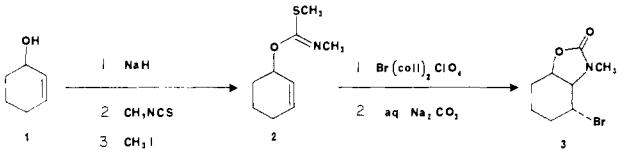
Bromocyclization of Unsaturated Thiocarbamidates. Synthesis of (±)-Sporamine

Spencer Knapp* and Dinesh V. Patel

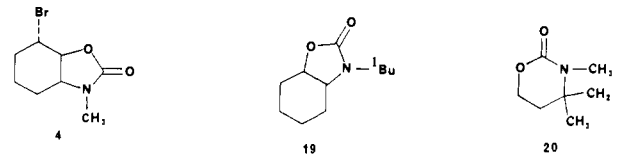
Department of Chemistry
Rutgers, The State University of New Jersey
New Brunswick, New Jersey 08903
Received May 20, 1983

Our efforts toward the synthesis of aminocyclitol antibiotics from non-carbohydrate precursors depend on stereo- and regiospecific olefin functionalization reactions.[1-3] In particular we have been concerned with the preparation of *cis*-1,2-methylamino alcohols, since this pattern, along with other amino alcohol groupings, commonly occurs among these structures.[4] We wish to report a new method for the unambiguous conversion of unsaturated alcohols to protected alkylamino alcohols, as illustrated below for cyclohexenol (**1**).

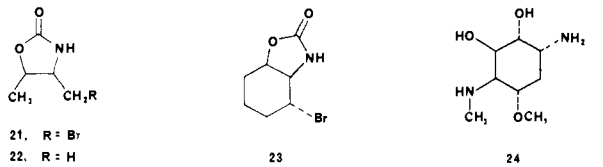


Treatment of the sodium salt of **1** (NaH, THF, 25 °C) with 1 equiv of methyl isothiocyanate gave an ambident anion that reacted with iodomethane at sulfur to produce the thiocarbamidate **2**. Without purification **2** was added to a solution of bis(collidine)bromonium perchlorate[5] (1.2 equiv) in dichloromethane solution at −78 °C. After 30–45 min the reaction mixture was quenched at −78 °C and stirred for 10 h at 25 °C with aqueous sodium carbonate. Extractive workup and chromatography gave the product of bromocyclization, carbamate **3**, in 65% overall yield from **1**. The synthesis of **3** from **1** amounts to stereo- and regiospecific functionalization of the alkene, provides the *cis*-1,2 methylamino alcohol group in protected form, and complements our previous conversion of **1** to bromocarbamate **4**.[3a]

Table I shows the application of this procedure to several cyclic and acyclic unsaturated alcohols using methyl, benzyl, and *tert*-butyl isothiocyanate. In all cases the condensation step (e.g., **1** → **2**) was essentially quantitative. The successful cyclizations each gave a single isomer except 1-buten-3-ol (**6**, entry 3), for which no sigificant relative stereochemical induction was observed under either mode of reagent addition. Two substrates, 4-hydroxycyclohexene (with MeNCS) and **8b** (with *t*-BuNCS), gave mostly recovered thiocarbamidate rather than a cyclized product. The structures of the cyclization products follow from their IR and ^{1}H NMR spectra and, in the cases of **5b** and **9b**, from their quantitative conversion to **19**[6] and **20**, respectively, using *n*-Bu_3SnH.[7]



To assign structures to the isomers of **7**, we developed a straightforward method for removing the *N*-*tert*-butyl group. When the isomer with lower R_f was dissolved in trifluoroacetic acid at 25 °C, the *N*-*tert*-butyl group of the starting material was cleanly converted to *tert*-butyl trifluoroacetate, according to ^{1}H NMR analysis.[8] Removal of the solvent gave a nearly quantitative yield of **21**. Reduction of **21** as above afforded *cis*-4,5-dimethyloxazolidin-2-one (**22**), a known compound.[9] The conversion of *cis*-**7** to **22** was also accomplished the other way around: *n*-Bu_3SnH reduction and then trifluoroacetic acid treatment. This dealkylation procedure[10] is a valuable accessory to the bromocyclization reaction, since it permits the synthesis of *N-unsubstituted* amino alcohols in protected form. For example, trifluoroacetic acid (25 °C, 24 h, 99%) converted **5b** to **23**, which is formally the product of hydroxyl-directed bromoamination of the alkene **1**.



The value of these transformations for the synthesis of aminocyclitols is illustrated by the conversion of bromocarbamate **13** to (±)-sporamine (**24**) in three steps (TFA; *n*-Bu_3SnH; aqueous NaOH, 25 °C) in better than 90% overall yield. Sporamine is the aminocyclitol portion of the broad-spectrum antibiotic sporaricin A.[11]

Several control experiments provided additional information about the bromocyclization reaction. In one case (entry 8), quenching with aqueous sodium *bicarbonate* allowed the isolation of the uncontaminated iminium salt **14**, whose structure is indicated by the deshielded resonances in its ^{1}H NMR spectrum.[12] Hydrolysis of **14** using aqueous sodium *carbonate* gave **5b**, as expected. From this example and literature precedent,[13,3a] it seems likely that iminum salt intermediates are involved in all these bromocyclizations. The thiocarbamidate (**16**, entry 9) derived from cyclohexanol (**15**) was subjected to the bromocyclization conditions to see if N-bromination occurred. The reaction mixture was warmed to 25 °C and diluted with ether to precipitate any salts, but only the original bromonium reagent was found, and **16** was recovered unchanged from the filtrate. The evidence thus suggests that the bromocyclization reaction proceeds by simple trans intramolecular capture of a bromonium ion by the thiocarbamidate nitrogen. Finally, exposure of cyclohexene (**17**, entry 10) to the bromonium reagent under the conditions used for bromocyclization resulted in rapid conversion to *trans*-2-bromo-1-cyclohexyl perchlorate (**18**), isolated after quenching with cold 1% aqueous sulfuric acid and identified by comparing the R_f and IR and ^{1}H NMR spectra with the published[14] values. The addition of perchlorate ion is thus a possible side reaction in cases where attack by the thiocarbamidate nitrogen is not sterically favored or is reversible.

In summary, bromocarbamates such as **3** and **13** may be efficiently prepared from unsaturated alcohols and transformed in several useful ways, opening up new avenues for the synthesis of amino alcohols. We are currently exploring further application

(1) The halolactonization reaction is the archetypal olefin cyclofunctionalization reaction. For references to this and other directed functionalizations of acyclic alkenes, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(2) For recent cyclofunctionalization reactions related to this work, see: (a) Pauls, H. W.; Fraser-Reid, B. *J. Org. Chem.* **1983**, *48*, 1392. (b) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1308.

(3) Recent related work from our laboratory: (a) Knapp, S.; Patel, D. V. *Tetrahedron Lett.* **1982**, *23*, 3539. (b) Knapp, S.; Ornaf, R. M.; Rodriques, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 5494.

(4) Rinehart, K. L.; Suami, T. "Aminocyclitol Antibiotics", American Chemical Society: Washington, D. C., 1980.

(5) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190.

(6) Compound **19** was independently synthesized by treating *cis*-2-(*tert*-butylamino)cyclohexanol with carbonyldiimidazole (Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628), confirming the cis ring fusion.

(7) Parnes, H.; Pease, J. *J. Org. Chem.* **1979**, *44*, 151.

(8) *cis*-**7** had a half-life in trifluoroacetic acid of 35 h at 25 °C and 2.3 h at 47 °C.

(9) Foglia, T. A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680.

(10) For methods of protecting amide nitrogen, see: McOmie, J. F. W. "Protective Groups in Organic Chemistry"; Plenum Press: New York, **1973**, 405. For reductive N-debenzylation of 2-oxazolidinones, see: Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.

(11) Deushi, T.; Nakayama, M.; Watanabe, I.; Mori, T. *J. Antibiot.* **1979**, *32*, 187.

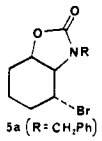
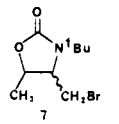
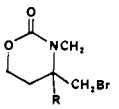
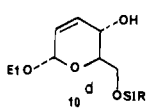
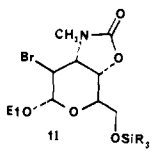
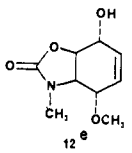
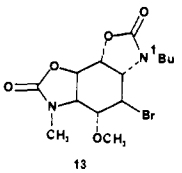
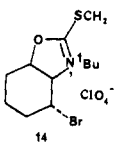
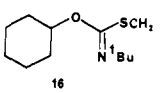
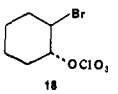
(12) Compound **14** ^{1}H NMR ($CDCl_3$, 60 MHz) 1.95 (s, 9 H), 1.4–2.6 (m, 6 H), 2.85 (s, 3 H), 3.97–4.33 (m, 1 H), 4.97 (dd, J = 5, 7, 1 H), 5.5–5.8 (m, 1 H).

(13) Winstein, S.; Goodman, L.; Boschan, R. *J. Am. Chem. Soc* **1950**, *72*, 2311.

(14) Zefirov, N. S.; Koz'min, A. S.; Zhdankin, V. V.; Nikulin, A. V.; Zyk, N. V. *J. Org. Chem.* **1982**, *47*, 3679.

0002-7863/83/1505-6985$01.50/0

Table I. Synthesis of Bromocarbamates[a]

entry	substrate	isothiocyanate	product	% yield[b]
1	1	$PhCH_2NCS$	 5a (R = CH_2Ph)	83
2	1	tBuNCS	5b (R = tBu)	86
3		tBuNCS	 7 (c t = 14 1)	68
4	 8a (R = H)	MeNCS	 9a (R = H)	69
5	8b (R = CH_3)	MeNCS	9b (R = CH_3)	83
6	 10	MeNCS	 11	82
7	 12	tBuNCS	 13	75
8	1	tBuNCS	 14	52
9	 15	tBuNCS	 16	99
10	 17		 18	94

[a] Reaction conditions are as described in the text unless otherwise specified. [b] The products were isolated by column chromatography on silica using petroleum ether–ethyl ether mixtures as eluant. Yields refer to the overall conversion of substrate to product. [c] Addition of the bromonium reagent *to* a solution of the thiocarbamidate from 6 gave 7 in 49% yield (1.9:1 cis/trans). [d] This substrate was prepared in 87% yield by selective monosilylation (Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* 1972, *94*, 6190) of ethyl 2,3-dideoxy-α-D-erythrohex-2-enopyranoside. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* 1969, 570. [e] Compound **12** was prepared in 9 steps from 1,3-cyclohexadiene. Knapp, S.; Sebastian, M. J.; Ramanathan, H. *J. Org. Chem.*, in press. [f] In this experiment the bromocyclization reaction was quenched with aqueous sodium *bicarbonate*. [g] In this experiment the thiocarbamidate (**16**) from **15** was recovered unchanged after treatment with the bromonium reagent under the usual conditions. [h] In this experiment **17** was subjected to the bromocyclization conditions directly.

of these reactions to aminocyclitol total synthesis.

Acknowledgment. This research was supported by grants from PHS (AI-18703) and the Merck Foundation. We are grateful to Robert J. DeVita and Cyndi Klausner for experimental contributions, Dr. Byron H. Arison, Merck Sharpe & Dohme, for 300-MHz ^1H NMR spectra, and Dr. Toshihito Mori, Kowa Co., for spectra of authentic sporamine.

Supplementary Material Available: Spectroscopic data (IR, ^1H NMR) and melting points for new compounds (3 pages). Ordering information is given on any current masthead page.

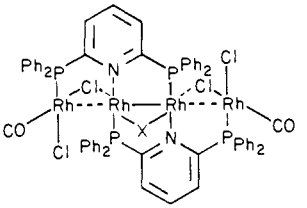
Rupture and Realignment of the Bridging Phosphine Framework in the Reactions of Polynuclear Rhodium Complexes of 2,6-Bis(diphenylphosphino)pyridine

Fred E. Wood, Jan Hvoslef, and Alan L. Balch*

Department of Chemistry, University of California Davis, California 95616

Received May 19, 1983

In recent years, a substantial body of information about the reactivity of binuclear, phosphine-bridged, metal complexes has developed.[1] Extensive studies of complexes of bis(diphenylphosphino)methane (dpm) have revealed a variety of reactions that interconvert the geometric forms known as face-to-face, side-to-side, A-frame and double A-frame dimers.[2] The catalytic activities of some species of this type are also believed to involve interconversions of these geometric forms.[3] A notable feature in these transformations is the apparent stability of the *trans*-$M_2(dpm)_2$ unit. A related body of data concerning transformations about a stable *trans*-$Rh_3(dpmp)_2$ core (dpmp is bis[(diphenylphosphino)methyl]phenylphosphine) is also emerging.[4] In contrast to this behavior, we present here an example of skeletal rupture and realignment in the reactions of the recently discovered, tetranuclear complex $Rh_4[\mu\text{-}(Ph_2P)_2py]_2(\mu\text{-}CO)(CO)_2(\mu\text{-}Cl)_2Cl_2$ **1**.[5]



1, X = CO

2, X = SO_2

Treatment of green **1** with carbon monoxide (1 atm) in chloroform produces a red orange solution from which crystals of $[Rh_2[\mu\text{-}(Ph_2P)_2py]_2(CO)_2(CH_3OH)Cl][PF_6]$ **2** are obtained in 65% yield by the gradual addition of ammonium hexafluoro-

(1) (a) Balch, A. L. *Adv. Chem. Ser.* **1982**, *No. 196*, 243–256. (b) Balch, A. L. In "Homogeneous Catalysis with Metal Phosphine Complexes"; Pignolet, L. H., Ed.; Plenum Press: New York, in press. (c) Brown, M. P.; Fisher, J. R.; Franklin, S. J.; Puddephatt, R. J.; Thomson, M. A. *Adv. Chem. Ser.* **1982**, *No. 196*, 231–242. (d) Kubiak, C. P.; Woodcock, C.; Eisenberg, R. *Inorg. Chem.* **1982**, *21*, 2119–2129. (e) Mague, J. T.; Sanger, A. R. *Ibid.* **1979**, *18*, 2060–2066. (f) Hoffman, D. M.; Hoffman, R. *Ibid.* **1981**, *20*, 3543–3555. (g) Shaw, B. L.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1982**, 956–957. (h) Farr, J. P.; Olmstead, M. M.; Wood, F. E.; Balch, A. L. *J. Am. Chem. Soc.* **1983**, *105*, 792–798.

(2) Benner, L. S.; Balch, A. L. *J. Am. Chem. Soc.* **1978**, *100*, 6099–6106.

(3) (a) Lee, C.-L.; Hung, C. T.; Balch, A. L. *Inorg. Chem.* **1981**, *20*, 2498–2504. (b) Kubiak, C. P.; Eisenberg, R. *J. Am. Chem. Soc.* **1980**, *102*, 3637. (c) Cowie, M.; Southern, T. G. *Inorg. Chem.* **1982**, *21*, 246.

(4) (a) Guimerans, R. R.; Olmstead, M. M.; Balch, A. L. *J. Am. Chem. Soc.* **1983**, *105*, 1677–1679. (b) Olmstead, M. M.; Guimerans, R. R.; Balch, A. L. *Inorg. Chem.* **1983**, *22*, 2473. (c) Guimerans, R. R.; Olmstead, M. M.; Balch, A. L., unpublished results.

(5) Wood, F. E.; Olmstead, M. M.; Balch, A. L. *J. Am. Chem. Soc.* **1983**, *105*, 6332.

0002-7863/83/1505-6986$01.50/0