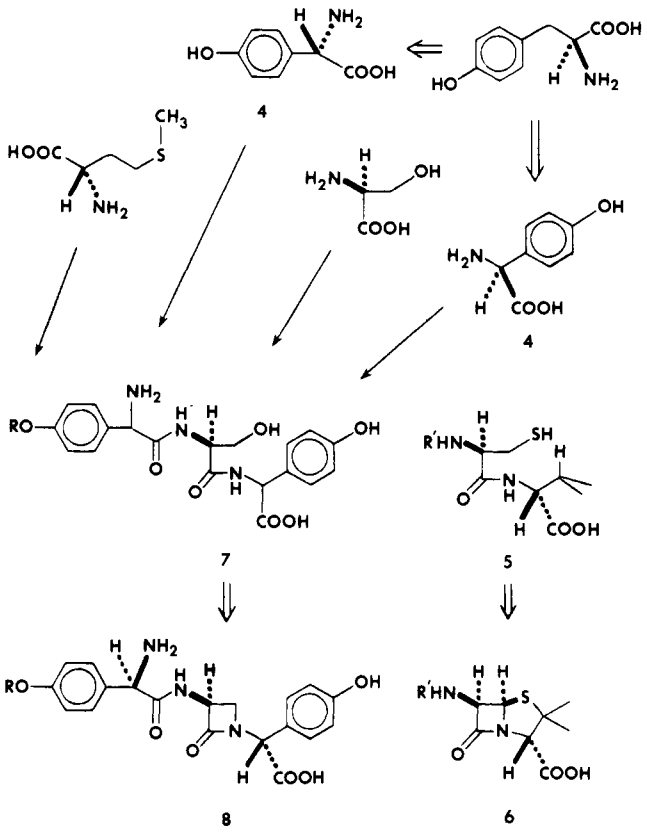

as the reaction partner to form this ether linkage. Inversion at the amino terminus (C-9′) in **1**, as is the case in the conversion of isopenicillin N (**6**) [R′ = δ-(L-α-aminoadipyl)] to penicillin N (**6**) [R′ = δ-(D-α-aminoadiphyl)], is presumably a late step in the pathway.

Neither L-alanine nor L-cysteine were incorporated to any significant degree into nocardicin A (**1**). However, it is interesting to note that the level of production of **1** was markedly reduced in the presence of cysteine to about 10% of that in the unsupplemented fermentation, an effect that was not reversed by added methionine. Glycine and L-serine on the other hand gave good incorporations into **1**, the latter being two to three times more efficient than the former. The positive incorporation of glycine almost certainly takes place by way of intermediate conversion to serine. This interpretation is supported by the relatively higher rate of incorporation of C-2 vs. C-1 labeled glycine where it is well-known[13] that radiolabel from C-2 will enrich the C_1 pool and through the action of serine hydroxymethyltransferase lead to the de novo synthesis of labeled serine in addition to that derived directly from labeled glycine. This ready conversion was unmistakably borne out on ^{13}C NMR analysis of a specimen of nocardicin A (**1**) obtained by feeding [2-^{13}C]glycine in a fashion analogous to that employed for the radiochemical studies summarized in Table I.[14] Appreciable enhancements of two resonances at 54.9 and 47.0 ppm were observed in the ^{13}C NMR in a ratio of roughly 3:2 corresponding to C-3 and C-4, respectively.[15] As expected, the corollary experiment with D,L-[3-^{13}C]serine[14] gave enrichment at C-4 alone.

Bearing in mind the apparently substantial serine hydroxymethylase activity present under the fermentation conditions, two double label experiments were carried out to investigate the overall redox chemistry at the serine β carbon during β-lactam ring formation. L-[3-^3H]Serine admixed separately with L-[U-^{14}C]- and L-[3-^{14}C]serine gave, respectively, 86% and 99% retention of tritium label on incorporation into nocardicin A (**1**). These results indicate that β-lactam formation takes place *without* change in oxidation state at the β carbon in sharp contrast to the complex oxidative chemistry acting in penicillin biosynthesis, *cf.* **5** → **6** and **7** → **8**.

In conclusion, like penicillin and cephalosporin with which it shares important stereochemical similarities, nocardicin A is entirely amino acid derived, the L-enantiomers of methionine, serine, and (*p*-hydroxyphenyl)glycine serving as the most direct precursors. The monocyclic β-lactam in nocardicin A is apparently formed simply and directly by nucleophilic displacement of a presumably activated seryl hydroxyl[16] by amide nitrogen, a sequence requiring no change in oxidation state. The roles of nucleophile and electrophile may by played again in more complex fashion in the corresponding cyclizations of **5** to penicillin **6**.

Acknowledgment. We are indebted to L. T. Nguyen for several preparations and resolution of the doubly labeled specimens of (*p*-hydroxyphenyl)glycine used in this work and Eli Lilly and Co. and Fujisawa Pharmaceuticals, Ltd., for analytical samples of nocardicin A sodium salt. We gratefully acknowledge the financial support of The Natural Institutes of Health (5 R01 AI14937 and 5 S07 RR07041), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Fellowship Fund (AMB). Single-frequency proton decoupling experiments were carried out at the Middle Atlantic Regional NMR Facility.

(13) Prodigiosin is a similar case: Wasserman, H. H.; Sykes, R. J.; Peverada, P.; Shaw, C. K.; Cushley, R. J.; Lipsky, S. R. *J. Am. Chem. Soc.* **1973**, *95*, 6874-6875 and references cited.

(14) This experiment was additionally carried out in the presence of 1 mM L-methionine to maximize the production of nocardicin A (**1**) (see footnote b, Table I).

(15) The published[1] ^{13}C assignments for the C-3 and C-5 methine carbons are incorrect and should be reversed. On the basis of single-frequency proton decoupling experiments, the correct assignments are C-3 (54.90 ppm) and C-5 (61.58 ppm).

(16) Phosphorylation is an attractive possibility for hydroxyl activation which has received support in these laboratories in a biomimetic synthesis of 3-aminonocardicinic acid (Townsend, C. A.; Nguyen, L. T., unpublished results).

Trapping and Chirality as Evidence for an Allene Structure for 2,3,6-Bicyclo[3.2.1]octatriene

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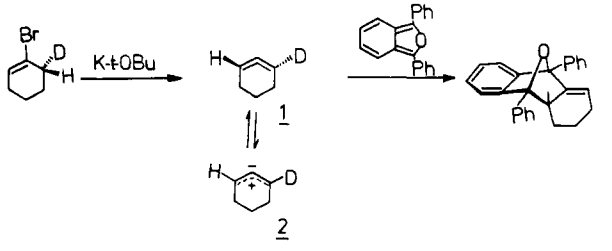
We have recently reported[1] evidence that has led us to the conclusion that, contrary to expectation,[2] at 53 °C the preferred structure of the intermediate formed from base-induced dehydrobromination of 1-bromocyclohexene is better represented by the twisted allene **1** than the less strained dipolar structure **2**. This



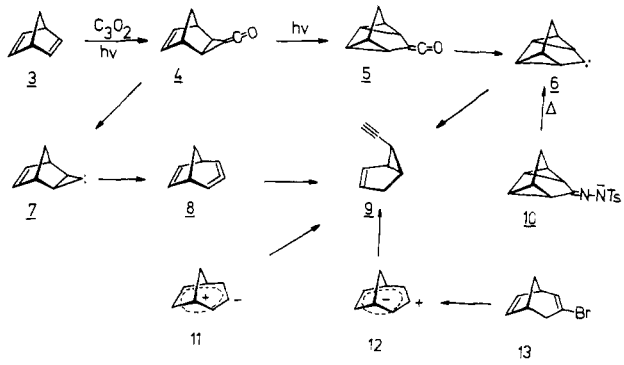
conclusion was based on the formation of optically active adduct from dehydrobromination of optically active 1-bromocyclo-

(1) Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7607.

(2) Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978; pp 126-130. Dillon, P. W.; Underwood, G. R. *J. Am. Chem. Soc.* **1974**, *92*, 779-787. Moore, W. R.; Moser, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 5469-5474. See also: Bottini, A. T.; Cabral, L. J.; Dev, V. *Tetrahedron Lett.* **1977**, 165-168 and references cited therein.

0002-7863/81/1503-2874$01.25/0

Scheme I



hexene-*6-d* in the presence of 1,3-diphenylbenzo[*c*]furan.

Some years ago Bergman and Rajadbyaksha[3] reported that the base-induced (potassium *tert*-butoxide in Me_2SO) dehydrobromination of **13** gives the hydrocarbon **9** in 29% yield. To rationalize this product, the authors suggested collapse of the bishomoaromatic carbene **12** as depicted in Scheme I. The same product was observed from thermal decomposition of **10** in methanol.

The following year, Klumpp and van Dijk[4] reported the same product from photolysis of carbon suboxide in norbornadiene and pointed out that the allene **8**, its nontwisted counterpart **11**, or the carbene **6** are all viable alternatives to the bishomoaromatic carbene **12**. However, no evidence was provided to distinguish between the different possibilities.

Recognizing that **8** is a bridged 1,2-cyclohexadiene and further recognizing that of the four intermediates suggested for the above reaction, only **8** is chiral, we undertook to apply the above method of trapping a chiral intermediate to probe the structure of the species formed from the dehydrobromination of **13**. At this time we report evidence that the allene structure **8** represents at least one energy minimum on the bicyclo[3.2.1]C_8H_8 energy surface. It may also represent the precursor to **9**, but this is not yet secure.

A reaction that appears to be characteristic of strained allenes[5] (although not by necessity limited to the twisted form) is addition to 1,3-diphenylbenzo[*c*]furan. 3-Bromo-2,6-bicyclo[3.2.1]octatriene (**13**), prepared according to the method of Moore, Moser, and LaPrade,[6] was therefore treated with potassium *tert*-butoxide (2 equiv., THF, 53 °C) in the presence of 1.1 equiv of 1,3-diphenylbenzo[*c*]furan. Indeed, four adducts, **14**–**17**, were isolated in yields of 21%, 7%, 21%, and 4%.[7]

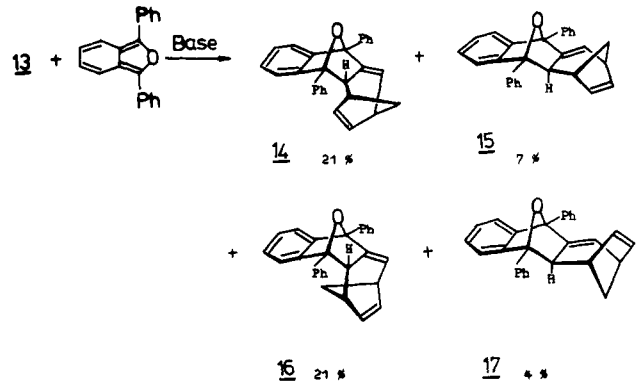
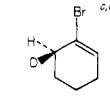
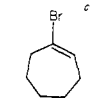
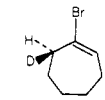


Table I. Rotations of 1,3-Diphenylbenzo[*c*]furan Adducts of Cyclic Allenes

halide[a]	base[a]	temp, °C	$[\alpha]^{25}_D$, deg[b]		ref
13	potassium menthoxide	53	−1.3[c]		this work
		80	−0.1		
		100	0.0		
	potassium menthoxide	53	−0.4[d]		this work
		100	0.0		
 18	potassium *tert*-butoxide	53	−0.3[d,f]	+1.6[e]	
		80	0.0	+0.3	1
		100	0.0	0.0	
	potassium menthoxide	53	−1.9[d]		this work
		100	−1.7		
 19	potassium *tert*-butoxide	53	+0.9[d]		
		100	+0.7		1
		140	+0.4		

[a] Reagent concentrations were the same in runs at different temperatures. [b] Maximum standard deviations were ±0.11°. [c] Rotations were measured on **16**. [d] Rotations were measured on the major (endo) isomer. [e] Minor isomer. [f] The standard deviation for the 80° run was ±0.2°.

Under these conditions no trace of **9** (or its expected adduct with 1,3-diphenylbenzo[*c*]furan) was observed. In the absence of the trap, **9** was formed (in the THF reaction), although low in yield (15%). The same four adducts were also formed from reaction of **13** with potassium *tert*-butoxide in Me_2SO (Bergman's conditions), although this reaction was not as clean as the THF runs. Again, no **9** was observed in the presence of the trap, although Bergman and Rajadbyaksha[3] reported 29% under these conditions in the absence of trap.

For a chirality test of the trapped intermediate, potassium menthoxide was substituted for potassium *tert*-butoxide in the THF reaction.[8] Again the same four adducts were formed although significantly more slowly. One of these was isolated and its optical activity measured. As noted in Table I, when the reaction was run at 53 °C adduct **16** (the most easily isolated) showed a specific rotation of $[\alpha]_D^{25}$ −1.3°. That the observed rotation of the adduct reflects chirality of the intermediate (rather than some spurious asymmetric induction) is supported by the similarity between the asymmetric induction experiments on 1-bromocyclohexene and 1-bromocycloheptene and *tert*-butoxide-induced elimination from chiral **18** and **19**. Activities in the latter reactions cannot result from spurious induction. It will also be noted in the table that the activity of **16** rapidly dropped to [α] 0° as the reaction temperature was raised. This was also found to be the case for dehydrohalogenation of active **18** but not **19**. The possibility that loss of activity of **16** results simply from decreased asymmetric induction with increase in temperature[1] is unlikely in view of the result of increasing temperature on the activity of the adduct of **19**.

From the above results we conclude that base-induced dehydrobromination of **13** in THF proceeds by a concerted cis elimination[9] to give a chiral intermediate that is best represented by

(3) Bergman, R. G.; Rajadbyaksha, V. J. *J. Am. Chem. Soc.* **1970**, *92*, 2163–1264.

(4) Klumpp, G. W.; van Dijk, P. M. *Recl. Tran. Chim. Pays–Bas* **1971**, *90*, 381–384.

(5) Wittig, G.; Fritze, P. *Angew. Chem. Int. Ed. Engl.* **1966** *5*, 846. Wittig, G.; Meske-Schuller, J. *Liebigs Ann. Chem.* **1968**, *711*, 76–81. Wittig, G.; Fritze, P. *Ibid.* **1968**, *711*, 82–87.

(6) Moore, W. R.; Moser, W. R.; LaPrade, J. E. *J. Org. Chem.* **1963**, *28*, 2209.

(7) All products gave acceptable C, H analyses. Structure assignments are based on complete NMR analysis and are secure.

(8) Asymmetric induction was used to study this reaction rather than elimination from optically active halide (as for 1,2-cyclohexadiene and 1,2-cycloheptadiene) because Bergman and Rajadbyaksha[3] found that active **13** rapidly racemizes (by a carbanion mechanism) under the conditions of their reaction. Fortunately, racemization of starting material does not preclude using chirality from asymmetric induction as a probe if the product-forming intermediate is formed from a concerted elimination, even if it is in competition with a nonproductive proton exchange.[9] In fact, to the contrary, rapid racemization of starting material would enhance the induction by replenishing the depleted enantiomer.

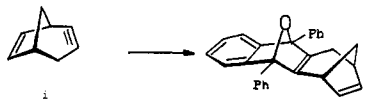
a twisted allene structure **8**.[10] The loss of activity with increase in temperature further suggests that **8** may rapidly racemize through an intermediate or transition state that can be represented by any of the three structures **6**, **11**, or **12** or a diradical.

Finally, since concerted opening of optically active **8** to **9** should give an active hydrocarbon, **13** was allowed to react with potassium menthoxide in the absence of the furan trap. Unfortunately, **9** was formed in only very low yield (only 2-3%; probably as a result of low thermal stability during the very slow reaction with the less reactive base). However, the small amount that was formed, after isolation as its silver salt and very thorough washing to remove all traces of menthol, was indeed found to be optically active ($[\alpha]_D^{25}$ +2.2 ± 0.2°; microcell). This suggests that the allene may be the progenitor of **9**, although further work will be required before this is secure.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation.

(9) Intuitively, a concerted elimination in competition with carbanion formation (without elimination) seems unlikely. However, unlike most β-eliminating systems, in this case the carbanion electrons are presumably orthogonal to the carbon-halogen bond and unlike orthogonal α-eliminating systems (such as bromoform) it is unlikely that much electron density is localized on the carbon with the leaving group. Intuition not withstanding, if this reaction does go via an allene intermediate (rather than an alkyne),[10] the results reported here require that at least a portion of the reaction go by a concerted mechanism.

(10) A possible alternative to the allene intermediate is the alkyne i. This is chiral and could therefore give active products. We feel, however, that this is unlikely for two reasons. First, despite careful searching, none of the alkyne adducts could be found and it seems unlikely that both syn and anti ii would completely tautomerize to the allene adducts. Second, in contrast to the allene,[3] the alkyne does not provide a viable mechanism for formation of **9** which is observed in the absence of trap but not in its presence.



i ii

Enantioselective Aldol Condensations. 3. Erythro-Selective Condensations via Zirconium Enolates[1]

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Contribution No. 6392 from the Laboratories of Chemistry California Institute of Technology Pasadena, California 91125

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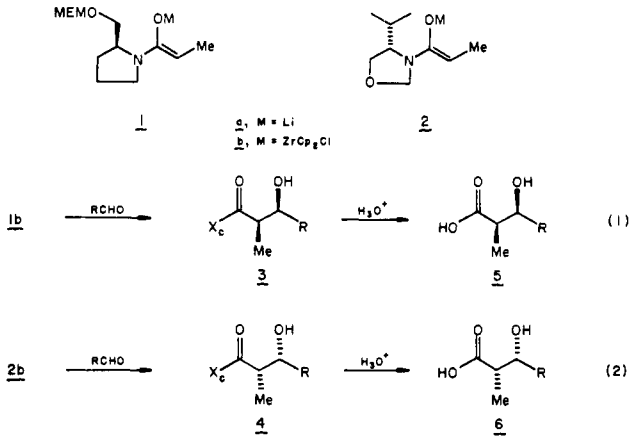
The important role that sterically demanding metal centers play in the enhancement of aldol stereoregulation has recently become apparent.[2,3] For dialkylboryl enolates kinetic aldol product stereochemistry has been shown to be strongly coupled to enolate geometry,[2] while for dicyclopentadienylchlorozirconium enolates kinetic erythro-selective condensations have been observed from either enolate geometry.[3] Recent studies from this laboratory have demonstrated that while the lithium enolates derived from prolinol amides exhibit excellent diastereoface selection (15-30) in alkylation reactions,[4] the complimentary aldol condensations were nearly stereorandom. The purpose of this communication is to report that high levels of aldol stereoregulation may be restored to the condensation process if zirconium enolates are employed and the complimentary amino acid derived amide enolates **1b** and **2b** exhibit excellent levels of asymmetric induction in the aldol process (eq 1, 2). Both of the illustrated chiral auxiliaries have been designed to incorporate a masked hydroxyl function which has been shown to assist in the acid-catalyzed amide hydrolysis vis N → O acyl transfer.[4]

Table I. Comparative Aldol Condensations of the Lithium and Zirconium Enolates **1** and **2** (eq 1, 2)[7]

enolate	metal[a]	RCHO	product 3:4	distribution[b] T_1:T_2	yield, %
1b	Zr	n-C_4H_9CHO	96:2	1:1	(3a) 69[c]
1a	Li		39:29	15:17	
2b	Zr		1:97	1:1	(4a) 96[d]
2a	Li		35:42	6:17	
1b	Zr	i-C_3H_7CHO	96:2	1.5:0.5	(3b) 77[c]
1a	Li		43:36	9:12	
2b	Zr		0.5:97.5	1:1	(4b) 77[c]
2a	Li		42:41	13:4	
1b	Zr	C_6H_5CHO	96:1	2:1	(3c) 71[c]
1a	Li		31:33	23:13	
2b	Zr		1.5:94.5	2:2	(4c) 71[e]
2a	Li		41:29	24:6	

[a] Zr refers to $ZrCp_2Cl$. [b] Determined by capillary GLC and standardized to base 100. T_1 and T_2 refer to the threo diastereomers. [c] Chromatographed to 99% of a single diastereoisomer. [d] Purified by molecular distillation. Diastereoisomer ratio unchanged. [e] Purified by recrystallization, mp 139.5-140 °C.



The lithium enolates **1a** and **1b**, which were generated from the respective propionamides[5] and LDA (THF, 0 °C, 30 min), were transformed into the corresponding zirconium enolates **1b** and **2b** by subsequent treatment with 1.1 equiv of Cp_2ZrCl_2 (0.16 M in THF).[3a] The aldol condensations with representative aldehydes were carried out between -78 and 0 °C as previously described.[3a] Complete aldol diastereomer analysis was carried out by capillary gas chromatography on the unpurified reaction products.[6] The comparative aldol condensations of the zirconium

(1) Presented at the 12th International Symposium on the Chemistry of Natural Products, Tenerife, Canary Islands. Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, in press. Evans, D. A.; McGee, L. R. Also presented at the 2nd Chemical Conference of the North American Continent, Las Vegas, NV, Aug 28, 1980; Abstract ORGN 288.

(2) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120-6123. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *Ibid.*, in press. (c) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665-1668. (d) Hirama, M.; Masamune, S. *Ibid.* **1979**, 2225-2228. (e) Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229-2232. (f) Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937-3940. (g) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174-178.

(3) (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, 3975-3978. (b) Yamamoto, Y.; Maruyama, K. *Ibid.* **1980**, 4607-4610.

(4) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, 4233-4236. (b) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3139-3141.

(5) (a) The propionamide precursor of enolate **1a** is formed by alkylation of prolinol propionamide[4a] with MEMCl.[17] After workup and bulb-to-bulb distillation [bp 110 °C (<0.001 mm)] the desired amide was obtained in an 86% yield, $[\alpha]_D$ -66.4° (*c* 3.79, CH_2Cl_2). (b) The propionamide precursor of enolate **2a** is formed by azeotropic removal of water from an equimolar mixture of *l*-valinol and paraformaldehyde in benzene followed by acylation with propionic anhydride. After workup and bulb-to-bulb distillation [bp 90 °C (0.01 mm)] the desired amide was obtained in an 80% yield, $[\alpha]_D$ +20.7° (*c* 2.34, CH_2Cl_2).

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