalyst)[22] gave the most reliable partial hydrogenation of the C≡C bond in **8**, but the purity of *Z*-alkene **9** was judged to be only 70% (the ^{1}H NMR spectrum indicated ca. 30% of alkane **11**, which is formed by further reduction of the C═C bond in **9**).[23] Unfortunately, alkene **9** and alkane **11** were inseparable by column chromatography. Alternative conditions and catalysts (e.g., use of quinoline and sulfur as catalyst poisons or Lindlar reduction) gave lower yields of alkene **9**.

Reduction of the ester group in **9** required only mild conditions and gave alcohol **10** in excellent yield (containing ca. 30% of alkane **12** derived from ester **11**).[23] Conversion of alcohol **10** into diene **5** was accomplished in 23% yield over two steps; however, a telescoped, one-pot cyclization and N-allylation of alcohol **10** gave diene **5** in an improved 58% yield (the purity was judged to be 75% as diene **5** contained ca. 25% of alkene **13** carried through from over-reduction of alkyne **8**).[24]

Radical cyclization of diene **5** with diethyl thiophosphite[13] proceeded with complete regioselectivity for the 6-*exo-trig* product **4** (Scheme 3). The ^{1}H and ^{13}C NMR spectra of the product indicated that the cyclization was diastereoselective, producing an inseparable mixture of only two of the four possible diastereomers. The efficiency and diastereoselectivity of the cyclization was not significantly affected by the reaction conditions. For example, using AIBN as initiator (in cyclohexane, 80 °C) afforded **4a** and **4b** in a combined 56−75% yield (dr 1:1.7−2.2),[23] whereas the use of Et_3B/O_2 as initiator (in cyclohexane, rt) afforded **4a** and **4b** in a combined 47−68% yield (dr 1:1.5−2.0).[23] NOESY experiments in vide showed that the major diastereomer **4b** had the same relative stereochemistry as (−)-quinine **1** with the minor diastereomer **4a** being epimeric at C-6. In addition, a byproduct was also isolated in 99% yield (based on alkene **13**), which was consistent with phosphonothioate **14**, derived from addition of diethyl thiophosphite to the C═C bond in alkene **13**.

SCHEME 3. Radical Cyclization of Diene 5 (Relative Stereochemistry is Indicated)



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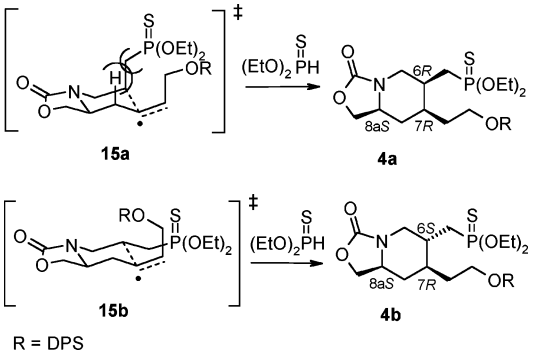
SCHEME 4. Transition States Leading to Phosphonothioates 4a and 4b (Relative Stereochemistry is Indicated)



The selective formation of phosphonothioates **4a** and **4b** can be explained by the transition states adopted in the radical cyclization of diene **5**. 6-*Exo-trig* radical cyclizations are known to proceed via "chairlike" transitions states,[25] and the thermodynamically most favored transition state, **15b**, has all substituents in *pseudo*-equatorial positions, which leads to the major diastereomer **4b** (Scheme 4). The minor diastereomer **4a** is formed from transition state **15a** that places the methylphosphonothioate group axially, so incurring one unfavorable 1,3-diaxial interaction. The relative stereochemistry at C-7 is fixed due to the presence of the oxazolidinone ring[26] and the *Z*-geometry of the acceptor alkene.[27]

Conversion of phosphonothioates **4a** and **4b** into quinuclidines required opening of the oxazolidinone ring, but the hydrolysis conditions were incompatible with the DPS ether in **4ab**. Therefore, the DPS ether was removed and primary alcohol **16** was reprotected to give trityl ether **17** in good yield (Scheme 5). The oxazolidinone ring in **17** was then hydrolyzed using aqueous sodium hydroxide and the primary alcohol was protected as its DPS ether to give piperidines **18a** and **18b** (separable by column chromatography, dr = 1:1.3). The trityl ether in **18a** and **18b** was selectively cleaved under acidic conditions in the presence of thiophenol (in the absence of thiophenol the separation of amino alcohols **19a** and **19b** from trityl alcohol was problematic).[28]

Using the conditions developed by Stork,[14b] the amino alcohols **19a** and **19b** were selectively O-mesylated without the need for temporary N-protection (Scheme 6). The crude mesylates then underwent cyclization on heating in acetonitrile to give quinuclidines **20a** and **20b** in good yield. It was found that reducing the amount of MsCl (1.05 to 0.6 equiv) gave improved yields of the quinuclidine **20a** (from 31% to 92%).

Novel HWE-type reactions of unstabilized quinuclidinyl methylphosphonothioates **20a** and **20b** with benzophenone proceeded to give **21a** in (unoptimized) 42% yield and **21b** in 93% yield.[13c] NOESY NMR experiments indicated that the major diastereomer **21b** had the same relative stereochemistry as (−)-quinine **1** and the minor diastereomer was the C-5 epimer (Figure 1).[20] Removal of the DPS group from **21b** with TBAF gave alcohol **22b** (Scheme 7).

In conclusion, a short and reasonably efficient synthesis of diene **5** has been developed starting from iodide **6** (four steps and 24% yield). Phosphorus hydride mediated radical cyclization of diene **5** was shown to proceed efficiently and diastereoselectivity to give trisubstituted piperidines **4a** and **4b** that were efficiently converted into quinuclidines. Novel HWE-type reactions of unstabilized quinuclidinyl methylphosphonothioates **20a** and **20b** were demonstrated to give excellent yields of alkenyl-substituted quinuclidines **21a** and **21b**. Quinuclidine **21b** was shown to have the same relative stereochemistry as (−)-quinine **1**, and current research is exploring adapting this approach to a stereoselective synthesis of (−)-quinine **1**.

Experimental Section[20]

***O,O*-Diethyl [*rel*-(6*S*,7*R*,8a*S*)-7-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-3-oxohexahydro-[1,3]oxazolo[3,4-*a*]pyridin-6-yl]methylphosphonothioate 4a and *O,O*-Diethyl [*rel*-(6*R*,7*R*,8a*S*)-7-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-3-oxohexahydro[1,3]oxazolo[3,4-*a*]pyridin-6-yl]methyl-phosphonothioate 4b.** To a solution of diene **5** (0.20 g containing 25% alkene **13** as judged from the ^{1}H NMR spectrum, 0.35 mmol) in degassed cyclohexane (15 mL) was added diethyl thiophosphite (0.14 g, 0.92 mmol) and AIBN (8 mg, 0.046 mmol). The reaction was heated to reflux for 12 h during which time further portions of AIBN (6 × 8 mg, 0.28 mmol) were added. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford phosphonothioates **4a** and **4b** (0.16 g, 75%) as a 1:2 mixture of diastereomers as indicated from the ^{1}H NMR spectrum (by comparison of the integral values of the signals at 4.39 and 4.32 ppm). R_f 0.3 (petroleum ether/Et_2O 1:2); IR (CH_2Cl_2) ν_{max} 2959, 2932, 2859, 1753, 1473, 1427, 1390, 1111, 1049, 1025, 959 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66−7.63 (m, 4H), 7.46−7.36 (m, 6H), 4.39 and 4.32 (2 × t, J = 8.5, 1H), 4.24−3.99 (m, 5H), 3.83−3.45 (m, 3H), 2.87 and 2.50 (d, J = 12.5 Hz and dd J = 13.0, 10.5 Hz, 1H), 2.30−2.19 (m, 1H), 2.00−1.36 (m, 8H), 1.32, 1.28 and 1.26 (3 × t, J = 7.0 Hz, 6H), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.3 (C), 156.3 (C), 135.5 (CH), 135.43 (CH), 135.41 (CH), 133.6 (C), 133.5 (C), 133.4 (C), 129.64 (CH), 129.61 (CH), 127.62 (CH), 127.59 (CH), 68.0 (CH_2), 67.6 (CH_2), 62.61 (d, J_{CP} = 7.0 Hz, CH_2), 62.63 (d, J_{CP} = 7.0 Hz, CH_2), 62.5 (d, J_{CP} = 7.0 Hz, CH_2), 62.4 (d, J_{CP} = 7.0 Hz, CH_2), 60.7 (CH_2), 60.6 (CH_2), 54.4 (CH), 53.6 (CH), 46.4 (d, J_{CP} = 2.5 Hz, CH_2), 45.5 (d, J_{CP} = 1.5 Hz, CH_2), 36.2 (d, J_{CP} = 15.0 Hz, CH), 35.8 (d, J_{CP} = 1.5 Hz, CH_2), 35.6 (d, J_{CP} = 112.0 Hz, CH_2), 35.5 (CH_2), 35.3 (d, J_{CP} = 3.0 Hz, CH), 34.9 (CH_2), 34.6 (d, J_{CP} = 13.5 Hz, CH), 31.5 (d, J_{CP} = 2.5 Hz, CH), 31.2 (CH_2), 29.9 (d, J_{CP} = 112.0 Hz, CH_2), 26.79 (CH_3), 26.76 (CH_3), 19.1 (C), 19.0 (C), 16.12 (d, J_{CP} = 7.0 Hz, CH_3), 16.10 (d, J_{CP} = 7.0 Hz, CH_3), 16.06 (d, J_{CP} = 7.0 Hz, CH_3), 16.04 (d, J_{CP} = 7.0 Hz, CH_3); LRMS (CI, NH_3) *m*/*z* 590 ([M + H]$^+$, 14%), 512 (100); HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ found 590.2525, calcd 590.2525 for $C_{30}H_{44}NO_5PSSi$.

***rel*-(2*S*,4*R*,5*R*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-5-(2,2-diphenylvinyl)-1-azabicyclo[2.2.2]octane 21a.** A solution of phosphonothioate **20a** (72 mg, 0.13 mmol) was dissolved in anhydrous THF (6 mL) and cooled to −78 °C. ^{s}BuLi (0.33 mL of a 0.80 M solution in cyclohexane, 0.26 mmol) was added and after 0.1 h of stirring at −78 °C, benzophenone (48 mg, 0.26 mmol) was added. The reaction was allowed to warm slowly to room temperature and was stirred at this temperature for 16 h before being quenched with NH_4Cl (saturated aqueous solution) and then

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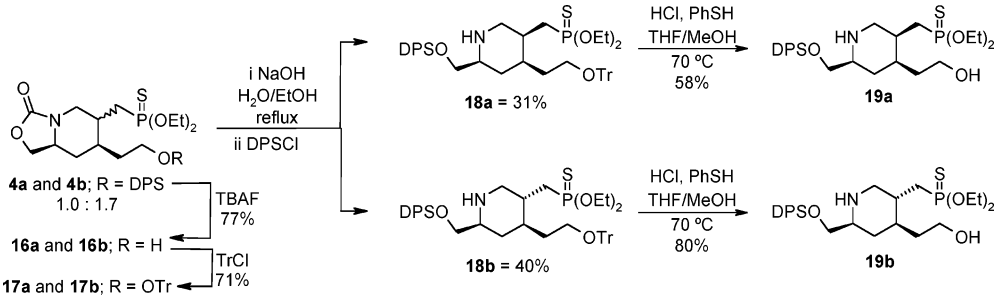
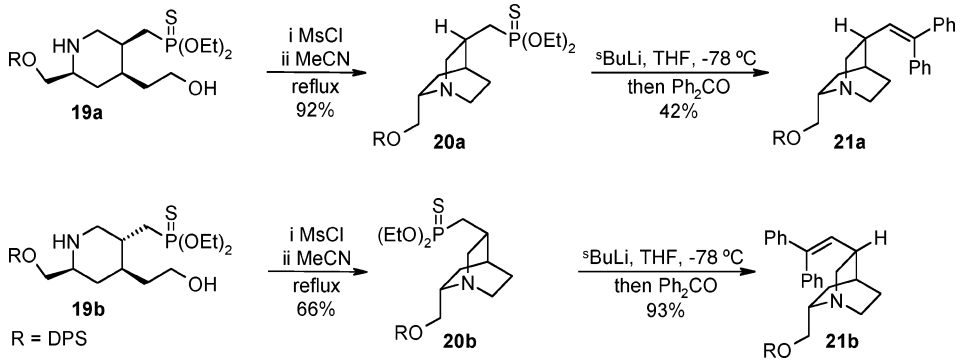
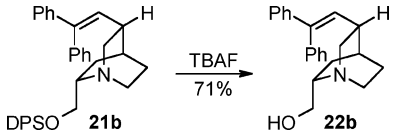
SCHEME 5. Synthesis of Amino Alcohols 19a and 19b (Relative Stereochemistry is Indicated)



SCHEME 6. Synthesis of Quinuclidines 21a and 21b (Relative Stereochemistry is Indicated)



SCHEME 7. Formation of Amino Alcohol 22b



extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil. Purification by flash column chromatography on silica, eluting with a solvent gradient of petroleum ether/Et_2O (1:1) to petroleum ether/Et_2O/Et_3N (33:67:1), afforded quinuclidine **21a** (31 mg, 42%) as a colorless oil. R_f 0.2 (petroleum ether/Et_2O 1:2); IR (CH_2Cl_2) ν_{max} 2958, 2931, 2860, 1603, 1493, 1471, 1444, 1427, 1315, 1279, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.60−7.63 (m, 4H), 7.41−7.32 (m, 9H), 7.27−7.20 (m, 5H), 7.15−7.13 (m, 2H), 6.20 (d, J = 10.0 Hz, 1H), 3.71 (d, J = 6.0 Hz, 2H), 3.11−3.00 (m, 2H), 2.85−2.74 (m, 2H), 2.62 (dd, J = 13.5, 7.0 Hz, 1H), 2.50−2.43 (m, 1H), 1.93−1.81 (m, 1H), 1.80−1.75 (m, 1H), 1.65−1.57 (m, 1H), 1.45−1.33 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.6 (C), 142.4 (C), 140.1 (C), 135.6 (CH), 133.5 (C), 133.4 (C), 131.7 (CH), 129.7 (CH), 129.6 (CH), 128.2 (CH), 128.1 (CH), 127.62 (CH), 127.59 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 66.2 (CH_2), 56.7 (CH_2), 56.4 (CH), 43.1 (CH_2), 35.4 (CH), 30.2 (CH_2), 28.4 (CH), 26.8 (CH_3), 21.5 (CH_2), 19.2 (C); LRMS (CI, NH_3) m/z 558 ([M + H]$^+$, 100%); HRMS (CI, NH_3) m/z [M + H]$^+$ found 558.3196, calcd 558.3192 for $C_{38}H_{43}NOSi$.

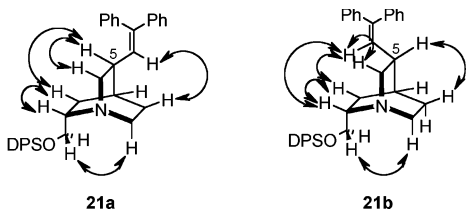


FIGURE 1. Key NOESY correlations for quinuclidine **21a** and quinuclidine **21b**.

***rel*-(2*S*,4*R*,5*S*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-5-(2,2-diphenylvinyl)-1-azabicyclo[2.2.2]octane 21b.** A solution of phosphonothioate **20b** (20 mg, 0.037 mmol) was dissolved in anhydrous THF (2 mL) and cooled to −78 °C. ^{s}BuLi (0.092 mL of a 0.80 M solution in cyclohexane, 0.073 mmol) was added and after 0.1 h of stirring at −78 °C, benzophenone (13 mg, 0.078 mmol) was added. The reaction was allowed to warm slowly to room temperature and was stirred at this temperature for 2 h before being quenched with NH_4Cl (saturated aqueous solution) and then extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil that was purified by flash column chromatography on silica (using petroleum ether/Et_2O/Et_3N (67:33:1) to (33:67:1) as eluent) to afford quinuclidine **21b** (20 mg, 93%) as a colorless oil. R_f 0.4 (petroleum ether/Et_2O 1:2); IR (neat) ν_{max} 3057, 2929, 2860, 1599, 1493, 1471, 1427, 1265, 1228, 1198, 1113, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.71−7.66 (m, 4H), 7.43−7.21 (m, 14H), 7.15−7.13 (m, 2H), 6.18 (d, J = 10.0 Hz, 1H), 3.79 (dd, J = 10.0, 5.5 Hz, 1H), 3.73 (dd, J = 10.0, 7.0 Hz, 1H) 3.08 (dd, J = 13.5, 10.0 Hz, 1H) 3.07−2.91 (m, 2H), 2.69 (dd, J = 13.5, 4.5 Hz, 1H), 2.58−2.49 (m, 1H), 2.43−2.36 (m, 1H), 2.08−2.01 (m, 1H), 1.78−1.74 (m, 1H), 1.46−1.36 (m, 2H), 1.32−1.22 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.7 (C), 141.9 (C), 140.1 (C), 135.6 (CH), 133.6 (C), 133.5 (C), 132.9 (CH), 129.8 (CH), 129.6 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 66.7 (CH_2), 57.9 (CH_2), 57.6 (CH), 42.0 (CH_2), 35.9 (CH), 27.9 (CH), 27.4 (CH_2), 26.9 (CH_3), 25.3 (CH_2), 19.3 (C); LRMS (CI, NH_3) m/z 558 ([M + H]$^+$, 100%); HRMS (CI, NH_3) m/z [M + H]$^+$ found 558.3197, calcd 558.3192 for $C_{38}H_{43}NOSi$.

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Supporting Information Available: Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra for compounds **4**, **5**, **7**−**10** and **16**−**22b**; 2D HSQC, COSY and NOESY spectra for compounds **21a**, **21b** and **22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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