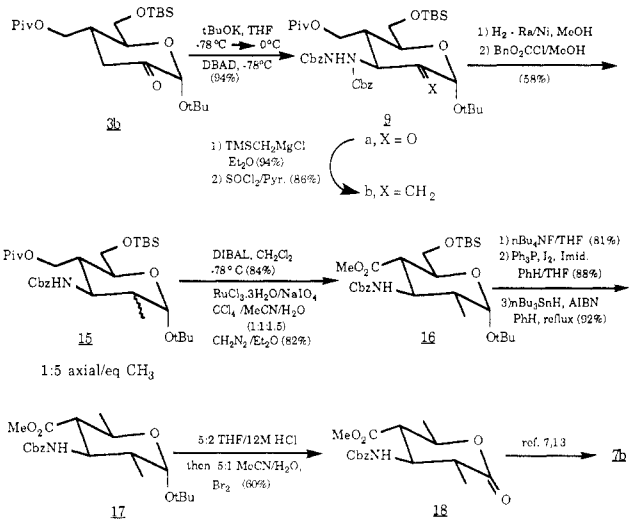
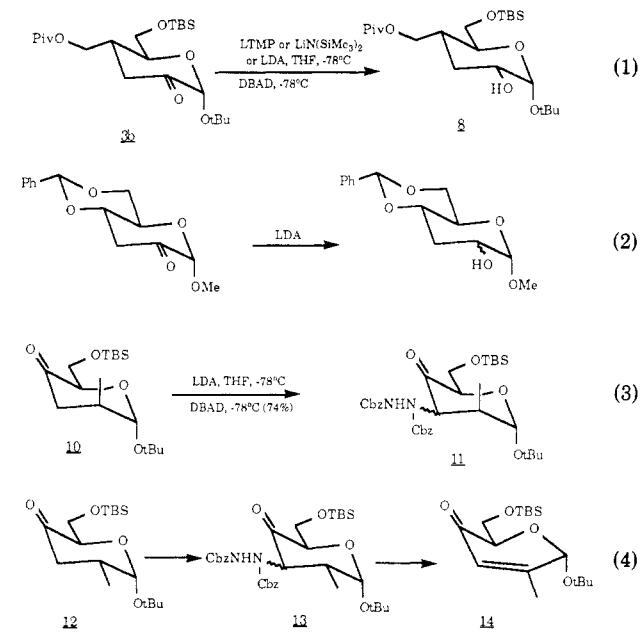
Scheme II



Although we are currently unable to offer a rationalization for these differences in stereoselection to give **3** and **4**, it was evident that the former was an attractive synthon for the synthetic carbapenem antibiotics.[6,7,12] The specific advantages for 1β-methylcarbapenem[6,7] can be appreciated by comparing the "Melillo lactone"[13] analogue **7b** with **3**. Thus, the hydroxymethyl and carbonyl groups of **3** are excellent implements for the carboxylic acid and C1 methyl groups of **7b**, respectively. The execution of an electrophilic amination would complete the retrosynthetic requirements for obtaining **7b** from **3a**, and a timely report by Trimble and Vederas[4a,16] suggested a solution.



However, treatment of ketone **3b** with LDA or lithium hexamethyldisilazide, followed by dibenzyl azodicarboxylate (DBAD),[16] led to the alcohol **8** (eq 1), instead of the aminated compound **9a** (Scheme II). A similar aberrant reduction of a pyranosid-2-ulose by LDA (eq 2) has been reported recently by Bonnert and Jenkins.[14] In contrast to these results, it was interesting to note that with the 4-ulose **10**, similar reaction conditions led to high yields of the amination product **11** (eq 3). With the epimeric methyl derivative **12**, amination did occur; but under the reaction conditions, the adduct **13** underwent ready elimination so that the degradation product **14** (eq 4) was formed in substantial amounts.

It transpires that deprotonation of **3b** could be achieved without incident by use of *t*-BuOK in THF, and subsequent addition of DBAD then led to the desired amination product **9a** in virtually quantitative yield. The most efficient procedure for obtaining the corresponding methylene derivative **9b** proved to be the addition of $TMSCH_2MgCl$[15] followed by reaction with thionyl chloride in pyridine. Hydrogenation in the presence of Raney nickel then gave the equatorial C2-CH_3 derivative (plus 15% of the C2 epimer) and simultaneously cleaved the hydrazine. Protection of the amine in situ led to compound **15** (Scheme II). The product was then ready for oxidation of one of the protected hydroxymethyl residues and deoxygenation of the other. These transformations were effected by standard procedures to obtain **16** and thence **17**. Hydrolysis of the glycoside and oxidation then afforded the protected Melillo lactone[13] analogue **18**, which is an established intermediate for a 1β-methylcarbapenem.[7]

Acknowledgment. We are grateful to the National Institutes of Health for support of this work (GM 32569). We are also indebted to Drs. Shinkai and Christensen of Merck, Sharp, and Dohme (Rahway, NJ) for helpful discussions.

(12) (a) Ikota, N.; Yoshiono, O.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 1929. (b) Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R. *Can. J. Chem.* **1982**, *60*, 2292. (c) Durette, P. L. *Carbohydr. Res.* **1982**, *100*, c27.

(13) Mellilo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron lett.* **1980**, *21*, 2783. Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913.

(14) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Comm.* **1987**, 6.

(15) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464. Carey, F. A.; Frank, W. C. *J. Org. Chem.* **1982**, *47*, 3548.

(16) We are grateful to Professor Vederas for disclosing details of his procedure prior to publication.

Uko E. Udodong, Bert Fraser-Reid*
Department of Chemistry
Paul M. Gross Chemical Laboratory
Duke University
Durham, North Carolina 27706
Received December 15, 1987

Samarium Diiodide Promoted Intramolecular Pinacolic Coupling Reactions[1]

Summary: Samarium diiodide promotes intramolecular reductive coupling of functionalized keto aldehyde substrates, generating stereodefined 2,3-dihydroxycyclopentanecarboxylate derivatives.

Sir: Samarium diiodide (SmI_2) is an exceedingly useful reagent for promoting intramolecular reductive coupling reactions. Investigations of such reactions have led to development of several useful and convenient strategies for construction of highly functionalized carbocycles and heterocycles. For example, intramolecular Barbier reactions,[3] intramolecular Reformatsky reactions,[4] intramo-

(1) Lanthanides in Organic Synthesis. 9.

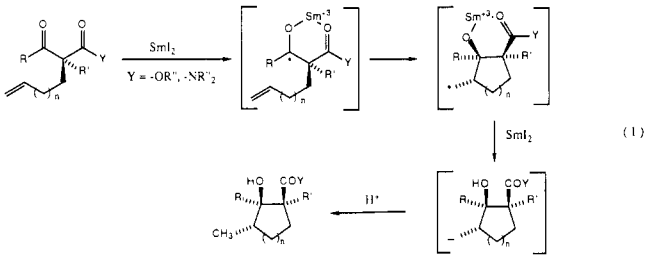
(2) Alfred P. Sloan Foundation Fellow, 1987-1989.

(3) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778. (b) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (c) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, *17*, 901.

0022-3263/88/1953-2132$01.50/0

lecular ketone–olefin reductive coupling reactions,[5] and other miscellaneous reductive cyclizations[6] mediated by SmI_2 have recently been described. Nearly all of these processes proceed in good to excellent yields and provide entry into functionalized cyclic molecules with high, predictable stereochemical control.

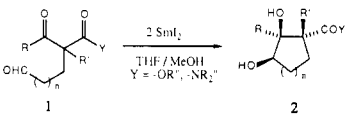
Evidence gathered to date indicates that ketyls are key intermediates in the intramolecular Barbier and ketone–olefin reductive coupling processes.[7] Stereochemical control has been established in these cases by chelation of the Sm^{3+} ion (generated during the reduction) with Lewis basic functional groups incorporated within the starting materials (eq 1).[3b,5a] Intramolecular pinacolic



(1)

coupling reactions represent another potential manifold of reactivity for ketyl intermediates. This type of intramolecular reductive coupling has seen limited use as a method for generation of carbocycles, and no reductants have emerged which permit reliably high chemical yields and consistent stereochemical control in this process.[8]

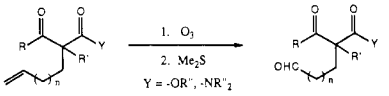
Intermolecular pinacolic coupling reactions mediated by SmI_2 have been described by Kagan and co-workers.[9] Although poor diastereoselectivity was achieved in these reactions, our success in utilizing SmI_2 as a template to control stereochemistry in other reductive cyclization reactions prompted us to explore the intramolecular version of the pinacolic coupling as a route to highly functionalized, stereodefined carbocycles (eq 2).



(2)

1 2

Starting materials (1) for our intramolecular pinacolic coupling study were readily prepared by ozonolysis of appropriate unsaturated β-keto esters and β-keto amides (eq 3). Substrates prepared in this manner were sub-



(3)

mitted to standard reductive cyclization conditions (2 equiv of SmI_2, 1–2 equiv of MeOH in THF at −78 °C). Reactions were extremely fast, proceeding to completion

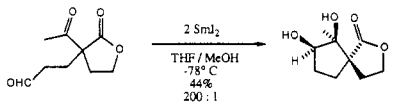
Table I. Samarium Diiodide Promoted Intramolecular Pinacolic Coupling Reactions

substr	n	Y	R	R′	% isoltd yield (2)[a]	diastereoselectivity
1a	1	OEt	Me	Me	77	200:1
1b	1	OEt	Et	Me	82	120:1
1c	1	OEt	*i*-Pr	Me	73	35:1
1d	1	OEt	Ph	Me	66	200:1
1e	1	OEt	Me	Et	75	>120:1
1f	2	OEt	Me	Me	47	3:1:<0.1
1g	1	NEt_2	Me	H	50	200:1
1h	1	NMe_2	Et	H	35	>120:1
1i	1	NMe_2	*i*-Pr	H	44	3:1

[a] Satisfactory ^1H NMR, ^{13}C NMR, IR, and exact mass spectral data were obtained for all new compounds.

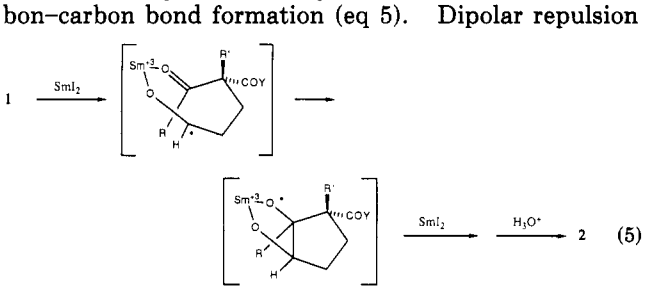
in minutes at this temperature. After slowly warming to room temperature and quenching with aqueous $NaHCO_3$ or pH 8 phosphate buffer, the pinacol products were isolated by flash chromatography. Good yields and excellent stereochemical control at three contiguous stereocenters was achieved in nearly all examples studied to date (Table I).

In addition to these monocarbocycles, spirocyclic systems were also readily generated, although in modest yield (eq 4). Diastereomeric ratios were determined from gas



(4)

chromatographic (25 M × 320 μM 5% phenyl SE-54 fused silica capillary columns) and GC/MS data. Relative stereochemistries of the major diol diastereomers in two representative examples (**2b** and **2f**) were determined by single-crystal X-ray diffractometry. Acetonide formation (2-methoxypropene, PPTS, CH_2Cl_2) established the cis diol relationship in some other examples (**2a** and **2i**). As indicated, the major diastereomer was found to be the cis diol with the carboxylate trans relative to the adjacent hydroxyl. Curiously, the relative stereochemistry between the carboxylate and the adjacent hydroxyl group observed in this series is opposite to that observed in the SmI_2-promoted intramolecular Barbier reactions and ketone–olefin reductive coupling reactions that we have studied (cf., eq 1).[3b,5a] From a synthetic point of view, this is highly advantageous because it provides entry into the manifold of diastereomeric products. The results also have mechanistic implications; electron transfer to the most readily reduced functional group (aldehyde) apparently initiates the process, with chelation control of stereochemistry now centered about the developing diol stereocenters. Perhaps the most plausible mechanism involves cyclization after one-electron reduction.[5a,8b,10] In this case, initial electron transfer to the aldehyde would generate the requisite ketyl. Cyclization would occur by coordination of Sm^{3+} to the ketone carbonyl, followed by (or concomitant with) carbon–carbon bond formation (eq 5). Dipolar repulsion



(5)

(4) (a) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556. (b) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.

(5) (a) Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, *28*, 4367. (b) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920.

(6) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195.

(7) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, Suppl. No. 1, 175.

(8) (a) Griffin, G. W.; Hager, R. B. *J. Org. Chem.* **1963**, *28*, 599. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. (c) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (d) Nakayama, J.; Yamaoka, S.; Hoshino, M. *Tetrahedron Lett.* **1987**, *28*, 1799.

(9) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765.

(10) Kariv-Miller, E.; Mahachi, T. J. *J. Org. Chem.* **1986**, *51*, 1041.

between the Sm^{3+} chelate and the carboxylate would account for the relative stereochemistry between the diol stereocenters and the carboxylate. Subsequent intermolecular reduction of the chelate complex by SmI_2 and hydrolysis would produce the observed products.

Several pertinent examples of apparent ketyl addition to Lewis acid complexed carbonyl substrates have been documented,[8b,11] and intramolecular addition of alkyl radicals to unactivated ketones and aldehydes is now even well established.[12] At present, we cannot definitively rule out a two-electron (diketyl) coupling. However, unless a single Sm^{3+} cation complexes both ketyls, one might not expect pure cis diols to be formed by such a two-electron process.[8b]

More will be learned about the detailed mechanism of the reaction through delineation of its scope. Analysis of products derived from functionalized diketone, dialdehyde, and keto aldehyde substrates of a variety of substitution patterns should provide further insight on the factors controlling the cyclization process. At present, the SmI_2-promoted intramolecular pinacolic coupling reaction represents an extremely efficient entry into highly functionalized, stereodefined carbocycles.

Acknowledgment. We are grateful to the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of our programs. We also thank Dr. Paul W. Zinke for performing initial experiments in this area and Curt Haltiwanger for the X-ray crystal structure determinations.

Supplementary Material Available: X-ray crystal structure data for the major diastereomer of **2b** and the two most predominant diastereomers of **2f** (18 pages). Ordering information is given on any current masthead page.

(11) (a) Clerici, A.; Porta, O. *Tetrahedron* **1983**, *39*, 1239. (b) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48*, 1690. (c) Clerici, A.; Porta, O. *J. Org. Chem.* **1987**, *52*, 5099.

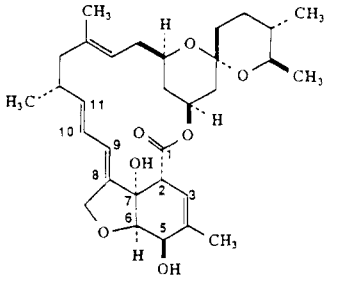
(12) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548, and references therein.

Gary A. Molander,*[,2] Caryn Kenny
Department of Chemistry and Biochemistry
University of Colorado
Boulder, Colorado 80309-0215
Received December 30, 1987

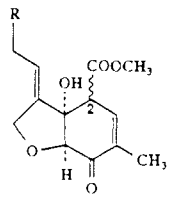
Intramolecular Claisen Condensations. An Efficient Route toward the Avermectins and Milbemycins[†]

Summary: Investigations of novel intramolecular Claisen condensations feature selective deprotonation and enolate formation in a series of dicarbonyl compounds. Ring closures occurred at −78 °C with excellent stereochemical control affording the bicyclic β-hydroxy lactones **13**, **15**, **19**, and **20**. The intramolecular Claisen strategy allows for an efficient preparation of the chiral hexahydrobenzofuran **3** as observed in the potent milbemycin–avermectin family of macrocyclic metabolites.

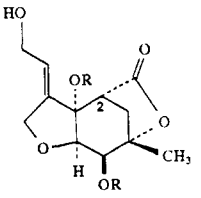
Sir: In recent years we have examined numerous pathways leading toward a fully functionalized hexahydrobenzofuran as exemplified by the southern portion ($C_1 \rightarrow C_{10}$) of milbemycin α_1 (**1**) and avermectin β_{1a}. Recently, several groups have communicated model studies and preliminary results toward this highly oxidized subunit,[1] and a total synthesis of avermectin A_{1a} has been achieved.[2] Our investigations have examined novel intramolecular Claisen condensations to afford the completed cyclohexenone **2**.[3] However, in the course of these studies we became aware of problems of epimerization at C-2 as subsequently detailed by Fraser-Reid and Hanessian for avermectin B_{1a} itself.[4,5] Thus, we sought to prevent isomerization by restricting the C-1 ester as a bicyclic lactone. This report communicates our successful studies of Claisen condensations leading to preparation of the chiral hexahydrobenzofuran **3**, as a potential precursor for total synthesis of the milbemycin–avermectin antibiotics.



Milbemycin α_1 (1)



2



3 R = CH_2OCH_3

Our route begins, as illustrated in Scheme I with the readily available 2,3-*O*-isopropylidene-L-erythose **4** as obtained in three steps from L-rhamnose in 71% overall yield following the literature procedures.[6,7] Reaction with

(1) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1565. Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291. Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 5071. Barrett, A. G. M.; Capps, N. K. *Tetrahedron Lett.* **1986**, *27*, 5571. For a review of earlier work in this area: Davies, H. G.; Green, R. H. *Nat. Prod. Chem.* **1986**, *3*, 87. After completion of our work, several groups have communicated their advances in this area. Danishefsky, S.; Armistead, D. M. *Tetrahedron Lett.* **1987**, *42*, 4959. Jung, M. E.; Usui, Y.; Vu, C. T. *Ibid.* **1987**, *42*, 5977. White, J. D.; Dantanarayana, A. P. *Ibid.* **1987**, *42*, 6417.

(2) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117, 8119.

(3) Sodium borohydride reduction of the C_5 ketone of **2** is known to stereoselectively yield the desired β-alcohol. Mishima, H.; Junya, I.; Muramatsu, S.; Ono, M. *J. Antibiot.* **1983**, *36*, 980. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *J. Antibiot.* **1983**, *36*, 980. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *J. Antibiot.* **1983**, *36*, 991. Furthermore, we had recognized that the presence of the C_5 ketone is essential to avoid facile isomerization of the carbon double bond into conjugation with the C_1 ester.

(4) Several years ago we had observed selective MnO_2 oxidation of the C_5 hydroxyl of ivermectin in ether (82%) followed by acid hydrolysis of the disaccharide moiety (1% H_2SO_4 in MeOH; 83%), and saponification of the macrocyclic lactone (LiOH, THF in aqueous MeOH) to afford approximately a 1:1 mixture of the separable C-2 epimeric carboxylic acids. No products of double bond migration or decarboxylation were obtained. Macrocyclic lactonization of the 7,13,19-trihydroxy 2α-carboxylic acid (using 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate) gave only esterification at the C-19 alcohol, producing a 3.5:1 ratio of natural to C-2 epimeric lactones. We thank Dr. Santi Sakdarat for conducting these experiments.

(5) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J. *J. Am. Chem. Soc.* **1987**, *109*, 933. See also; Hanessian, S.; Dubé, D.; Hodges, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 7063.

(6) For preparation of the acetonide of L-rhamnose (86% yield): Baker, B. R.; Hewson, K. *J. Org. Chem.* **1957**, *22*, 966.

[†] Date of original receipt at the *Journal of the American Chemical Society*: August 6, 1987.

0022-3263/88/1953-2134$01.50/0