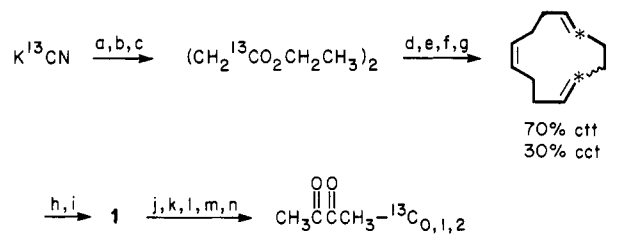
Scheme II



[a] $BrCH_2CH_2Br$, KI, CH_3CH_2OH, Δ. [b] H_2SO_4, Δ. [c] C_6H_6 ($-H_2O$), CH_3CH_2OH, Δ (50% overall). [d] $LiAlH_4$, THF (85%). [e] 40% HBr, H_2SO_4 (80%). [f] $(C_6H_5)_3P$ (82%). [g] *n*-BuLi, THF, *cis*-oct-4-enedial (35%). [h] Br_2, CH_2Cl_2, CH_3COOH (73%). [i] $NaOCH_2CH_2OH$, $HOCH_2CH_2OH$, THF, Δ (15%). [j] 500 °C, 45 torr of N_2, 10 mL/min flow. [k] Br_2, CH_2Cl_2. [l] H_2, Pd/C. [m] O_3, CH_3COCH_3. [n] $(CH_3)_2S$.

Table I. Calculated and Experimental[a] Relative Peak Intensities (in %) for the M^+ Peak of Butanedione according to Various Mechanisms

m/e	observed for unlabeled butanedione	[2 + 2 + 2]	[3.3]	predicted for spiro-[3.3]	random	obsd
86	96	51.5	39	47.2	44	41.5
87	4.0	34	59	42.4	49	58.5
88	0.0	14.5	2	10.3	7	<1.5

[a] Data averaged from four runs, standard deviation less than 1.5. The sum of the mass spectral line intensities *m/e* 87 and 86 was always greater than 30 000 counts.

if **2** is an intermediate ("[2 + 2 + 2]"), 0:2:1 if the rearrangement involves **4b** and **5** (but not **7**) ("[3.3]"), and 2:6:7 if **7** is readily accessible ("spiro[3.3]").[20] Should there somehow be scrambling of the label over all the ring carbons ("random"), that ratio would be 1:10:7.

Inspection of the parent peak envelope at *m/e* 86–88 for unlabeled butanedione[21] allows one to predict the peak ratios expected for the above options by taking into account 90% ^{13}C label incorporation and the presence of natural abundance label in the unenriched positions (Table I). Perhaps most obvious is the necessity for the formation of doubly labeled degradation product from any mechanism other than that proceeding directly through [3.3] shifts (e.g., **1** → **4b** → **5** → **3b**).

The observed ratios in Table I are clearly incompatible with the generation of **3a**, and hence **2** and/or **7**, but show admirable coincidence with the values calculated for the direct sigmatropic shift sequence. These results constitute a truly surprising experimental manifestation of the theoretical prediction that thermal [2 + 2 + 2] alkyne cycloadditions are prohibitively costly in kinetic terms. Since now disproven for **1**, the feasibility of a concerted thermal ethyne to benzene conversion remains to be demonstrated.

Acknowledgment. This work was supported by NIH-CA 20713. K.P.C.V. is a Camille and Henry Dreyfus Teacher–Scholar (1978–1983). We thank Professor E. L. Muetterties for a sample of perdeuteriohexamethylbenzene and Professor M. A. Darensbourg for details of its preparation.

(20) With assumption of complete reversibility of **4** and **1**. Note that the scheme indicates only one of the several possible modes of undergoing [3.3] shifts, all of which have to be considered. Complete equilibration of **1** via **7** (and its isotopomers) furnishes an equimolar mixture of [1,2-$^{13}C_2$]- [1,6-$^{13}C_2$]-, and [1,10-$^{13}C_2$]-**1**, which in turn results in a 2:1 ratio of **3a**:**3b** and therefore the quoted ratio for the dione.

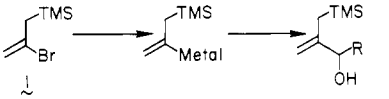
(21) These data were obtained under standardized conditions by GC mass spectrometry on a Finnigan 4000 instrument equipped with an Incos data system. Glass silica capillary columns coated with SE-54 served to separate product from solvent and impurities.

2-Bromo-3-(trimethylsilyl)propene. An Annulating Agent for Five-Membered Carbo- and Heterocycles

Barry M. Trost* and Brian P. Coppola

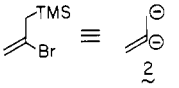
McElvain Laboratories of Organic Chemistry
Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706
Received June 1, 1982

In conjunction with our program on the use of bifunctional conjunctive reagents for substrates for transition metals, we reported the synthesis of 2-bromo-3-(trimethylsilyl)propene (**1**) and



(1)

its addition to carbonyl groups according to eq 1, in order to generate precursors for substituted trimethylenemethanepalladium complexes.[1-4] By combination of the ability to effect transmetalation of the vinyl bromide with the nucleophilic properties of the allylsilane, this readily available reagent can become a synthon for the dianion **2**. In this communication we report the



realization of this proposal as a route to five-membered carbo- and heterocycles.

Lewis acid catalyzed addition of **1** to carbonyl groups[5] showed a sensitivity to the nature of the carbonyl partner. As Table I reveals, aldehydes react well even at concentrations of 0.1 M. Aliphatic ketones fail to react at all at such dilutions. Increasing the concentration to 1 M permits obtention of the desired adducts in excellent yields. Aromatic ketones fail to react at any concentration, although their corresponding ketals form the expected addition products. In each case where stereoisomers are possible, only one results. Most noteworthy is the case of the aldehyde **1** (entry 8), which provides only one isomer in this reaction in contrast to the addition of allylmagnesium bromide, which gives a 1:1 stereoisomeric mixture. In the case of entry 6, the stereochemical assignment was verified by reductive debromination and comparison to an authentic sample. For entries 7 and 8, the stereochemistry is based upon analogy in related systems and must be considered tentative at present.[6,7]

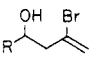
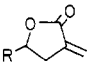
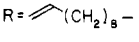
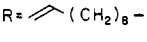
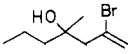
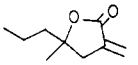
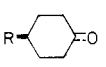
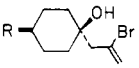
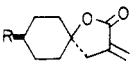
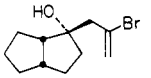
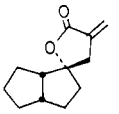
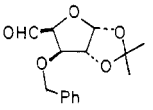
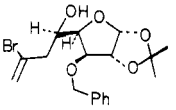
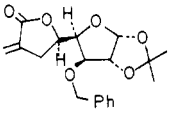
The second anion equivalent from the vinyl bromide was envisioned to involve metalation with a nickel complex in order to achieve carbonylation and thus an α-methylene-γ-butyrolactone synthesis.[8] Indeed, treatment with 1.5 equiv of $(Ph_3P)_2Ni(CO)_2$ in refluxing THF in the presence of 2 equiv of $(C_2H_5)_3N$ gave the α-methylene-γ-butyrolactones in high yields. The exclusive formation of a single stereoisomer from 4-*tert*-butylcyclohexanone is in contrast to other methods.[9] The example in entry 8 is most intriguing in terms of the synthesis of polyether ionophores.

Reversing the unmasking of the two pronucleophilic centers permits a methylenecyclopentane annulation. Copper-catalyzed

(1) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733.
(2) In addition to the copper coupling of (trimethylsilyl)copper with 2,3-dibromopropene, **1** also arises from reaction of this dibromide with trichlorosilane [$(C_2H_5)_3N$, CuCl] followed by methylmagnesium bromide; cf. ref 3.
(3) For 1-bromo-3-(trimethylsilyl)propene see: Nishigawa, H.; Narimatsui, S.; Itoh, K. *Tetrahedron Lett.* **1981**, *22*, 5289.
(4) For an independent related study see: Nishigawa, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267.
(5) For addition of allylsilanes to carbonyl groups see: Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.
(6) Cf.: Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601.
(7) Cf.: Heathcock, C. H.; White, C. T.; Morrison, J. J.; Van Derveer, D. J. *J. Org. Chem.* **1981**, *46*, 1296.
(8) Semmelhack, M. F.; Brickner, S. J. *J. Org. Chem.* **1981**, *46*, 1723.
(9) Schlewer, H.; Stampf, J.-L.; Benezra, C. *J. Med. Chem.* **1980**, *23*, 1031. O'Donnell, D. J.; Ramalingam, K.; Berlin, K. D.; Ealick, S. E.; van der Helm, D. *J. Org. Chem.* **1978**, *43*, 4259. Ohler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457.

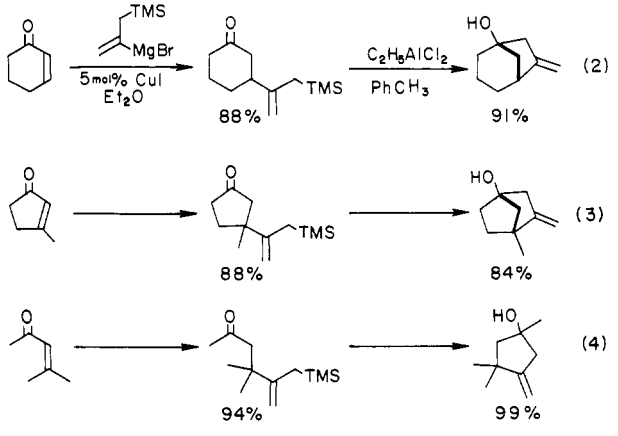
0002-7863/82/1504-6879$01.25/0

Table I. α-Methylene-γ-butyrolactone Synthesis

entry	carbonyl partner	adduct[a]	yield, %	carbonylation product	yield,[e] %
	RCHO				
1	R = C_4H_9	R = C_4H_9	96		
2	R = C_5H_9	R = C_5H_{11}	88[b]	R = C_5H_{11}	94
3			76		90
4			86[b]		90
					
5	R = H	R = H	96[b]	R = H	100
6	R = t-C_4H_9	R = t-C_4H_9	80	R = t-C_4H_9	99
7			94[b]		92
8			86[c]		70

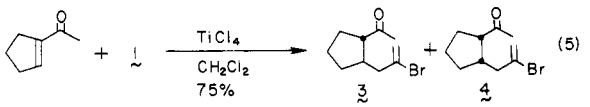
[a] All reactions were performed at 0.1 (entries 1-3, 8) or 1 M (entries 4-7) in CH_2Cl_2 by using 1 equiv of $TiCl_4$ initially at −78 °C typically for 1-2 h and then warming to 0 °C or room temperature. [b] Unless otherwise indicated, the adduct was characterized spectrally. Except for entry 3, the apparent lability of these adducts allowed neither satisfactory high-resolution mass spectra nor combustion analysis within acceptable ranges. In this case, the adduct—isolated via filtration through a short plus of silica gel—was pure by TLC and spectral criteria. It was utilized directly in the lactone synthesis. [c] The corresponding benzoate shows mp 105-106 °C. [d] All reactions were performed with 1.5 equiv of $(Ph_3P)_2Ni(CO)_2$ and 2 equiv of C_2H_5N in refluxing THF for 10-30 min. The products were fully characterized spectrally and, in the case of new compounds, for elemental composition. [e] Isolated via distillation.

Grignard addition generates the expected conjugate adducts (see eq 2-4). The Grignard reagent can be generated directly from

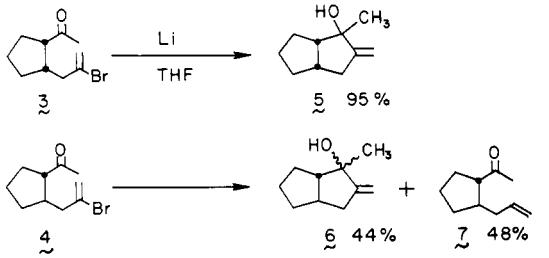


1 in the normal fashion;[1] however, for small-scale reactions it was found more convenient to treat the bromide with *tert*-butyllithium followed by magnesium bromide. Attempts to generate stoichiometric cuprates were always complicated by oxidative dimerization.[10] Fluoride ion and titanium tetrachloride[11] induced cyclizations of these adducts suffered from protodesilylation. Ethylaluminum dichloride[12,13] should and does avoid this complication, which presumably arises from the adventitious presence of HX. Subjecting each conjugate adduct to 2 equiv of $C_2H_5AlCl_2$ in $PhCH_3$ at 0 °C produces the bicyclo[*n*.2.1] systems in high yield (see eq 2, 3). Spectral characterization readily identifies the structures as shown.

The reverse orientation is also possible by reversing the order of unmasking of the two pronucleophilic centers. For example, in preliminary work 1-acetylcyclopentene participates in $TiCl_4$-catalyzed conjugate addition of the allylsilane in CH_2Cl_2 at -78 °C[14] to give a kinetically controlled mixture of adducts (eq 5). An intramolecular Barbier reaction[15] with Li containing 1%



Na in THF in a sonicator[16] with **3** led to an excellent yield of the cyclopentanol **5**. The utility of such a cyclization is clearly



demonstrated by its application to the trans-isomer **4** to produce the highly strained trans-fused bicyclo[3.3.0]octane system[17] **6**, albeit in diminished yield due to competing protodebromination. While **5** appears to be a single stereoisomer, **6** is clearly a mixture, neither of which corresponds to **5**—a fact indicating that the

(10) For applications of 2,3-bis[(trimethylsilyl)methyl]buta-1,3-diene see: Trost, B. M.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 4299.
(11) Trost, B. M; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680.
(12) Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886.
(13) Cf.: Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(14) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.
(15) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.
(16) Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926. Conventional methods of organometallic generation with Li and Mg failed to give satisfactory reaction; also, use of low-temperature halogen–metal exchange (*t*-BuLi/−120 °C) did not yield any closure products.
(17) (a) Barrett, J. W.; Linstead, R. P. *J. Chem. Soc.* **1935**, 436. (b) Chang, S.; McNally, D.; Sharg-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109.

stereochemistry of the substituents in the precursor is retained in the cyclization.

Bifunctional silicon reagents offer an excellent opportunity to store chemical reactivity, which can be selectively unleashed. While a halosilane can be thought of as a zwitterion equivalent, the ability to selectively metalate the bromide or activate the allylsilane also permits such species to serve as dianion equivalents. As the results herein show, this dianion equivalence can serve as a valuable cyclization approach to both carbo- and heterocyclic compounds with extraordinary high stereocontrol.

Acknowledgment. We thank the National Science Foundation and the General Medical Sciences Institute of NIH for their generous support of our programs.

Supplementary Material Available: Complete experimental details for the reactions described (11 pages). Ordering information is given on any current masthead page.

Palladium-Mediated Macroheterocyclization. A Synthesis of Inandenin-12-one

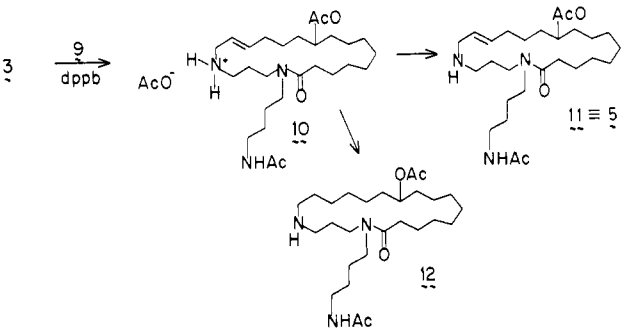
Barry M. Trost* and Janine Cossy

McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

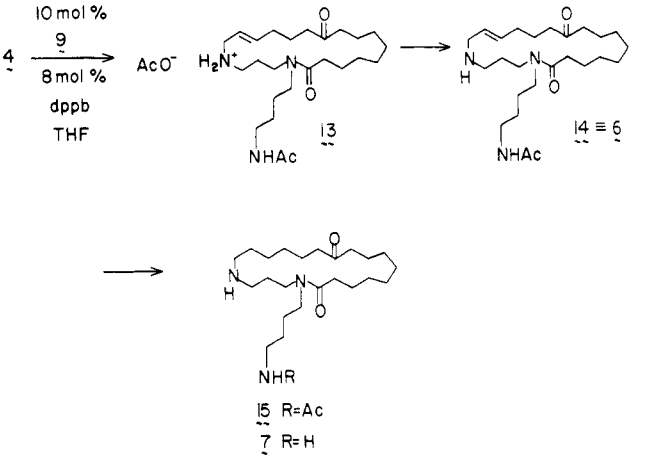
Received September 13, 1982

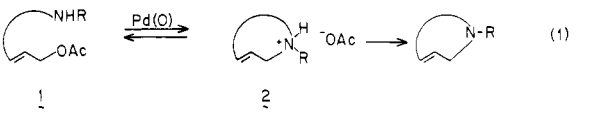
Increased attention focuses on large heterocyclic rings because of their ionophoric properties. Such properties may be responsible for much of the observed biological activity of naturally occurring macroheterocycles. Among the more interesting classes of macrocyclic amines are those derived from spermine and spermidine.[1] The synthetic approaches to these compounds have been limited up to the present, to a macrolactamization as the key ring-forming step.[2,3] The general advantages of transition-metal-templated macrocyclizations involving C–C bond formation such as in the case of palladium-mediated reactions[4] raises the question of the applicability of such transition-metal catalysts in forming a C–X bond where X is oxygen or nitrogen.[5,6] In the case of nitrogen, the initial cyclization is simply an isomerizaiton (**1** ⇌ **2**, eq 1). Since allylammonium salts are known substrates for Pd(O),[6b,7] this isomerization becomes an equilibration. Thus, the success of this approach depends upon both kinetics and thermodynamics.

Scheme I. Cyclization of 3

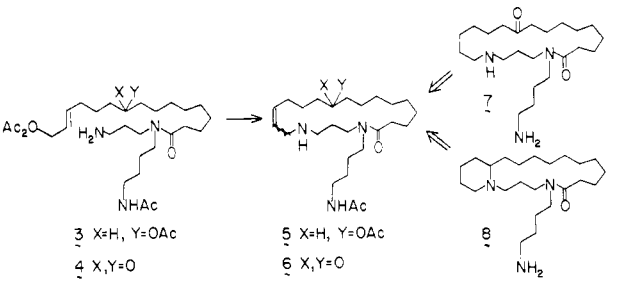


Scheme II. Synthesis of Inandenin-12-one





To explore this question, we examined the cyclizations of **3** and **4** since their cyclization products **5** and **6** represent possible common intermediates to the naturally occurring spermidine alkaloids inandenin-12-one (**7**)[8] and oncinotine (**8**)[2a,9]—a strategy that may mimic the biosynthetic pathway to **8**. Furthermore, since inandenin-12-one coexists with inandenin-13-one and this mixture



(1) Badawi, M. M.; Bernauer, K.; van den Broek, P.; Groger, D.; Guggisberg, A.; Johne, S.; Kombis, I.; Schneider, F.; Veith, H.-J.; Hesse, M.; Schmid, H. *Pure. Appl. Chem.* **1973**, *33*, 81. Guggisberg, A.; Dabrowski, B.; Heidelberger, C.; Kramer, U.; Stephanou, E.; Hesse, M. *Symp. Pap. -IUPAC Int. Symp. Chem. Nat. Prod., 11th* **1978**, *4*, 314.

(2) (a) Guggisberg, A.; van den Broek, P.; Hesse, M.; Schmid, H.; Schneider, F.; Bernauer, K. *Helv. Chim. Acta* **1976**, *59*, 3013. (b) Walchli-Schaer, E.; Eugster, C. H. *Ibid.* **1978**, *61*, 928. (c) Nagao, Y.; Seno, K.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 4931. (d) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461. (e) Nagao, Y.; Takao, S.; Miyasaka,; Fujita, E. *J. Chem .Soc., Chem. Commun.* **1981**, 286. (f) Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 280. (g) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Hausler, J. *Ibid.* **1981**, *20*, 281. (h) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465.

(3) Nagao, Y.; Seno, K.; Miasaka, T.; Fujita, E. *Chem. Lett.* **1980**, 159. Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493. Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 6133. Jenny, C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 1807.

(4) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743; **1979**, *101*, 1595; **1977**, *99*, 3867; *Tetrahedron Lett.* **1978**, 2275. Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864.

(5) Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516. Trost, B. M.; Godleski, S.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. Trost, B. M.; Godleski, S.; Belletire, J. *J. Org. Chem.* **1979**, *44*, 2052. Andriamialisoa, R.; Langlois, N.; Langlois, Y. *Heterocycles* **1980**, *14*, 1457.

(6) (a) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779; (b) *J. Org. Chem.* **1979**, *44*, 3451. (c) Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392. (d) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1979**, 3821. (e) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (f) Murahashi, S. I.; Shimamura, T.; Moritani, I. *J. Chem. Soc., Chem. Commun.* **1974**, 931. (g) Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *59*, 889. (h) Backvall, J. E.; Nordberg, R. E.; Nystrom, J.-E.; Hogberg, T.; Ulff, B. *J. Org. Chem.* **1981**, *46*, 3479.

(7) Wier, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926. Hirao, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *J. Organomet. Chem.*, in press.

(8) Guggisberg, A.; Veith, H.-J.; Hesse, M.; Schmid, H. *J. Organomet. Chem.* **1976**, *59*, 3026.

(9) Veith, H. J.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1970**, *53*, 1355.

0002-7863/82/1504-6881$01.25/0