(Z)-14, 93564-77-3; 15, 93711-46-7; 16, 93564-78-4; 17, 93564-79-5; 18, 89951-15-5; 19, 93711-47-8; 20, 93564-80-8; 21, 93564-81-9; 22, 93564-82-0; 23, 93564-83-1; 24, 93564-84-2; 25, 93564-85-3; 26, 93564-86-4; 27, 93564-87-5; 28, 90025-53-9; 29, 93564-88-6; 30, 93564-89-7; 31, 93564-90-0; 32, 89951-17-7; 33, 89951-20-2; 34, 89951-21-3; 35, 93564-91-1; 36, 89951-22-4; malononitrile, 109-77-3; [(ethoxycarbonyl)methylene]triphenylphosphorane, 1099-45-2; ethyl orthoacetate, 78-39-7.

Model Studies of a Conceptually New Approach to the Total Synthesis of Quinine

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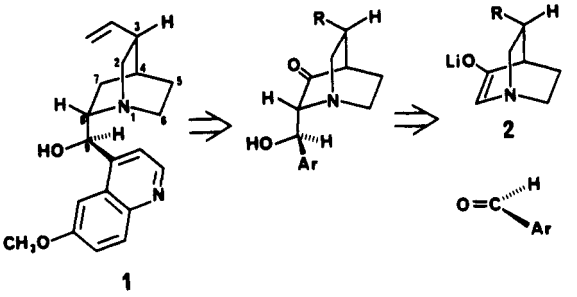
Received May 30, 1984

3-Quinuclidinone was converted to diastereomer-pure racemic *erythro*-2-(α-hydroxybenzyl)quinuclidine (**9**) in 40% yield over five steps. Erythro stereochemistry was established by using a stereoselective aldol condensation of the lithium enolate of 3-quinuclidinone with benzaldehyde at −78 °C. Hydride reduction of the intermediate β-ketoalkoxide afforded a single diastereomer of the resulting diol. Reductive removal of the C-3 hydroxyl led to **9**. This model study demonstrates a conceptually new approach to the total synthesis of quinine.

Although several total syntheses of quinine (**1**) have been reported,[2] none of these has satisfactorily demonstrated solutions to two sets of related stereochemical problems: efficient generation of C-8/C-9 erythro stereochemistry and communication of configurational control from C-3/C-4 to C-8 during or prior to formation of the N-1/C-8 bond. An alternative (Scheme I) to these "classical" methodologies[2] could avoid the troublesome aspects of this step altogether by employing a substrate[3] which contains an intact quinuclidine ring system. A diastereoselective aldol condensation[4] of enolate **2** with an appropriate aldehyde[5] under aprotic, kinetic conditions could, in fact, establish the desired C-8/C-9 erythro stereochemistry of **1**; and these

Scheme I



new chiral centers should also have the correct relationships to those already present in **2**, *if* R (vinyl or vinyl group equivalent) were sufficiently bulky to force the condensation to occur only from the opposite side of the C-2/C-3 bridge. Although the latter aspect of our stereochemical hypothesis has not yet been demonstrated, the viability of this new approach has now been illustrated in part (for the specific case **3**: i.e., **2** where R = H) by the conversion of 3-quinuclidinone to *erythro*-2-(α-hydroxybenzyl)quinuclidine (**9**) in 40% overall yield (Scheme II).

The enolate **3** was generated by reaction of 3-quinuclidinone hydrochloride[6] with 2 equiv of lithium diisopropylamide (LDA) and condensed with benzaldehyde at −78 °C. After workup, the resulting erythro β-ketol **4** (structure confirmed by single-crystal X-ray analysis[7a]) was produced with at least 90% stereoselectivity.[8] Unfortunately, **4** was not particularly stable in solution; substantial equilibration of **4** with its threo isomer via epimerization at C-2 was observed by NMR spectrometry after several

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(2) (a) Woodward, R. B.; Doering, W. von E. *J. Am. Chem. Soc.* **1944**, *66*, 849; **1945**, *67*, 860 and references cited therein. (b) Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425 and references cited therein. (c) Uskokovic, M. R.; Gutzwiller, J.; Henderson, T. *J. Am. Chem. Soc.* **1970**, *92*, 203 and references cited therein. (d) Gutzwiller, J.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 204; **1978**, *100*, 576 and references cited therein. (e) Gates, M.; Sugavanam, B.; Schreiber, W. L. *J. Am. Chem. Soc.* **1970**, *92*, 205 and references cited therein. (f) Uskokovic, M. R.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1971**, *93*, 5903 and references cited therein. (g) Grethe, G.; Lee, H. L.; Mitt, T.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 5904; **1978**, *100*, 581; **1978**, *100*, 589 and references cited therein. (h) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1972**, *94*, 6218 and references cited therein. (i) Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571 and references cited therein.

(3) For two different approaches to the preparation of C-3/C-4 diastereomer-pure 3-functionalized 7-quinuclidinones (quinine numbering) which may serve as useful precursors to enolate **2** where R ↛ H, see: (a) Coffen, D. L.; McEntee, T. E., Jr. *J. Chem. Soc. D.* **1971**, 539. (b) Friedman, M. D. Ph.D. Dissertation, 1978, The University of Texas at Austin.

(4) For an excellent review and leading references, see: Mukaiyama, T., *Org. React. (N.Y.)* **1982**, *28*, 203.

(5) (a) The aldol condensation of **3** with 6-methoxyquinoline-4-carboxaldehyde[11] proved analogous to that of **3** with benzaldehyde (the latter described in the text for preparation of β-ketol **4**). However, for a variety of reasons, 6-methoxyquinoline-4-carboxaldehyde proved unsuitable in the corresponding condensation/reduction (analogous to the preparation of diol **5** reported in the text). Preliminary results suggest that **3** and *N*-carbomethoxy-6-methoxy-1,2-dihydroquinoline-4-carboxaldehyde[5b] can be used in a condensation/reduction and that a product analogous to *erythro-trans*-**5** is formed. (b) Prepared via mild acid hydrolysis of the corresponding dioxolane (reported as **9g** in Minter, D. E.; Stotter, P. L. *J. Org. Chem.* **1981**, *46*, 3965).

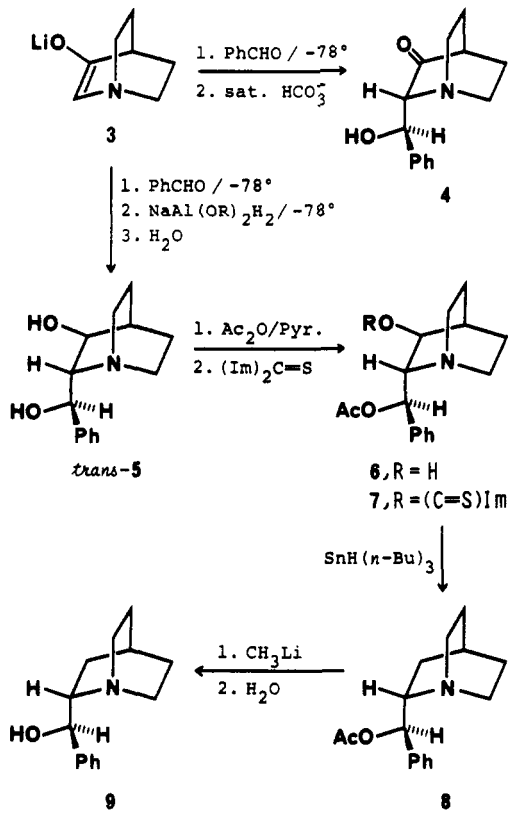
(6) Obtained from either Aldrich or Fluka, or by synthesis as described: Daeniker, H. U.; Grob, C. A. *Org. Synth.* **1964**, *44*, 86.

(7) Harlow, R. L.; Simonsen, S. H. *Cryst. Struct. Commun.* (a) **1976**, *5*, 465; (b) **1976**, *5*, 785.

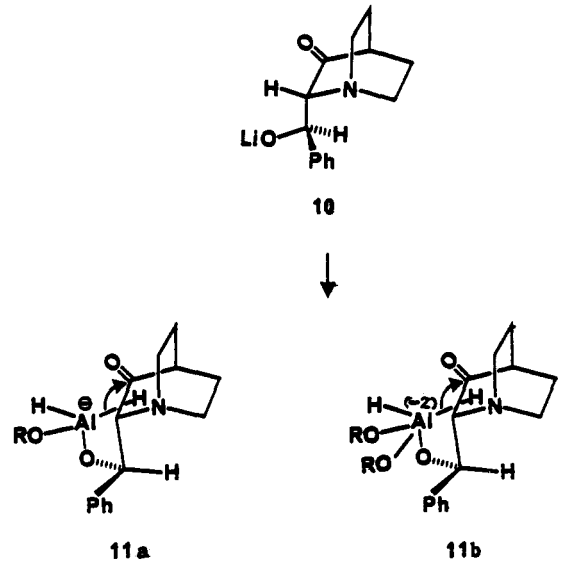
(8) As demonstrated in the text, the exact stereoselectivity (at or near 100%) of the aldol condensation which generated erythro β-ketol **4** was obscured by subsequent equilibration (an artifact of workup). In most cases, less than 10% of the threo diastereomer was observed as a contaminant in the NMR spectrum of crude **4** when precautions were taken to isolate the β-ketol from solution as rapidly as possible. Note that complete equilibration of purified *erythro*-**4** could be effected within 48 h at ambient temperature in $CDCl_3$ containing trace DCl and produced a 1:1 mixture of erythro and threo isomers.

0022-3263/85/1950-0029$01.50/0

Scheme II



Scheme III



hours, even in acid-free $CDCl_3$.[8] Thus, the extreme lability of **4** precluded the possibility of converting **4** to **9** in a single step by standard reactions.

Attempts to reduce the carbonyl of **4** to an alcohol by using $NaBH_4$ or $LiAlH_4$ led, in high yield, to mixtures of *erythro-trans*-**5** and its C-3 epimer *erythro-cis*-**5** (with *trans*-**5** predominating). While it would appear that either isomer could be deoxygenated to give **9**, only *erythro-trans*-**5** readily underwent the required oxygen manipulations selectively, as discussed in subsequent paragraphs. Direct reduction of the β-ketoalkoxide **10** (rather than its conjugate acid **4**) gave particularly interesting results. Thus, although $LiAlH_4$ reduction of **10** gave both *erythro-trans*-**5** and *erythro-cis*-**5**, sodium bis(2-methoxyethoxy)aluminum dihydride afforded *erythro-trans*-**5** almost exclusively (structure confirmed by single-crystal X-ray analysis[7b]). The very high selectivity of this reduction may result from internal hydride delivery via the intermediacy of complexes **11** (tetra- or pentacoordinate aluminum hydride species). Formation of **11** rather than direct, bimolecular hydride delivery to **10** may be favored at low temperature by the use of an alkoxy-substituted aluminum hydride reducing agent (Scheme III), a rather weak hydride donor which may nevertheless be capable of exchanging alkoxide ligands (to form **11a**) or of adding an additional ligand (to form **11b**). To some extent, operation of a similar intramolecular hydride delivery may explain the predominant formation of *erythro-trans*-**5** when erythro β-ketol **4** was reduced with $LiAlH_4$ and $NaBH_4$, although the control of C-3 stereochemistry in these reactions was far from complete.

Of particular importance, both synthetically and mechanistically, the low-temperature in situ reduction of **10** afforded "double diastereoselectivity" in the production of diol **5**: not only was hydride delivery itself highly stereoselective but it also prevented equilibration at C-2 (via enolization). Only by analyzing the mother liquor from recrystallization of *erythro-trans*-**5** could any trace of *erythro-cis*-**5** be detected; and no diol derived from the threo isomer of **10** was observed. Thus, a further consequence of this highly selective formation of *erythro-trans*-**5** is a more accurate assessment of kinetic stereoselection in the aldol condensation of **3** with benzaldehyde. Generation of intermediate **10** must be essentially 100% stereoselective.[8]

Reductive removal of the C-3 hydroxyl of *erythro-trans*-**5** required selective protection of the benzylic alcohol. Acylation was employed since both formation and removal of the protecting group could be effected without the use of acidic conditions (thus avoiding possible epimerization via a benzylic carbocation). As expected from an examination of molecular models, monoacetate **6** was obtained when the less hindered benzylic alcohol was selectively acetylated by using acetic anhydride/pyridine. In contrast, *erythro-cis*-**5** gave a mixture of starting diol, benzylic acetate, and diacetate under the same acetylation conditions. Since the benzylic hydroxyl appears to be the more accessible in both trans and cis isomers of *erythro*-**5**, it is likely that the diacetate of *cis*-**5** arises subsequent to benzylic acetylation and intramolecular transesterification.

Barton's method[9] for the deoxygenation of secondary alcohols was used to convert **6** into **8** in 65% yield. Cleavage of the acetyl protecting group gave **9** as a single diastereomer.

This model study forms the groundwork for a conceptually new approach to the total synthesis of quinine and represents a significant improvement over earlier attempts[10] to use quinuclidine precursors. Future research will concentrate on identifying the best group R for directing condensations of **2** with 6-methoxyquinoline-4-carboxaldehyde[5,11] or its equivalent.[5]

Experimental Section

All reactions were carried out by using degassed solvents under a nitrogen atmosphere. Anhydrous tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. ^1H

(9) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(10) See, for example: Bender, D. R.; Coffen, D. L. *J. Org. Chem.* **1968**, *33*, 2504; *J. Heterocycl. Chem.* **1971**, *8*, 937. Coffen, D. L.; Korzan, K. *J. Org. Chem.* **1971**, *36*, 390; as well as ref 3a.

(11) Most efficiently prepared from 6-methoxy-4-methylquinoline[11a] by the method of Bender et al.[10] or by a modification[3b] of the method of Schreiber.[11b] (a) Campbell, K. N.; Schnaffner, I. J. *J. Am. Chem. Soc.* **1945**, *67*, 87. (b) Schreiber, W. L. Ph.D. Dissertation, 1970, University of Rochester.

NMR spectra were recorded on Varian A60, A60A, T60 and/or EM390 spectrometers using $CDCl_3$ solutions with Me_4Si as an internal standard; the spectral data reported below were obtained at 60 MHz unless otherwise indicated. IR spectra were recorded on a Beckman IR4220 or IR5A spectrophotometer. Melting points were determined with a Fischer-Johns hot stage and are uncorrected. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN; all new compounds gave satisfactory analyses for carbon and hydrogen.

Preparation of *erythro-trans*-5. Lithium diisopropylamide was prepared by dropwise addition of 7.8 mL of 1.6 M ethereal CH_3Li (12.5 mmol) to a solution of 1.30 g (12.9 mmol) of diisopropylamine in 60 mL of dry THF at 0 °C. After 30 min, 1.00 g (6.2 mmol) of finely powdered 3-quinuclidinone hydrochloride was added all at once; and the resulting mixture was allowed to stir at 0 °C until homogeneous (20–30 min). The solution was then cooled to −78 °C and 0.68 g (6.4 mmol) of benzaldehyde was added. After 25 min, 3.4 mL (11.9 mmol) of Red-Al (Aldrich) [sodium bis(2-methoxyethoxy)aluminum dihydride, 3.5 M in benzene] diluted with 5 mL of THF was added and the cooling bath was removed. The reaction mixture was allowed to warm to room temperature and stir for an additional 30 min. Addition of 10 mL of water (caution) resulted in the precipitation of aluminum salts which adhered to the flask allowing the clear yellow organic solution to be decanted. The solution was dried over Na_2SO_4, and most of the solvents were removed by rotary evaporation. Remaining volatiles were removed at 0.1 mm (room temperature, 24 h).[12] Recrystallization of the crude residual semisolid from THF/pentane gave 1.10 g (76%, 2 crops) of pure *erythro-trans*-5: mp 146–147 °C; ^1H NMR (90 MHz) δ 1.03–2.04 (5 H, m, H4, H5, H8), 2.13–3.00 (5 H, m, H2, H6, H7), 3.18 (2 H, br s, OH), 3.85 (1 H, unresolved d of multiplets appearing as a br d, J = 5.4 Hz, H3), 4.54 (1 H, d, J = 9.0 Hz, PhCH), 7.37 (5 H, br s, Ph); IR ($CHCl_3$) 1449, 1214, 1085, 1055, 1033, 986, 966 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.20; H, 8.24.

Preparation of Erythro β-Ketol 4. 3-Quinuclidinone hydrochloride (1.50 g, 9.3 mmol) was converted to its enolate by using 18.8 mmol of lithium diisopropylamide in THF (70 mL) at 0 °C, which was then treated with benzaldehyde (0.98 g, 9.2 mmol) at −78 °C according to the procedure described above. After 25 min at −78 °C, the reaction mixture was poured into 200 mL of saturated $NaHCO_3$ at 0 °C (rapid stirring). The product was extracted with ether (4 × 70 mL), dried over Na_2SO_4, and isolated as a pale yellow solid after removal of solvents by rotary evaporation. Residual volatiles were removed at 0.1 mm. Recrystallization from ether gave 1.83 g (85%) of pure 4: mp 128–129 °C; ^1H NMR δ 1.62–2.18 (4 H, m, H5, H8), 2.43 (1 H, quintet, J = 3.0 Hz, H4), 2.57–3.10 (4 H, m, H6, H7), 3.26 (1 H, br d, J = 7.7 Hz, H2), 4.39 (1 H, br s, OH), 4.93 (1 H, d, J = 7.7 Hz, PhCH), 7.30 (5 H, br s with fringes, Ph).

Monoacetate 6. Acetic anhydride (0.45 g, 4.4 mmol) was added dropwise in 5 min to a stirred solution of 0.95 g (4.0 mmol) of *erythro-trans*-5 in 12 mL of dry pyridine at room temperature. After 20 h at room temperature, the reaction mixture was poured into 25 mL of saturated $NaHCO_3$ at 0 °C. When evolution of CO_2 had ceased, the product was extracted (3 × 20 mL of CH_2Cl_2) and dried over Na_2SO_4. Removal of solvents by rotary evaporation followed by pumping for 3 h at 0.1 mm gave 1.15 g of crude solid. Recrystallization from CH_2Cl_2/pentane gave 0.93 g (84%, 2 crops) of pure 6: mp 155–156 °C; ^1H NMR δ 1.00–1.96 (5 H, m, H4, H5, H8), 2.05 (3 H, s, $COCH_3$), 2.22 (1 H, s, OH), 2.42–3.08 (5 H, m, H2, H6, H7), 3.69 (1 H, unresolved d of multiplets, H3), 5.81 (1 H, d, J = 9.7 Hz, PhCH), 7.32 (5 H, br s with fringes, Ph). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.60; H, 7.65.

Imidazolide 7. A solution of 1.01 g (3.67 mmol) of 6 and 1.23 g (6.9 mmol) of *N,N'*-thiocarbonylbis(imidazole) in 8 mL of dry THF was heated at reflux for 24 h under N_2 atmosphere. The reaction mixture was cooled, diluted with 50 mL of ether, and washed with 5% $NaHCO_3$ (2 × 25 mL). The organic layer was dried over $MgSO_4$, and the solvents were removed by rotary evaporation. Recrystallization of the yellow residual solid (1.21 g) from CH_2Cl_2/pentane gave 1.04 g (74%, 2 crops) of white needles: mp 165–166 °C; ^1H NMR (90 MHz) δ 1.17–2.08 (4 H, m, H5, H8), 1.94 (3 H, s, $COCH_3$), 2.35 (1 H, sextet, J = 3.0 Hz, H4), 2.46–3.24 (4 H, m, H6, H7), 3.35 (1 H, ddd, J = 9.7, 5.4, 1.1 Hz, H2), 5.67 (1 H, ddd, J = 5.4, 3.0, 1.1 Hz, H3), 5.96 (1 H, d, J = 9.7 Hz, PhCH), 7.40 (5 H, br s with fringes, Ph), 7.12 (1 H), 7.69 (1 H), and 8.40 (1 H) [narrow multiplets, Im ring H's]; IR ($CHCl_3$) 1730, 1453, 1373, 1330, 1276, 1096, 986, 901 cm^{-1}. Anal. Calcd for $C_{20}H_{23}N_3O_3S$: C, 62.32; H, 6.01. Found: C, 62.13; H, 6.23.

Acetate 8. A solution of 0.39 g (1.01 mmol) of imidazolide 7[13] in 30 mL of dry toluene was added dropwise in 45 min to a refluxing solution of 1.63 g (5.6 mmol) of tri-*n*-butyltin hydride in 30 mL of toluene. After an additional 3 h at reflux, the reaction mixture was cooled in ice and then extracted with 0.3 M HCl (3 × 15 mL). The aqueous extracts were combined, saturated with NaCl, and made basic by addition of solid KOH. The product was extracted (5 × 20 mL of CH_2Cl_2) and dried over Na_2SO_4. Removal of solvents by rotary evaporation followed by pumping for 30 min at 0.1 mm gave 0.25 g of crude solid. Recrystallization from hexane gave 0.23 g (88%) of pure 8: mp 100–101 °C; ^1H NMR δ 1.10–1.93 (7 H, m, H3, H4, H5, H8), 2.03 (3 H, s, $COCH_3$), 2.46–3.48 (5 H, m, H2, H6, H7), 5.81 (1 H, d, J = 9.5 Hz, PhCH), 7.30 (5 H, br s with fringes, Ph); IR ($CHCl_3$) 1723, 1446, 1365, 1317, 1230 (br), 1013, 984, 901 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 74.30; H, 8.37.

***erythro*-2-(α-Hydroxybenzyl)quinuclidine (9).** A solution of 0.127 g (0.49 mmol) of acetate 8 in 30 mL of dry ether was cooled to 0 °C, and 0.8 mL of 1.3 M ethereal CH_3Li (1.04 mmol) was added via syringe. After 20 min at 0 °C, 2 mL of water was added and the organic layer was washed with saturated NaCl solution (3 × 10 mL). The brine washings were combined and extracted with CH_2Cl_2 (2 × 20 mL). The CH_2Cl_2 extracts were combined with the original organic layer and dried over $MgSO_4$. Rotary evaporation of the solvent afforded 0.113 g of white powder which, upon recrystallization from ether/hexane, yielded 0.099 g (93%, 2 crops) of pure 9: mp 140–141 °C; ^1H NMR δ 1.17–2.00 (7 H, m, H3, H4, H5, H8), 2.17–3.60 (5 H, m, H2, H6, H7), 4.58 (1 H, br s, OH), 4.80 (1 H, d, J = 5.6 Hz, PhCH), 7.27 (5 H, br s with fringes, Ph); IR ($CHCl_3$) 1447, 1321, 1273, 1003, 984, 904 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.35; H, 8.65.

Acknowledgment. This research was supported in part by grants from Research Corporation (to P.L.S.), the Morrison Trust (Grant RA-41 to P.L.S.), Cadbury Schweppes, Limited (to P.L.S. and D.E.M.), The Robert A. Welch Foundation (Grants F-345 and AX-637 to P.L.S. and P-853 to D.E.M.), and the National Institutes of Health (Grant RR-08194 to The UTSA and PHS Award to D.E.M.). We express specific thanks to G. Stork, M. R. Uskokovic, D. L. Coffen, D. McHale, and T. G. Halsall for useful discussion at various stages during the conduct of this model study.

(12) The crude product does not crystallize readily unless 2-methoxyethanol (from hydrolysis of aluminum alkoxides) and benzyl alcohol (from reduction of excess benzaldehyde) are removed in vacuo. Partitioning of the crude product mixture between ether and aqueous acid efficiently removes these alcohols from the desired amine, but recovery of the amine after basification of the aqueous extract is inefficient because *erythro-trans*-5 is highly water soluble.

(13) For effective reduction of imidazolide 7 with tri-*n*-butyltin hydride, highly purified 7 must be used; in particular, 7 must be uncontaminated by residual imidazole (produced in the reaction of excess *N,N'*-thiocarbonylbis(imidazole) with 6 and in the subsequent aqueous workup), since imidazole apparently catalyzes decomposition of the tin hydride reagent.[9]