Synthetic and Mechanistic Studies of the Retro-Claisen Rearrangement. 3. A Route to Enantiomerically Pure Vinyl Cyclobutane Diesters via a Highly Diastereoselective *Syn* S_N2' Reaction and Their Rearrangement to Enantiomerically Pure Dihydrooxacenes

Robert K. Boeckman, Jr.* and Michael R. Reeder

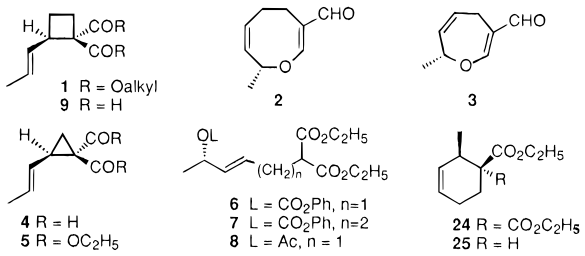
Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

Received July 8, 1997

As part of a program to investigate the retro-Claisen rearrangement[1,2] and its application to the synthesis of biologically interesting natural molecules (e.g. Methymycin and Laurencin),[3] we required an efficient enantioselective route to the precursor vinyl cyclobutane diesters such as **1**. Realization of a general enantioselective synthesis of **1** should then make possible preparation of the related enantiomerically pure medium ring ethers like dihydrooxacene **2** for which few general synthetic routes exist.[4]

Prior efforts had led to the preparation of enantiomerically pure dihydrooxepins such as **3** *via* retro-Claisen rearrangement of **4**. In turn, **4** and related structures are accessible from the cyclopropane diesters **5** obtainable from acyclic precursors **6** using π-allyl palladium chemistry.[2] However, this methodology had not been utilized to prepare cyclobutane derivatives like **1** with the exception of two cases.[5,6] Our investigations into the use of π-allyl palladium chemistry to prepare cyclobutane diesters **1** from acyclic precursors **7** revealed that this route is generally not feasible.[7] Unfortunately, cyclization of acyclic substrates such as **7**, *via* intramolecular S_N2' alkylation, did not initially appear attractive since our work established that cyclization of the acyclic diester **8** proceeded with poor facial discrimination.[2,8]

In this paper, we report development of a general highly enantioselective route to the cyclobutane diesters **1** *via* a highly π facially selective *syn* S_N2' ring closure of acyclic substrates such as **7** and rearrangement of the derived dialdehyde **9** to dihydrooxacenes **2**.



Two routes to the required acyclic substrates have been established. The first, which utilizes a [2,3] Wittig rearrangement,[9] begins with an α-alkoxymethoxy vinyl ketone such as **10** obtained from ethyl lactate.[10] Chelation controlled reduction of **10** with $Zn(BH_4)_2$ followed by alkylation with (iodomethyl)tributylstannane affords the *anti* bis ether **11** in 86% overall yield (Scheme 1).[9,11] Exposure of **11** to *n*BuLi at −78°C affords homoallylic alcohol **12** in ∼45% yield. Alcohol **12** was routinely trans formed to the allylic phenyl carbonate (*S*)-(−)-**7** *via* malonate **13** in 40−50% overall yield. This route was limited by the modest yields obtained in the [2,3] rearrangement. Thus, as outlined in Scheme 2, we generally employed an enzymatic resolution of the related racemic allylic alcohols. The known aldehyde **14**[12] was coverted to the enones **15**−**17** and the related allylic alcohols (±)-**18**−**20** using standard methods in 65−75% overall yields. The corresponding (*S*) alcohols **18**−**20** were isolated in ∼85−90% yield (of theoretical) upon exposure to Lipase PS30[13] and shown to be enantiomerically pure (>99% ee) upon conversion to the related Mosher ester.[14] The corresponding phenyl carbonates (*S*)-(−)-**7** and (*S*)-(−)-**21**−**22** were prepared as before (>95% yield). Enantioselective reduction of the precursor enones **15**−**17** has, thus far, not afforded material of high enantiomeric purity.

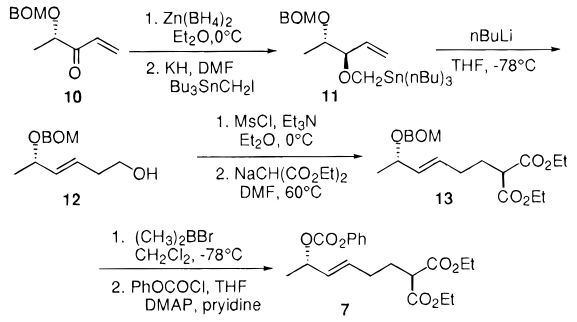
We initially examined cyclization of (*S*)-(−)-**7**. Surprisingly, exposure of (*S*)-(−)-**7** to NaH in THF failed to provide the expected cyclobutane diester **23**. Similar behavior was observed in a variety of solvents including *t*BuOCH$_3$ and DMF and for several leaving groups (e.g. OAc, OBz). The only products resulted from deacylation to (*S*)-(−)-**18** accompanied by recovered (*S*)-(−)-**7** in some cases. *Quite remarkably, when cyclization was attempted using NaH in toluene at 50−60 °C, smooth cyclization was observed to afford cyclobutane diester (+)-**23**, $[\alpha]^{25}_D$ 136 (c = 1.7, $CHCl_3$), in ∼75% yield and >99% ee, accompanied by some recovered (S)-(−)-**18**.* The enantiomeric purity of (+)-**23** was established by GLC analysis of the bis Mosher ester obtained by reduction of (+)-**23** with LAH and derivatization.[14] The absolute configuration of (+)-**23** was established by chemical correlation with cyclohexene diester (*R*)-(−)-**24** ($[\alpha]^{25}_D$ −183 (*c* = 1.7, $CHCl_3$)) obtained by acylation of the known ester (3*R*,4*S*)-(−)-**25**.[15] Cyclobutane diester (+)-**23** was then treated with $Pd(dppe)_2$ affording (*S*)-(+)-**25** ($[\alpha]^{25}_D$ 183 (*c* = 1.8, $CHCl_3$)), a process known to proceed *via* overall retention, thus establishing the configuration of (+)-**23** as *R*.[16]

This cyclization appears general, proceeding under the same conditions for the related substrates **21** and **22** to

(1) Boeckman, R. K., Jr.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58*, 1295.
(2) Boeckman, R. K., Jr. New Methodology And Applications to the Synthesis of Antibiotics and Other Bioactive Complex Molecules. In *Antibiotic and Antiviral Compounds: Chemical Synthesis and Modification*; Krohn, K., Kirst, H., Maas, H., Eds.; VCH: Weinheim, 1993; pp 15−30.
(3) For related studies of the retro-Claisen rearrangement, see: Hofmann, B.; Reissig, H.-U. *Synlett* **1993**, 27.
(4) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **1995**, *117*, 10227 and subsequent papers. Overman, L. E.; Matthisa, B.; Bullock, W. H.; Takemoyo, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. Holms, A. B.; Robinson, R. A.; Clark, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 10400. Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn* **1979**, *52*, 135.
(5) Trost, B. M.; Verhoven, T. R. *J. Org. Chem.* **1976**,*41*, 3125. Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611.
(6) Malacria, M.; Le Bideau, F.; Zucco, M. *Tetrahedron Lett.* **1995**, *36*, 2487.
(7) Boeckman, R. K., Jr.; Reeder, M. R. Manuscript in preparation. Reeder, M. R. Ph. D. Dissertation, University of Rochester, Rochester, NY, 1996.
(8) Boeckman, R. K., Jr.; Vargas, J. R. Unpublished results, 1989.
(9) Kallmerten, J.; Tong, X. *Synlett* **1992**, 845. Kallmerten, J.; Ballstra, M. *Tetrahedron Lett.* **1988**, *29*, 6901. Mikami, K.; Nakai, T. *Synthesis* **1991**, 594 and the reference cited therein. Mikami, K.; Nakai, T. *Chem Rev.* **1986**, *86*, 8.
(10) Rapoport, H.; Palkowitz, A. D.; Knudsen, C. G.; Maurer, P. J. *J. Org. Chem.* **1985**, *50*, 325.
(11) Oishi, T.; Tanaka, T.; Nakata, T. *Tetrahedron Lett.* **1983**, *24*, 2653.
(12) Warner, D. T.; Moe, O. A. *J. Am. Chem. Soc.* **1948**, *70*, 3470.
(13) *Enzymes in Synthetic Organic Chemistry*; Whitesides, G. M., Wong, C. H., Eds.; Pergamon Press: New York, 1994.
(14) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.
(15) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

S0022-3263(97)01225-5 CCC: $14.00

Scheme 1



Scheme 2

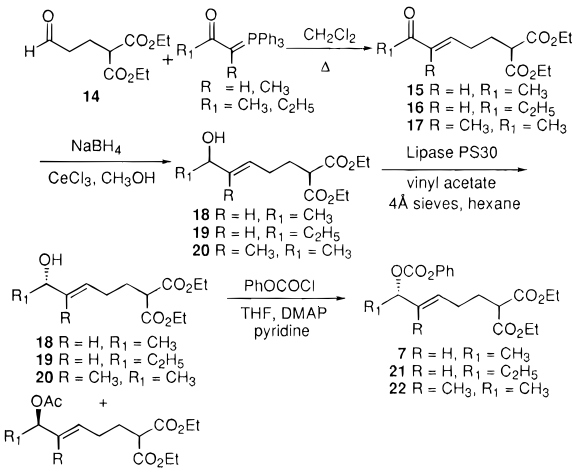
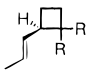
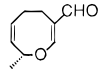
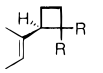
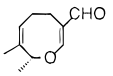
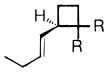
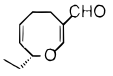


Table 1

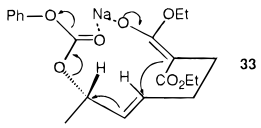
vinylcyclobutane	$[\alpha]_D^{25}$	dihydrooxacene	$[\alpha]_D^{25}$	yield (%)
				
23 R = $CO_2C_2H_5$ **28** R = CH_2OH	136.0 20.3	**2**	31.7	70
				
26 R = $CO_2C_2H_5$ **29** R = CH_2OH	101.0 15.1	**31**	25.3	85
				
27 R = $CO_2C_2H_5$ **30** R = CH_2OH	68.4 6.4	**32**	21.6	82

afford the expected cyclobutane diesters (*R*)-(+)-**26** and (*R*)-(+)-**27** in 72 and 78% yields, respectively (Table 1).

The cyclobutane diesters **23**, **26**, and **27** were smoothly transformed to the dihydrooxacenes using our general protocol.[1] Reduction of **23**, and **26**, and **27** with LAH in Et_2O at 0 °C afforded the diols **28**−**30** in 84−95% yields. Subsequent oxidation with 3 equiv of Dess−Martin periodinane[17] in CH_2Cl_2 buffered with 8 equiv of pyridine afforded the dihydrooxacenes (*R*)-(+)-**2**, (*R*)-(+)-**31**, and (*R*)-(+)-**32** in 70−85% yields and >99% ee, indicating complete chirality transfer as expected.[1] The enantiomeric purity of (*R*)-(+)-**2**, (*R*)-(+)-**31**, and (*R*)-(+)-**32** were established by NMR and GLC analysis of the Mosher esters of the alcohols obtained by reduction of **2** and **31** and **32** with $NaBH_4$.[14,18]

The stereochemical outcome observed for the cyclizations to **23**, **26**, and **27** requires that the S_N2' substitution occur *syn* to the departing group. While *syn* substitution has been commonly observed for both cyclic and acyclic substrates,[19,20] S_N2' substitutions are known to occur *via* both *syn* and *anti* pathways depending on the substrate, substrate substitution, nucleophile, and leaving group.[19−21] The high degree of fidelity seen for the *syn* pathway in these cases is noteworthy, especially in light of our prior observation that ring closure of **8** to **5** proceeds with much poorer facial discrimination (84:16 *syn*/*anti*).[2,8]

Given the high stereoselectivity seen in the S_N2' cyclizations of **7** and related substrates and the unusual solvent dependence, we attempted to determine the mechanism of this process. When the base was changed to KH or LDA, only deacylation products were observed, even in toluene. Addition of 18-crown-6 to the anion prepared from **7** using NaH in toluene at rt gave no ring closure upon heating, giving unreacted **7** (short time) and deacylation upon prolonged heating. Thus, it would appear that both the malonate anion and the leaving group must be associated with the counterion to observe cyclization in the nonpolar medium. Within the geometric constraints, this outcome is consistent with previous theoretical models.[19,22] A preorganized complex such as **33** could account for the observed results, since such a complex is geometrically constrained to afford only *syn*



substitution. Such a complex cannot as readily form in the case of the lower homolog **8**, and in this case, cyclization may ensue from aggregates with less preference for *syn* or *anti* substitution.[23] Isolated examples of highly stereoselective intramolecular S_N2' reactions of carbon nucleophiles have been reported in which both *syn* and *anti* substitution pathways have been observed.[19,21] The most closely analogous cases where both *syn* and *anti* pathways are geometrically possible have been considered to be proceding by such an associative mechanism,[24] although such counterion assistance in the departure of the leaving group in alkylation reactions carried out in nonpolar media has been invoked on numerous occasions.[23]

Applications to the *Laurencia* group are in progress.

Acknowledgment. We are grateful to the NIGMS and the NCI of the NIH for research grants (GM-29290, GM-30345, and CA-29108) in support of these studies. Thanks to Dr. J. Ramon Vargas for performing some of the cyclization experiments involving **8**.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **7**, **21**−**32** (12 pages).

JO9712254

(16) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(18) In contrast to the dihydrooxepines such as **3**,[1] reduction of the formyldihydrooxacenes **2**, **31**, and **32** afforded only the dihydrooxacene alcohols which were converted to the related Mosher ester for analysis.
(19) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. Altenbach, H.-J. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 830−832. March, J. *Advanced Organic Chemistry, 4th ed.; J. Wiley & Sons: New York, 1992; pp 327−330.*
(20) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1959**, *78*, 4609. Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4619.
(21) Schultz, A. G.; Godfrey, J. D.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 1276. Stork, G.; Kreft, A. F., III. *J. Am. Chem. Soc.* **1977**, *99*, 3850, 3851.
(22) Yates, R. L.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1975**, *97*, 6615 and references therein.
(23) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927. Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buendia, J. *Bull. Soc. Chim. Fr.* **1978**, II-131. Martel, J.; Toromanoff, E.; Mathieu, J.; Nominé, G. *Tetrahedron Lett.* **1983**, *24*, 2653.
(24) Caine, D. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 12−18.