Table I

species	basis set	bond lengths, Å R_{14}	R_{23}	R_{12}	R_{34}	energy, au
ethene	STO-3G				1.306	-77.0739555519
	3-21G				1.315	-77.6009887270
	6-31G*				1.315	-78.0316951773
ethene cation radical	STO-3G			1.430		-76.7975470693
	3-21G			1.405		-77.2714570308
	6-31G*			1.405		-77.7123115073
long-bond complex	3-21G	2.227	3.062	1.381	1.378	-154.904010083
	6-31G*	2.227	3.062	1.381	1.378	-155.766664364
loose complex	STO-3G	3.121	4.400	1.349	1.429	-153.877752947
transition state	STO-3G	2.350	4.350	1.423	1.423	-153.870959900
	3-21G	1.756	2.550	1.503	1.413	-154.892619984
	6-31G*	1.819	2.600	1.484	1.399	-155.754794531
cyclobutane cation radical	STO-3G	1.574	1.870	1.528	1.531	-153.969240946
	3-21G	1.602	2.004	1.514	1.509	-154.908773084

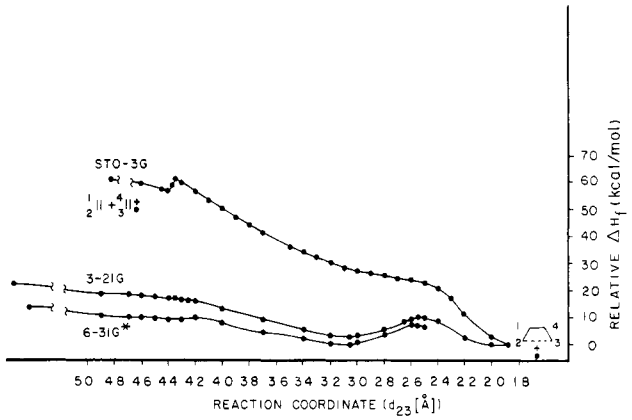


Figure 1.

has ethenic moieties that are approximately equivalent and, very significantly, that retain very extensive π character (see R_{12} and R_{34} lengths), and all four carbons remain essentially sp^2 hybridized. The shorter intermolecular distance R_{14} (2.227 Å) is interestingly close to that of the stable long (one electron) bond in the ethane cation radical (2.022 Å in 3-21G),[11] suggesting a possible widespread tendency of cation radicals to form one-electron bonds. For emphasis of this point, the 3-21G complex will be referred to as a *long-bond complex*. Point calculations in the 6-31G* basis set, using the optimized 3-21G geometries, closely reproduce the shape of the 3-21G profile (Figure 1) and provide strong support for the validity of the 3-21G results. Interestingly, the 6-31G* profile does suggest an extremely shallow minimum (*ca.* 0.4 kcal mol^{-1}) for a loose π complex.

All of the calculations confirm a phenomenally low activation energy for hole-catalyzed olefin cyclodimerization, which contrasts vividly with the 62.5 kcal mol^{-1} activation energy required for the corresponding neutral reaction.[12] The extended basis set calculations implicate a long-bond complex as an intermediate (Scheme I). The extensive ethenic π character of both moieties in this intermediate, however, precludes cis–trans isomerization and permits stereospecific suprafacial addition, as observed experimentally in the dimerization of *trans*- and *cis*-anethole.[8] This stereochemical behavior contrasts with that expected for a tetramethylene cation radical (**5**), the structure of the intermediate predicted by MNDO,[6] which should be subject to at least some *cis*–trans isomerization prior to cyclization to the long-bond cyclobutane cation radical. As shown previously, the energy of the one-electron bond in the latter is easily sufficient to maintain stereochemical integrity.[9]

Acknowledgment. We thank the Robert A. Welch Foundation (F-149) and the University of Texas Computation Center for substantial support.

(11) This work.

(12) Benson, S. W. "Thermochemical Kinetics"; Wiley: New York, 1968; Section 3.10.

Asymmetric Synthesis of Quaternary Carbon Centers

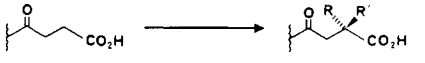
A. I. Meyers,* Michael Harre, and Robert Garland[1]

Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

Received October 31, 1983
Revised Manuscript Received January 3, 1984

A recent review by Martin[2] outlining synthetic methods to furnish quaternary carbon centers also points to the lack of efficient routes for generating this moiety in an enantioselective manner. If one sets aside the useful routes now available for chiral tertiary alcohols[3] and amino acids,[4] the statement in the Martin review is a correct assessment of the situation. Except for the studies by Koga wherein high enantioselectivity is observed for α,α'-disubstituted cycloalkanones[5] and α-substituted cyclic carboxaldehydes[6] no efficient methodology exists to date.

We now report that α-disubstituted carboxylic acids of the type **2** can be enantioselectively prepared from γ-keto acids **1** via a



1 **2**

novel and stereoselective sequence. Furthermore the method also provides a route to enantiomerically pure 3,3-disubstituted dihydronaphthalenes, **11**. The asymmetric synthesis of **2** is based on the bicyclic lactam **3**, which was prepared from *l*-valinol and 3-benzoylpropionic acid by azeotropic removal of water (toluene, *p*-TsOH, 8 h).[7] A single diastereomer of **3** was obtained in 85%

(1) G. D. Searle Laboratories, Skokie, IL.

(2) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(3) Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *22*, 2855. Jaouen, G.; Meyer, A. *J. Chem. Soc., Chem. Commun.* **1974**, 787. Mioskowskij, C.; Solladie, G. *Ibid.* **1977**, 163. Terashima, S.; Jew, S.-S.; Koga, K. *Tetrahedron Lett.* **1978**, 4937. Frater, G.; Muller, U.; Gunther, W. *Ibid.* **1981**, *22*, 4221 and earlier references cited. Seebach, D., Naef, R.; Calderari, G. In "Tetrahedron Symposium in Print"; Meyers, A. I., Ed.; in press.

(4) Schollkopf, U.; Neubauer, H. J. *Synthesis* **1982**, 861, and earlier references cited. Seebach, D., Boes, M.; Naef, R., Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(5) Hashimoto, S.-i.; Koga, K. *Tetrahedron Lett.* **1978**, 573.

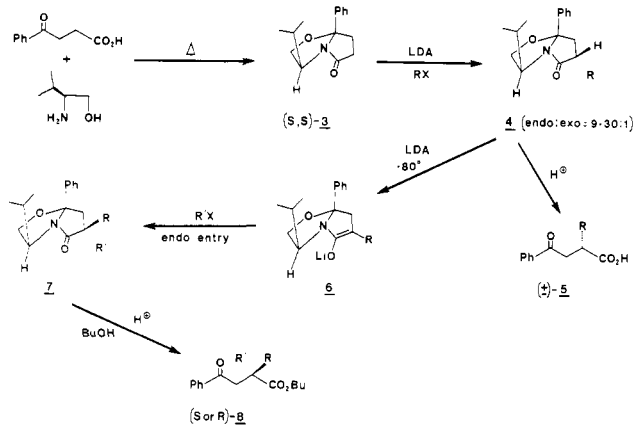
(6) Kogan, H.; Tomioka, K.; Hashimoto, S.-i; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4005.

Table I. Dialkylation of Lactams 7 and Benzoyl Esters 8

		dialkylated lactam 7		α,α-dialkylated ester 8		
4, R	R'X	R' entry (endo/exo)	yield, %[a]	yield, %[b]	$[\alpha]^{23}_D$ (*c*, $CHCl_3$)	confn
Me	$PhCH_2Br$	42:1	75	79	+23.90 (1.25)	*S*
$PhCH_2$	MeI	12:1	74	78	−24.80 (1.56)	*R*
Me	EtI	7.5:1	80	71	−29.96 (4.15)	*S*
Et	MeI	10:1	75	87	+31.50 (4.20)	*R*
Me	*p*-$MeOPhCH_2Br$	30:1	85	88	+22.23 (2.38)	*S*
p-$MeOPhCH_2$	MeI	13:1	90	92	−23.08 (1.98)	*R*
Me	*i*-PrI[c]	3:1	59			
i-Pr	MeI	1:10	49			

[a] Yield of pure diastereomer from chromatography (silica, 10% ethyl acetate, hexane). All gave correct elemental and spectral analyses and were homogeneous by HPLC. [b] Alcoholysis performed on single diastereomer 7 and yields represent pure, isolated material, which gave correct elemental and spectral analyses. [c] Alkylation occurred only at 0 °C in the presence of HMPA.

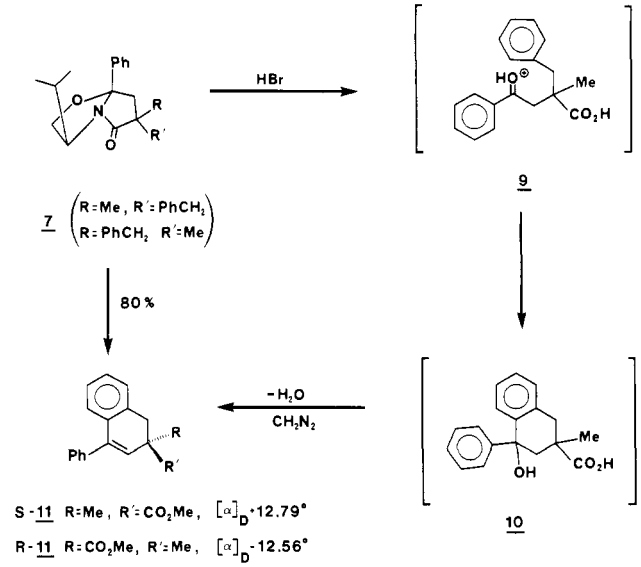
yield after chromatography with the absolute configuration shown to be *S,S* by X-ray diffraction techniques. Metalation of **3** (LDA, THF, −78 °C) and addition of iodomethane gave the monomethyl product **4** (R = Me) as a 9:1 ratio of endo:exo isomers by HPLC.[8] Kugelrohr distillation or crystallization gave the major pure diastereomer, which was shown by X-ray determination to be *endo*-methyl-**4** (R = Me). In a similar fashion alkylation of *S,S*-**3** with other alkyl halides gave **4** with the endo isomer predominating by 9–30:1. However, attempts to regenerate, by hydrolytic means, the α-alkyl acids **5** gave mainly racemic products (<20% ee). The



acids were found to be quite stable to racemization (less than 5% D incorporation at the α-position on heating with DCl or D_2SO_4).[9] Thus the racemization occurs at one of the intermediate hydrolysis stages of **4**.

The monoalkylated lactams (Table I), either as mixtures or diastereomerically pure, were again metalated (THF, −78 °C, 1.1 equiv of LDA, 2 h) and alkylated (2–3 equiv, THF, −78 °C) to give the disubstituted derivatives **7** with good to excellent stereoselectivity (ratios given in Table I). The use of mixtures of **4** are obviously of no consequence since the enolate **6** is devoid of any stereochemistry at the α-carbon, and the electrophile enters from the endo face to give **7**. With racemization no longer a problem, the newly formed quaternary center was cleaved by using 10% sulfuric acid-butanol (reflux 90–96 h) to afford the butyl esters **8** in 70–90% yield after chromatography (preparative TLC or column). The absolute configuration of the esters **8** was initially assumed to be derived from endo entry of the second electrophile and finally confirmed by transformation to (*S*)-dimethyl 2-methyl-2-ethylsuccinate[10] by ozonolysis of **8** (R = Me, R = Et). Thus, all the chiral esters **8** with quaternary centers were obtained in good yields with >95% enantiomeric purity. It can be seen from the table that the order of introduction of electrophiles will predictably provide either enantiomer. In the case of isopropyl iodide, both orders of addition gave the same major diastereomer of **7**. This may be due to the bulky isopropyl groups, which cannot be readily positioned into the exo face of the lactam thus causing the methyl iodide to enter the enolate **6** (R = *i*-Pr) from the exo face.

The method was extended to dihydronaphthalenes containing a quaternary carbon by heating the pure epimeric lactams **7** with 48% HBr for 24 h followed by esterification with diazomethane. Both (*S*)- and (*R*)-**11** were were obtained with complete optical



purity through the expected intermediates **9** and **10**. Structure proof for **11** was gathered by chemical correlation[11] and the absolute configuration again based on the starting lactams, **7**.

In summary, the chiral bicyclic lactam **3** and others under active study are potentially highly useful precursors to quaternary carbon centers generated with high enantioselectivity. Experimental details and complete characterization of all products are provided as supplementary material.

Acknowledgment. Financial assistance for this work was provided by the National Institutes of Health. The Nicolet R3m/E

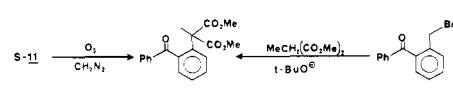
(7) **3**: mp 52–54 °C, $[\alpha]_D$ 80.1° (*c* 1.5, $CHCl_3$); PMR (100 MHz) ($CDCl_3$) 7.4 (m, 5 H), 4.2 (t, 7 Hz, 1 H), 3.6 (m, 1 H), 3.4 (t, 7 Hz, 1 H), 2–3 (m, 4 H), 1.1 (m, 1 H), 1.05 (d, 1 Hz, 3 H), 0.65 (d, 6 Hz, 3 H); IR ($CHCl_3$) 1700 cm^{-1}. Anal. Calcd (Found): 73.44 (73.80); H, 7.80 (7.53).

(8) This and all other alkylation ratios were determined by using a μ Porosil column eluted with 5–20% hexane in ethyl acetate.

(9) Chiral α-alkyl carboxylic acids are well-known to be reasonably stable toward racemization under acidic conditions: Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

(10) Overberger, C. G.; Wang, D. W. *J. Org. Chem.* **1981**, *46*, 2757.

(11) When **11** was ozonized in methanol (−78 °C) and worked up with 30% H_2O_2 it gave the keto ester i after diazomethane–ether treatment, which was identical in all respect with the product obtained from the benzophenone ii and the malonic ester:



X-ray diffractometer and computing system was purchased with funds provided by the National Science Foundation (CHE 810 3011). We are grateful to Prof. O. P. Anderson and C. Schauer for performing the X-ray studies.

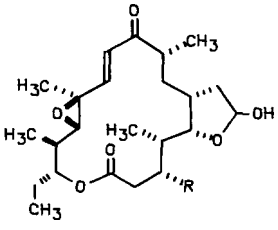
Supplementary Material Available: Physical data, experimental details, and X-ray data for **3** and **4** (R = Me) (21 pages). Ordering information is given on any current masthead page.

Macrocyclic Stereocontrol. Total Synthesis of (±)-3-Deoxyrosaranolide

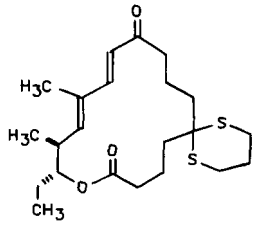
W. Clark Still* and Vance J. Novack

Department of Chemistry, Columbia University
New York, New York 10027
Received November 23, 1983

The conformational structure of medium- and large-ring molecules provides an effective medium through which asymmetric centers may efficiently control the stereochemical outcome of remote chemical reactions. To investigate the potential of this approach to stereocontrol in complex synthesis, we have undertaken an extensive application of the methodology[1] to a derivative of the macrolide antibiotic rosaramicin[2] (aglycon **1a**). Starting from the simple macrocycle **2**, we synthesized the racemic 3-deoxy



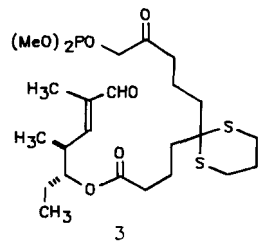
1a, R = OH
1b, R = H



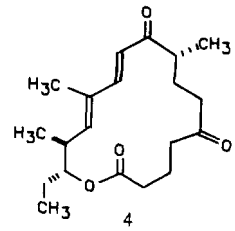
2

aglycon **1b** using the two adjacent asymmetric centers at C11 and C12 to efficiently control the six others spanning C4–C10.

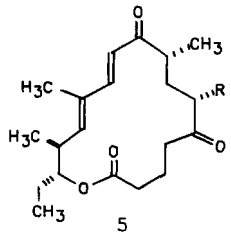
The starting ketomacrolide **2** was readily prepared from acyclic ester **3**[3] by Horner–Emmons cyclization[4] (K_2CO_3, 18-crown-6, 0.01 M in toluene, 75 °C; 76%). On deprotonation with KN(Me_3Si)$_2$ and alkylation with CH_3I (THF, −78 → 20 °C), a single C8-methylated material was produced in 70% yield and with diastereoselection 20:1.[5] Deprotection (HgO, HBF_4/THF; >95%)[6] and X-ray crystallographic analysis[3] of the product **4** showed the natural 8-α configuration. Regio- and stereoselective introduction of the second side chain was accomplished (73%) with >20:1 regioselection for C6 and 6–10:1[7] α stereoselection by using LiN(Me_3Si)$_2$ and CH_3I. The identity of the product as **5a** (R = CH_3) was shown by X-ray crystallography.[3] An analogous alkylation using $BrCH_2COO$-*t*-Bu proceeded with the same regio- and stereoselection to yield **5b** (R = CH_2COO-*t*-Bu) (73%) as



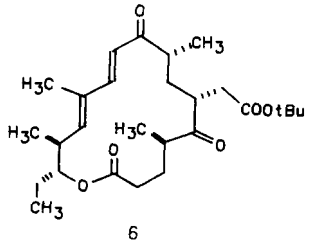
3



4



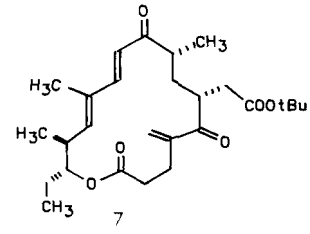
5



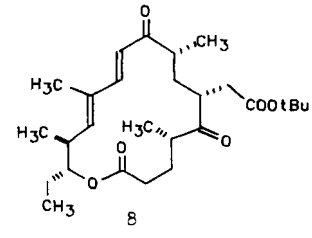
6

shown by spectral comparison with **5a** and by further conversions. Highly stereoselective (>40:1) introduction of the C4 methyl followed (LiN(Me_3Si)$_2$, THF, CH_3I; 71%) but led to the unnatural 4-β isomer **6**.[5]

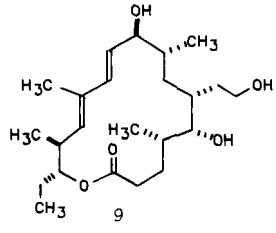
Assuming that the desired 4-α stereochemistry could be obtained by a stereoanalogous enolate protonation, the C4 lithium enolate was treated with gaseous HCHO to give a single 4-hydroxymethyl ketone (62%), which was eliminated via the mesylate to the methylene ketone **7** (90%). Addition of thiophenol



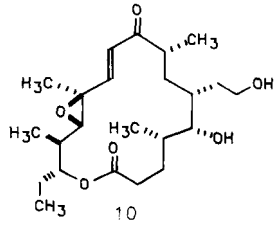
7



8



9



10

(catalytic Et_3N; 71%) and Raney nickel desulfurization (W2 Ra Ni, EtOH; 62%) then gave the required 4-α **8** with >25:1 stereoselection. Alternatively, catalytic reduction with H_2/(Ph_3P)$_3$RhCl (C_6H_6) gave 9:1 **8**:**6** (75%).

Final conversions to **1b** included stereoselective reduction and epoxidation. While the 5-β alcohol was formed with >20:1 stereoselection by direct $NaBH_4$–$CeCl_3$[8] reduction, the 5-α alcohol **9** could be prepared with 5:1 stereoselection at C5 by reduction ($NaBH_4$, CH_2Cl_2/*i*-PrOH) of the mixed anhydride prepared by *tert*-butyl ester hydrolysis (CF_3COOH) and acylation (Et_3N, ClCOOEt) (50% overall). Oxidation (MnO_2; 75%) and epoxidation (MCPBA, Na_2CO_3, CH_2Cl_2; 88%) then led to diastereomer **10** (>15:1), which was further oxidized to **1b** with (Ph_3P)$_3$$RuCl_2$[9] in 47% yield at 56% conversion. Racemic **10** thus prepared was indistinguishable from naturally derived material[3] by ^{13}C NMR, 270-MHz ^1H NMR, IR, and MS.

In all, 11 kinetic reactions were used in various conversions that establish stereochemistry in the 16-membered macrolide described above. Among these reactions, conditions were readily found that gave eight of the reactions at least 15:1 stereoselection and the

(1) Previous macrocylic addition reactions: Still W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.-e.; Nambiar, K. P.; Falck, J. R. *Ibid.* **1979**, *101*, 7131. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, *249*. Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774. Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *Ibid.* **1983**, *105*, 127. Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *Ibid.* **1983**, *105*, 625. Vedejs, E.; Gapinski, D. M. *Ibid.* **1983**, *105*, 5058. Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *Ibid.* **1984**, *105*, 260.

(2) Ganguly, A. K.; Liu, Y.-T.; Sarre, O.; Jaret, R. S.; McPhail, A. T.; Onan, K. K. *Tetrahedron Lett.* **1980**, *21*, 4699.

(3) Supplementary material.

(4) Cf.; Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *Ibid.* **1979**, *44*, 4011. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; *J. Am. Chem. Soc.* **1982**, *104*, 2030.

(5) Equilibration with base gave ca. 1:1 diastereomeric mixture at the newly established center only.

(6) Degani, I.; Fochi, R.; Regondi, V. *Synthesis* **1981**, *13*, 51.

(7) Ratio by isolation (6:1) and by calibrated HPLC (10:1).

(8) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(9) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

0002-7863/84/1506-1148$01.50/0