Iodocyclization of *O*-(3-Cyclohexenyl)thiocarbamidates. An Unexpected Approach to Vicinal *cis*-Aminocyclohexenols

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An unprecedented and unexpected iodocyclization of *O*-(3-cyclohexenyl)thiocarbamidates **2a**−**c** to diiodides **7a**−**c**, followed by alkaline hydrolysis and iodide elimination, has uncovered an alternative approach to vicinal *cis*-aminocyclohexenols **10a**−**c** and **11a**−**c**. This represents a new approach to these interesting building blocks.

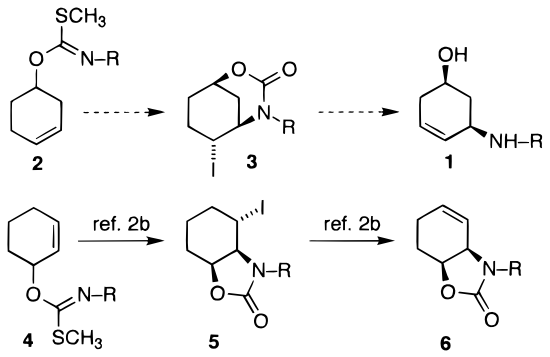
In the course of our work toward the synthesis of new azasugar analogues, we required the preparation of several *cis*-5-alkylamino-3-ciclohexenols **1** on a multigram scale.[1]

On the basis of the well-precedented synthesis of tetrahydrobenzoxazol-2-ones **6** from iodocyclization of *O*-(2-cyclohexenyl)thiocarbamidates **4** followed by dehydroiodination of the intermediate iodobenzoxazolones **5**,[2] we became interested in the exploration of the synthetic potential of isomeric *O*-(3-cyclohexenyl)thiocarbamidates **2** for an analogous transformation into the corresponding iodocarbamates **3** as potential precursors of target amino alcohols **1** (Scheme 1).[3]

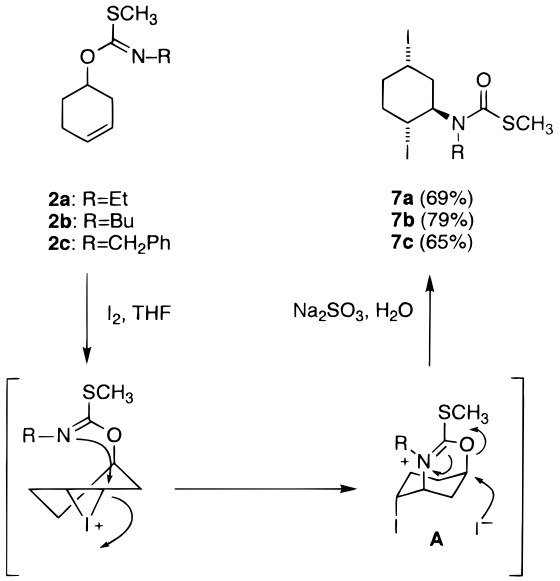
However, treatment of thiocarbamidates **2a**−**c** with iodine[4] in THF followed by sodium sulfite quench,[2b] afforded the unexpected *S*-methyldiiodothiocarbamates **7a**−**c** in 65−79% yield, whose structural assignment was confirmed from X-ray diffraction analysis of **7a** (Scheme 2).[5]

Formation of **7a**−**c** can be interpreted as the result of iodide attack upon a transient 1,3-bridged iminium salt **A**[6] (Scheme 2) arising from regio- and stereocontrolled *trans*-iodocyclization of the starting thiocarbamidates **2a**−**c**. No trace of the expected iodocarbamates **3a**−**c**, arising from hydrolysis of the above iminium salts, were

Scheme 1



Scheme 2



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|| X-ray diffraction analysis.

(1) Amino alcohols **1** had already been prepared in our laboratory according to described procedures by a multistep synthesis in low overall yields (unpublished results).

(2) (a) Knapp, S.; Patel, D. V. *J. Am. Chem. Soc.* **1983**, *105*, 6985−6986. (b) Knapp, S.; Patel, D. V. *J. Org. Chem.* **1984**, *49*, 5072−5076. (c) Knapp, S. *Chem. Soc. Rev.* **1999**, 61−72.

(3) For examples of related 1,3-iodocyclizations in cyclohexene derivatives, see: (a) Carrol, F. I.; Abraham, P.; Pitner, J. B.; Jablonski, S. D.; Sing, P.; Kwon, Y. W.; Triggle, D. J. *J. Chem. Soc., Chem. Commun.* **1992**, 795−796. (b) Knapp, S.; Lal, G. S.; Sahai, D. *J. Org. Chem.* **1986**, *51*, 380−383.

(4) Iodocyclization of **2b** with N-iodosuccinimide afforded diiodide **7b** in low yield together with other unidentified byproducts.

(5) Compounds **7a**−**c** showed very similar spectral patterns. Structural assignment of thiocarbamates **7a**−**c** by direct inspection of their NMR data was not possible due to extensive peak broadening as a result, in part, of the rotameric equilibrium associated with the thiocarbamate moiety.

(6) Iminium salts have been proposed as intermediates in related halocyclization processes. See, for example, ref 2a and: (a) Knapp, S.; Patel, D. V. *Tetrahedron Lett.* **1982**, *23*, 3539; (b) Winstein, S.; Goodman, L.; Boschan, S. *J. Am. Chem. Soc.* **1950**, *72*, 2311.

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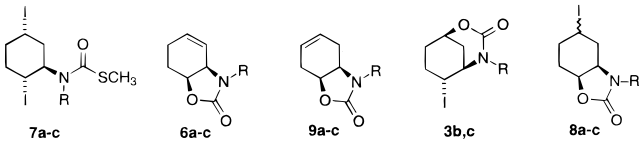
Table 1. Alkaline Hydrolysis of 7a−c, 3b−c, and 8b−c with Saturated Aqueous Na_2CO_3/THF/Dioxane (60/35/5)



entry	starting material	R	*T* (°C)	time (h)	products[a] (%)
1	**7a**	Et	reflux	18	**6a** (71), **9a** (24)
2	**7a**	Et	rt	60	**8a** (15)[b]
3	**7b**	Bu	reflux	18[c]	**3b** (46), **8b** (40)
4	**7b**	Bu	rt	60	**8b** (12)[b]
5	**7c**	$PhCH_2$	reflux	18[d]	**3c** (67), **8c** (22)
6	**7c**	$PhCH_2$	rt	60	**8c** (10)[b]
7	**3b**	Bu	reflux[e]	24	no reaction
8	**3c**	$PhCH_2$	reflux[e]	24	no reaction
9	**8b**	Bu	reflux[e]	24	**6b** + **9b** (<10)[b,f]
10	**8c**	$PhCH_2$	reflux[e]	24	**6c** + **9c** (<10)[b,f]

[a] Isolated yields. [b] Together with unreacted starting material. [c] After refluxing for 36 h, small amounts of **6b** and **9b** (<10% by ^{1}H NMR) were also detected in the crude reaction mixture. [d] After refluxing for 36 h, small amounts of **6c** and **9c** (<10% by ^{1}H NMR) were also detected in the crude reaction mixture. [e] No reaction was observed at room temperature. Reactions were carried out in the presence of catalytic iodide. [f] Determined by ^{1}H NMR.

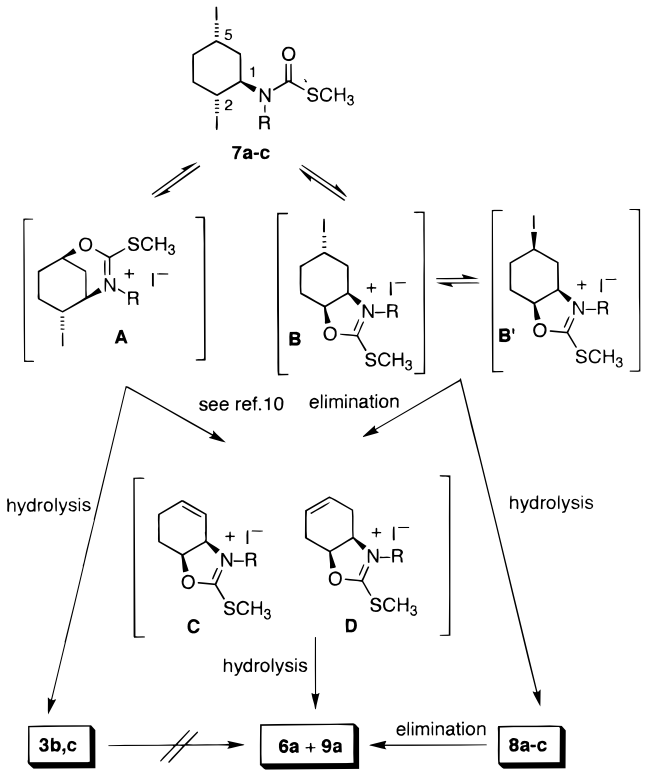
detected at this stage under these mild hydrolytic conditions (saturated aqueous Na_2SO_3, room temperature). To our knowledge, this iminium salt reactivity is unprecedented in the literature.

Under harsher conditions (saturated aqueous Na_2CO_3/THF/dioxane 60/35/5, reflux) hydrolysis of **7a**−**c** turned out to be dependent on the nature of the starting diiodothiocarbamate (see Table 1).

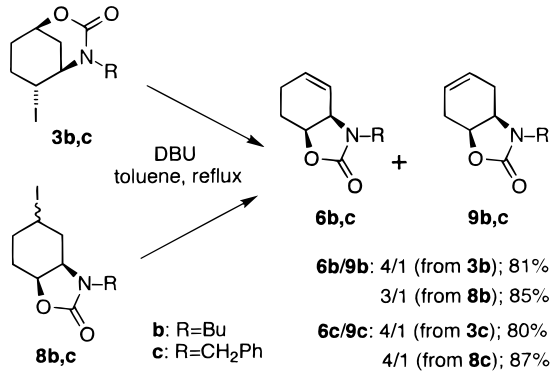
Thus, whereas **7a** afforded a 3:1 mixture of tetrahydrobenzoxazolones **6a** and **9a** in 95% overall yield (entry 1), treatment of **7b** and **7c** under identical conditions afforded iodocarbamates **8b**,**c** (each of them as a 9:1 mixture of epimeric iodides[7]) and **3b**,**c** in good overall yields (entries 3 and 5). Treatment of **7a**−**c** at room temperature in the above solvent system afforded only a 10−15% of **8a**−**c** together with unreacted starting material (entries 2, 4, and 6).[8] No interconversion between iodocarbamates **3** and **8** was observed when pure samples of **3b**,**c** and **8b**,**c** were treated separately both at reflux (entries 7−10) and at room temperature under the above conditions in the presence of catalytic iodide.[9]

Formation of iodocarbamates **3b**,**c** and **8a**−**c** can be explained by hydrolysis of the transient iminium salts **A** or **B**/**B′**, respectively, arising from the stereocontrolled displacement of each of the iodine atoms of the starting diiodide **7** (Scheme 3). Alternatively, HI elimination from either **A**[10] or **B**/**B′** followed by hydrolysis of the mixture of iminium salts **C** and **D** thus generated, would account

Scheme 3



Scheme 4



for the formation of carbamates **6a** and **9a** (Scheme 3). In light of these results, it seems reasonable to assume that both pathways are competing processes that depend mainly on the nature of the nitrogen substitution on the starting *S*-methylthiocarbamates **7**.

Dehydroiodination of **8b**,**c** with DBU in refluxing toluene afforded a mixture of isomeric tetrahydrobenzoxazolones **6b**,**c** and **9b**,**c** in high yields. Surprisingly, the same mixture was also obtained in comparable ratio and yields after treatment of iodocarbamates **3b**,**c** under the above conditions (Scheme 4). These last results point out the unusual reactivity of the carbamate moiety in these bridged systems.

Although the mechanism of this transformation remains elusive, the reaction outcome can be explained by H_a or H_b removal from **3b**,**c** followed by stereocontrolled iodide displacement by the transient carbamate anion thus generated (Scheme 5). Base-induced elimination of

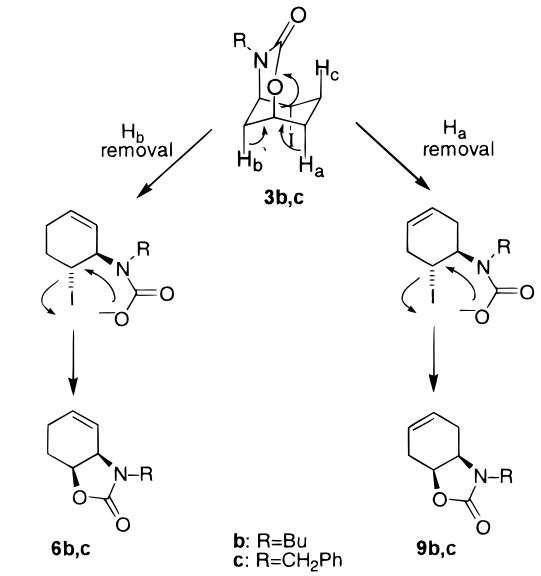
(7) Epimerization of iodocarbamates **8b** and **8c** might arise from iodide promoted inversion-equilibration of the C_5−I bond (**7a**−**c** numbering, see Scheme 3).

(8) Since no epimerization of starting dioidides **7a**−**c** was observed, direct equilibration between **7a**−**c** and the iminium salt **B′** can be ruled out (see Scheme 3).

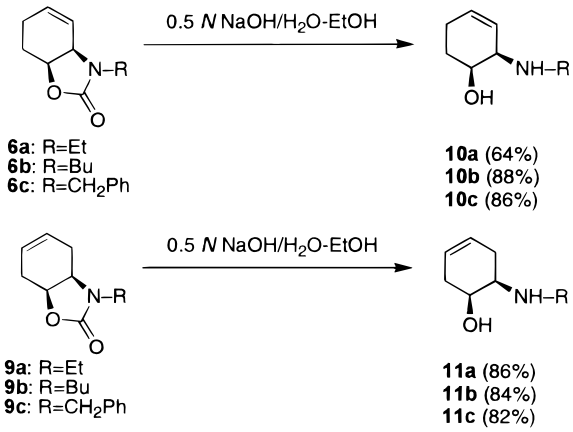
(9) The identity of the reaction products was confirmed as follows: (a) dehydroiodination of iodocarbamates **8b**,**c** afforded the corresponding tetrahydrobenzoxazolones **6b**,**c** and **9b**,**c** (see text); (b) the structure of iodocarbamates **3b**,**c** was secured by X-ray diffraction analysis of **3c**; (c) carbamates **6a**−**c** were obtained independently from thiocarbamidates **4a**−**c** *via* the iodocyclization-dehydrohalogenation sequence outlined in Scheme 1 (ref 2b); d) the structure of carbamates **9a**−**c** was inferred from spectroscopic data and by their conversion into amino alcohols **11a**−**c** (Scheme 7).

(10) Formation of **C** + **D** from **A** could be explained by analogy to the postulated mechanism for the formation of **6** + **9** from **3** (see text and Scheme 5).

Scheme 5



Scheme 6



carbamate vs iodide would be favored by the rigid carbamate bridge forcing a *trans*-diaxial relationship between the carbamate oxygen and both H_a and H_b. Compounds arising from HI elimination via H_c abstraction have not been isolated probably due to the steric hindrance around H_c. It can be assumed that this alternative pathway does not compete with carbamate elimination under our reaction conditions.

Alkaline hydrolysis of each of the carbamates **6a**−**c** and **9a**−**c** afforded the corresponding *cis*-amino alcohols **10a**−**c** and **11a**−**c**, respectively, in high yields (Scheme 6).

In summary, the unexpected outcome of *O*-(3-cyclohexenyl)thiocarbamidate iodocyclization has uncovered an alternative and versatile approach to vicinal *cis*-aminocyclohexenols involving a mechanistically interesting 1,4-oxygen migration in a cyclohexenyl system.

Experimental Section

Melting points are uncorrected. FT-IR spectra are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions at 200 MHz (for ^1H) and 50 MHz (for ^{13}C), respectively, unless otherwise indicated. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the singlet at 7.24 ppm of $CDCl_3$ for ^1H and in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C. GC−MS were determined on a mass spectrometer coupled to a gas chromatograph equipped with a fused silica capillary column SPB-5 (30 m × 0.32 mm i.d.). This technique was used as a standard criterion of purity. In all cases, the mass of the major peak (>95%) was consistent with the molecular ion or a fragmentation thereof. Solvents were distilled prior to use and dried by standard methods. Usual reaction workup consists of drying the organic extracts over sodium sulfate, filtration and evaporation under reduced pressure. Thiocarbamidates **2a**−**c** were prepared from 3-cyclohexenol[11] following the experimental procedure described in ref 2b.

Iodocyclization of Thiocarbamidates 2a−**c**. A solution of the corresponding thiocarbamidate **2a**−**c** (25 mmol) in THF (40 mL) is treated under Ar with a solution of iodine (4.5 g, 37.5 mmol) in THF (80 mL) at room temperature until consumption of starting material (checked by TLC). The mixture is treated with excess aqueous sat. Na_2SO_3 solution and volatiles are removed under reduced pressure. The remaining aqueous phase is extracted with CH_2Cl_2 and worked up in the usual way to afford the corresponding thiocarbamate **7a**−**c** as a solid. **7a**: 69%; mp 87−88 °C (after crystallization from ether); ^1H NMR 0.89 (3H), 1.4−2.8 (2H), 2.1 (1H), 2.2 (2H), 2.6 (1H), 3.5 (3H), 4.9 (1H), 5.1 (1H); ^{13}C NMR 12.7, 14.2, 30.2, 32.9, 36.5, 37.4, 39.9, 46.8, 65.8, 168.5; IR 1645, 1359. Anal. Calcd for $C_{10}H_{17}I_2NOS$: C, 26.51; H, 3.78; I, 56.01; N, 3.85. Found: C, 26.17; H, 3.58; I, 55.73; N, 3.67. **7b:** 79%; mp 92−94 °C (after crystallization from ether); ^1H NMR (300 MHz) 0.89 (3H), 1.24−1.4 (3H), 1.56 (4H), 1.78 (1H), 2.1 (1H), 2.22 (3H), 2.49 (1H), 3.26−3.49 (3H), 4.94−5.20 (2H); ^{13}CNMR 12.8, 13.7, 19.9, 30.1, 30.6, 32.8, 36.5, 37.5, 40.1, 52.2, 66.2, 168.6; IR 1649, 1361. Anal. Calcd for $C_{12}H_{21}I_2NOS$: C, 29.95; H, 4.40; I, 52.75; N, 2.91. Found: C, 30.30; H, 4.07; I, 52.46; N, 3.21. **7c:** 65%; mp 130−131 °C (crystallized from ether); ^1H NMR 1.4−1.8 (2H), 2.36 (3H), 2.45 (2H), 3.6 (1H), 4.39 (1H), 4.69 (1H), 4.90 (1H), 5.18 (1H); ^{13}CNMR 13.2, 29.8, 31.8, 36.5, 37.5, 39.7, 55.6, 63.2, 128.0, 128.6, 137.5; IR 2931, 1645, 1357. Anal. Calcd for $C_{15}H_{19}I_2NOS$: C, 34.97; H, 3.72; I, 49.26; N, 2.72. Found: C, 35.21; H, 3.69; I, 49.31; N, 2.67.

Hydrolysis of Diiodothiocarbamates 7a−**c.** A solution of 8 mmol of the corresponding diiodothiocarbamate **7a**−**c** in THF (30 mL), dioxane (5 mL), and aqueous saturated Na_2CO_3 solution (50 mL) was heated at reflux temperature. After 18 h, volatiles were removed and the remaining aqueous phase was extracted with CH_2Cl_2. Usual workup gave an oil which was flash chromatographed on silica gel on hexanes/EtOAc/Et_3N (10/2/0.5) to afford tetrahydrobenzoxazolones **6a** and **9a** (from **7a)** or iodocarbamates **3b** and **8b** (from **7b)** and **3c** and **8c** (from **7c**). **6a**: 71%; ^1H NMR 1.14 (3H), 1.71−2.20 (4H), 3.07 (1H), 3.44 (1H), 4.08 (1H), 4.68 (1H), 5.37 (1H), 6.02 (1H); ^{13}CNMR 12.9, 19.7, 24.6, 36.6, 51.5, 72.3, 121.5, 132.7, 157.5. **9a** (24%); ^1H NMR 1.08 (3H), 1.60−2.45 (4H), 2.98 (1H), 3.40 (1H), 3.98 (1H), 4.73 (1H), 5.84 (2H); ^{13}C NMR 12.4, 27.8, 24.9, 36.1, 52.9, 72.1, 125.9, 126.5, 157.5. **3b**: 46%; ^1H NMR 0.86 (3H), 1.1−2.3 (10H), 2.85 (1H), 3.30−3.63 (2H), 3.87 (1H), 4.46 (1H); MS (EI) 323, 243, 196, 154, 152. **3c**: 67%; ^1H NMR 1.6−2.0 (5H), 2.54 (1H), 3.53 (1H), 4.22 (1H), 4.27 (1H), 4.58 (1H), 4.81 (1H), 7.25 (5H); ^{13}CNMR 26.6, 27.2, 27.5, 51.5, 56.1, 72.9, 127.7, 127.9, 128.0, 128.7, 136.7, 154.0. Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.08; H, 4.52; I, 35.53; N, 3.92. Found: C, 47.17; H, 4.68; I, 35.75; N, 3.76. **8b** (40%, 9:1 mixture of epimers): major isomer: ^1H NMR 0.87 (3H), 1.2−1.6 (4H), 1.7−2.2 (6H), 2.86 (1H), 3.36 (1H), 3.75 (1H), 4.41 (2H); MS (EI) 323, 196, 154, 152. **8c** (22%, 9:1 mixture of epimers) major isomer: ^1H NMR 1.75−2.2 (6H), 3.6 (1H), 4.04 (1H), 4.26 (1H), 4.40 (1H), 4.61 (1H), 7.27 (5H); ^{13}CNMR 23.0, 26.5, 31.2, 37.0, 46.1, 54.3, 71.9, 128.0, 128.9, 135.9, 158.3. Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.08; H, 4.52; I, 35.53; N, 3.92. Found: C, 47.32; H, 4.77; I, 35.84; N, 4.23.

Dehydroiodination of Iodocarbamates 3b,c and 8b,c. A solution of 0.3 mmol of the starting iodocarbamate **3b,c** or **8b,c** (9:1 mixture of epimers on the C_5−I bond) in toluene is treated with DBU (0.47 mmol). The reaction mixture is heated

(11) Gogek, C. J.; Moir, R. Y.; Purves, C. B. *Can. J. Chem.* **1951**, *29*, 946-948.

at reflux temperature until no starting material is observed by TLC (typically 4−6 h). The mixture is diluted with CH_2Cl_2 and worked-up in the usual way to give an oil which, after flash-chromatography (hexanes/EtOAc/Et_3N 20/4/1) afforded a mixture of benzoxazolones **6b**,**c** and **9b**,**c**. **6b** (65% from **3b**; 64% from **8b**): selected spectroscopic data: ^{1}H NMR 4.06 (1H), 4.66 (1H), 5.73 (1H), 6.02 (1H); ^{13}C NMR 51.9, 72.2, 121.4, 132.7, 157.8. **6c**[2b] (64% from **3c;** 70% from **8c**). **9b** (16% from **9b**; 21% from **11b)**: selected spectroscopic data: ^{1}H NMR 3.75 (1H), 4.72 (1H), 5.69−5.86 (2H); ^{13}C NMR 52.9, 72.4, 126.1, 126.4. **9c** (16% from **3c**; 17% from **8c**): selected spectroscopic data: ^{1}H NMR 1.75−2.45 (4H), 3.75 (1H), 4.01 (1H), 4.65 (1H), 4.72 (1H), 5.69−5.86 (2H), 7.24 (5H); ^{13}C NMR 24.6, 27.8, 45.7, 52.9, 72.4, 126.1, 126.4.

Hydrolysis of tetrahydrobenzoxazolones 6a−c and 9a−c. A solution of the corresonding benzoxazolone (1.5 mmol) in aqueous 0.5 N NaOH (25 mL) and EtOH (10 mL) was heated at reflux temperature until total consumption of starting material (TLC monitoring). The cooled reaction mixture was extracted with CH_2Cl_2, and the organic extracts were evaporated to dryness. The residue was purified by flash chromatography or by sublimation to give the corresponding amino alcohols **10a−c** or **11a−c** in the yields indicated in Scheme 6. Selected NMR data for amino alcohols **10**: ^{1}H NMR 2.9−3.1 (1H), 3.6−3.7 (1H), 5.5−5.6 (1H), 5.7−5.8 (1H); ^{13}C NMR 55, 65, 126, 129. **10c**. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.02; H, 8.64; N, 6.76. Amino alcohols **11**: ^{1}H NMR 2.6−2.8 (1H), 5.5 (2H), 3.8−3.9 (1H); ^{13}C NMR 51, 65, 124, 125. **11c**. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.50; H, 8.12; N, 6.96.

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Supporting Information Available: X-ray coordinates for **3c** and **7a**, and ^{1}H NMR copies for **2a**,**c**, **3c**, **6a**,**c**, **7a**, **9a**,**c**, **10a−c**, and **11a**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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