On the Absolute Stereochemistries of (-)-Benzocyclohepten-3-ol, (-)-2,3,4,5-Tetrahydro-1-benzoxepin-5-ol, and (-)-Benzocycloocten-3-ol

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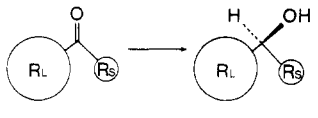
The configurations of (-)-benzocyclohepten-3-ol (**2a**), (-)-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (**6a**), and (-)-benzocycloocten-3-ol (**9a**), which were prepared by microbial reduction of the corresponding keto compounds by *Cryptococcus macerans*, were established as *S* by conversion to dimethyl α-acetoxy dicarboxylate esters of known configuration. The elution order of the enantiomers of each of these three carbinols and their acetates from a Pirkle chiral-phase HPLC column was not consistent with that found for the lower homologues, 1-indanol and 1-tetralol. These results indicate great care must be exercised in the use of elution order for the determination of configurations.

In the course of our studies on the use of microbial methods for the reduction of ketones[2a,b] and for the enantioselective hydrolysis of a series of acetates[2c] of acyclic and cyclic alklarylcarbinols, we needed an analytical procedure for establishing the enantiomeric excess (ee) of the alcohols formed. The recent reports by Pirkle et al.[3] offered such a procedure; the use of a chiral phase on an HPLC column that could resolve alkylarylcarbinols without the need of derivatization. Furthermore, the authors suggested that their column also provided a method for assigning the absolute stereochemistry of an enantiomer from its elution volume relative to that of its antipode. This suggestion has been explored in detail by examining the order in which enantiomers of over 40 acyclic and cyclic alkylarylcarbinols and their acetates are eluted; we found that each group of compounds exhibited a characteristic relation between elution order and absolute stereochemistry.[4] There were few exceptions to these patterns. Since the analysis is rapid and requires only nanograms of material, many compounds can be examined (a) to confirm previous assignments, (b) to aid in making tentative new assignments, and (c) to study exceptions to the rules in an effort to understand better the interactions responsible for effecting resolution.

In an earlier study[2a] of the microbial reduction of several 1-tetralone and 1-indanone derivatives it was shown that the absolute stereochemistry of the alcohols formed could be rationalized by a rule formulated by Prelog[5] to account for the configuration of the microbial reduction products of saturated ketones. The absolute stereochemistry of the carbinol formed is that shown in eq 1 when R_L is larger



(1)

than R_S. In order to account for the correct configuration about the carbinol carbon in the above reductions, it was necessary to treat the fused aromatic moiety as the larger substituent (R_L). The only exception occurred in the reduction of 2-bromoindan-1-one where, to be consistent with Prelog's rule, the bromomethine group had to be effectively larger than the fused aromatic moiety. The reversal appeared to have a reasonable physical basis.

In using microbial reductions for the preparation of alcohols of known configuration,[2a] we tentatively assigned an *S* configuration to (-)-benzocyclohepten-3-ol (**2a**), the product from benzosuberone. When the chromatographic behavior of (-)-**2a** was examined, it was found that this enantiomer was eluted more rapidly than its antipode. On the basis of the relation between the absolute stereochemistries established for numerous substituted 1-indanols and 1-tetralols, this result suggested that the configuration of the alcohol might be *R* and not *S* or, alternatively, that the relation between configuration and elution order for five- and six-membered benzocycloalkenols does not apply to other benzocycloalkenols. In order to distinguish between these explanations, we first determined the absolute stereochemistry of (-)-**2a**. In an attempt to examine the broader implications of the mutually incompatible configurational assignments, we then also examined the microbial reduction products of 3,4-dihydro-1-benzoxepin-5(2*H*)-one (**5**) and benzocycloocten-3-one (**8**). The absolute stereochemistry of each of the alcohols formed was determined, and the HPLC behavior of the alcohols and their acetates was investigated.

The absolute stereochemistry of (-)-**2a** was established by a comparison of a sample of dimethyl α-acetoxyheptanedicarboxylate prepared from (-)-**2b** with one prepared from (*S*)-cyclohepten-3-ol ((-)-**4a**) of known absolute stereochemistry (see Scheme I). Cyclohepten-3-ol was resolved by fractional crystallization of the camphanate ester as described by Crabbé et al.[6] for the corresponding cycloocten-3-ol, with subsequent reductive cleavage of the ester. The (-) alcohol **4a** which had been assigned an *S* configuration by Iriuchijima and Kojima[7] was acetylated, and the resulting **4b** was oxidized with RuO_4 by using a procedure recently described by Sharpless and co-workers.[8] Methylation with diazomethane of the dicarboxylic acid obtained yielded (*S*)-dimethyl α-acetoxyheptanedicarboxylate ((-)-**3**) which had a specific rotation of the same sign as that of a sample prepared from (-)-**2b**. Thus, the absolute stereochemistry of microbially derived **2a** was

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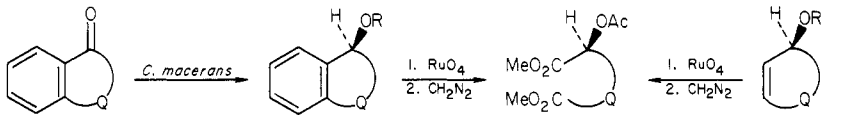
Scheme I



Q = $(CH_2)_4$	(*S*)-(-)-**2a**, R = H b, R = Ac	(*S*)-(-)-**3**	(*S*)-(-)-**4a**, R = H b, R = Ac
5, Q = $(CH_2)_3$-O	(*S*)-(-)-**6a**, R = H b, R = Ac	(*S*)-(-)-**7**, Q = Q'[a]	
8, Q = $(CH_2)_5$	(*S*)-(-)-**9a**, R = H b, R = Ac	(*S*)-(-)-**10**	(*R*)-(-)-**11a**,[b] R = H b,[b] R = Ac

[a] Q' = $(CH_2)_2$. [b] Experiment was done on antipode.

Table I. Summary of Data on Elution Order and Absolute Stereochemistry[a]

compd	HPLC data[b]	enantiomer retained	compd	HPLC data	enantiomer retained
2a	α = 1.03 k' = 7.7	*R*	**2b**	α = 1.14 k' = 1.3	*S*
6a	α = 1.00 k' = 18		**6b**	α = 1.04 k' = 2.4	*S*
9a	α = 1.05 k' = 11	*R*	**9b**	α = 1.32 k' = 1.3	*S*

[a] The column [(*R*)-*N*-[(3,5-dinitrobenzoyl)phenyl]glycine ionically bonded to an α-aminopropyl-silanized silica column] is commercially available from Regis Chemical Co. The solvent mixture was 0.5% 2-propanol in hexane. [b] α is defined as the retention volume of second peak less the dead volume divided by the retention volume of the first peak less the dead volume. k' = (retention volume of the first peak)/(column volume).

established as *S*, i.e., that predicted by Prelog's rule and the assumption that the fused aromatic moiety was effectively larger than the methylene group flanking the carbonyl. Therefore (-)-**2a** is the first cyclic benzylic alcohol in which the configuration shown is not preferentially retained on the Pirkle column.

Microbial reduction of the oxa analogue **5** proceeded smoothly to the alcohol (-)-**6a** in good yield. Determination of the configuration of **6a** was initially complicated by the need for oxidizing both the methylene group bearing the ether oxygen and the fused aromatic ring to carboxylic acid functions, in order to obtain a compound o f known configuration. This problem was solved by using the RuO_4 oxidation procedure developed by Sharpless et al.,[8] which these investigators had shown was capable of converting an ether into a lactone. Oxidation of **6b** by the Sharpless procedure smoothly converted both the aromatic ring and the methylene group bearing the ether oxygen into carboxyl groups. Methylation of the acidic mixture with diazomethane yielded (*S*)-dimethyl α-acetoxyglutarate (**2a**); consequently, the configuration of **6** is *S* as shown in Scheme I. The stereochemical course of the microbial reduction of **5** was not influenced by the fact that the carbonyl was part of a vinylogous ester or part of a benzocycloheptenone system.

The unexpected HPLC results for compounds **2a** and **6a** (Table I) prompted us to prepare samples of racemic and optically active benzocycloocten-3-ol and to examine their chromatographic behavior. Hüisgen and co-workers[9] showed from ultraviolet absorption spectral measurements that the carbonyl group in **8** was not coplanar with the aromatic ring. Molecular models indicate that the molecule can exist in several conformations which may affect the stereochemical course of the carbonyl reduction. For example, Jones and co-workers[10] have found that horse liver alcohol dehydrogenase (HLAD) reduces cyclooctanone only very slowly, while cyclohexanone is readily reduced. The reduction of cycloheptanone proceeds at an intermediate rate. HLAD has been used to examine the kinetic and stereochemical characteristics of oxido reductases analogous to those present in *C. macerans*. Therefore, in order to determine whether *C. macerans* would reduce **8** and what the stereochemical consequences of such a reduction would be, we prepared a sample of **8** by cyclization of ω-phenylhexanoyl chloride[12] with aluminum chloride as described by Hüisgen and Rapp.[13]

Reduction of (**8**) with *C. macerans* yielded the alcohol (-)-**9a** in good yield. Its absolute stereochemistry was determined as shown in Scheme I. A sample of (*R*)-cycloocten-3-ol was prepared by fractional crystallization of its camphanate as described by Crabbé et al.,[6] followed by reductive cleavage of the ester. Acetylation of the alcohol followed by oxidation with RuO_4 yielded a mixture of acids which was methylated. Chromatographic purification yielded (*R*)-dimethyl α-acetoxyoctanedicarboxylate, whose specific rotation was opposite in sign to that of the same compound obtained from **9b** by the sequence shown in Scheme I. The configuration of **9a** therefore is *S*.

With the absolute stereochemistry of (-)-**2a**, (-)-**6a**, and (-)-**9a** established, we used these alcohols, their acetates, and the racemic compounds to identify the enantiomers retained preferentially on a Pirkle column.[3] The results are summarized in Table I; they show that the *R* enantiomer of each alcohol is eluted later than its antipode. Compound **6a** was not resolved on the column. This pattern differs from that obtained for a series of 2-substituted 1-indanols and 1-tetralols where it is the enantiomer shown in **1a** and **1b** which is preferentially retained on the column.[4] This elution order, however, is the same as that shown by a series of acyclic alkylarylcarbinols. Another difference in the behavior of acyclic and cyclic alkylarylcarbinols[4] is that the acetates of the former are better separated (larger α values) than the corresponding

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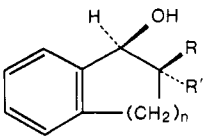

1
(a) n=1
(b) n=2

alcohols, while for the cyclic compounds examined (**1a** and **1b**) the α values of the alcohols are larger than those of the corresponding acetates. The α values for the racemic acetates **2b**, **6b**, and **9b** were each larger than those for the corresponding alcohols, a pattern similar to that noted for the acyclic compounds.

The acetates of the *S* enantiomers **2b**, **6b**, and **9b** were each more strongly retained on the chiral phase than their antipodes. This pattern is consistent for these three compounds but differs from the observed for the acetates of substituted 1-indanols and 1-tetralols.

In summary, this study shows that microbial reduction of seven- and eight-membered benzocycloalkenones proceeds in good yield to produce *S* alcohols. These *S* alcohols are eluted more rapidly from a "Pirkle HPLC column" than their antipodes. The elution pattern of compounds **2a** and **9a** resembles that exhibited by alcohols of the acyclic series. These results and those previously reported for acyclic and cyclic alkylarylcarbinols indicate that in using elution orders to assign the configuration about a carbinol carbon, it is critical to choose as a model system one as close as possible to the compound in question. Factors such as ring size and perhaps other as yet unknown factors can reverse the elution order of enantiomers. The safest approach makes use of more than one of the existing methods in assigning configurations.

Experimental Section

Microbial Reductions. A 2-L Erlenmeyer flask containing 600 mL of a solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was inoculated with a culture of *Cryptococcus macerans*. The flask was shaken at 30 °C for 1 day, and approximately 250 mg of a substrate was added as a neat liquid or dissolved in 1–2 mL of THF. The flask was shaken for approximately 5 days, and the mixture was extracted with ethyl acetate (3 × 100 mL); the extracts were concentrated in vacuo, and the alcohol formed was purified by chromatography on silica gel. The proton NMR (220 MHz) of the alcohol was identical with that of a racemic sample.

(−)-Benzocyclohepten-3-ol (2a). The alcohol **2a** ($[\alpha]^{25}_D$ −26.6° (*c* 4.0, $CHCl_3$)) was prepared by microbial reduction of the corresponding ketone as previously described.[2a] The optical purity of the alcohol is greater than 98% based on the HPLC behavior of the corresponding acetate.

(−)-2,3,4,5-Tetrahydro-1-benzoxepin-5-ol (6a). Microbial reduction of **5**[11] yielded **6a** in essentially quantitative yield; the starting material was completely consumed; $[\alpha]^{25}_D$ −15.5° (*c* 2.48, $CHCl_3$).

(−)-Benzocycloocten-3-ol (9a). A sample of ω-phenylhexanoic acid prepared by the procedure of Hünig and Lendle[12] was cyclized to benzocycloocten-3-one as described by Hüisgen and Rapp.[13] The ketone was reduced as described for **2a** to yield the alcohol in 47% yield (recovered ketone 53%). The alcohol showed a specific rotation of $[\alpha]^{25}_D$ −35.3° (*c* 1.16, $CHCl_3$). The optical purity of the alcohol is greater than 99% based on the HPLC behavior of the corresponding acetate.

(±)-Cyclohepten-3-ol (4a). A sample of the racemic alcohol was prepared by allylic bromination of cycloheptene as described by Cope et al.[14] The bromide (8.75 g) was hydrolyzed by treatment with 12.6 g of $NaHCO_3$ in a mixture of 35 mL of THF and 52.5 mL of H_2O for 23 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate; the extracts were combined, dried, and concentrated. The residue was distilled in vacuo [bp 58–60 °C (2 mm)] to yield 4.66 g (83%) of cyclohepten-3-ol.

(*S*)-Cyclohepten-3-ol (4a). The camphanyl ester was prepared as described by Crabbé et al.[6] and recrystallized four times from hexane: mp 67–70 °C; $[\alpha]^{25}_D$ −32.8° (*c* 1.20, CH_2Cl_2). The NMR spectrum of the camphanate showed the following absorption bands: δ 0.94 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 5.41 (d, 1 H), 5.52 (m, 1 H), 5.70 (m, 1 H).

The ester was reduced with $LiAlH_4$ in THF at room temperature, and the resulting (*S*)-cyclohepten-3-ol was purified by chromatography: $[\alpha]^{25}_D$ −7.5° (*c* 1.98, MeOH). The alcohol was acetylated in the usual manner to yield **4b**, $[\alpha]^{25}_D$ −13.3° (*c* 4.69, hexane) [lit.[7] for *S* enantiomer $[\alpha]^{25}_D$ −15.1° (*c* 1.18, hexane); 20% ee]. Sharpless et al. reported[15] $[\alpha]^{23}_D$ +30.1° (*c* 1.36, hexane) and 80% ee for the *R* enantiomer.

(*S*)-Dimethyl 2-Acetoxyheptanedicarboxylate (3). A biphasic mixture of 73 mg of **4b** in 1.0 mL of CCl_4, 1.0 mL of CH_3CN, and 1.4 mL of H_2O containing 0.407 g of $NaIO_4$ and 0.02 mL of a RuO_4–CCl_4 solution (100 mg/mL) was stirred vigorously for 21 h at room temperature. The reaction mixture was poured into a 2 N HCl solution saturated with NaCl and extracted several times with ethyl acetate. The combined extracts were washed with 2 N HCl saturated with NaCl and then dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was methylated with freshly prepared diazomethane in diethyl ether. The reaction mixture was concentrated and chromatographed on silica gel to yield 96 mg of (*S*)-dimethyl 2-acetoxyheptanedicarboxylate: yield 82%; $[\alpha]^{25}_D$ −8.5° (*c* 4.82, $CHCl_3$).

Ruthenium Tetraoxide Oxidation of 2b. To a biphasic solution of **2b** (99.9 mg) in 2.0 mL each of CCl_4 and CH_3CN and 2.9 mL of H_2O were added 1.57 g of $NaIO_4$ and 0.019 mL of a RuO_4–CCl_4 solution (100 mg/mL), and the mixture was stirred vigorously for 21 h at room temperature. The reaction mixture was worked up as above to yield 67.5 mg of (*S*)-dimethyl 2-acetoxyheptanedicarboxylate: yield 56%; $[\alpha]^{25}_D$ −18.4° (*c* 3.38, $CHCl_3$).

Ruthenium Tetraoxide Oxidation of 6b. The oxidation of **6b** (110.7 mg) was carried out as described for **2b** to yield 57.2 mg (49%) of (*S*)-dimethyl 2-acetoxyglutarate: $[\alpha]^{25}_D$ −25.0° (*c* 2.29, $CHCl_3$); $[\alpha]^{25}_{320}$ −36.4° (*c* 0.69, $CHCl_3$) [lit.[2a] for *S* enantiomer $[\alpha]^{25}_{320}$ −74°].

(±)-Cycloocten-3-ol. The racemic alcohol was prepared by allylic bromination of cyclooctene as described by Cope and Estes.[16] The bromide was then hydrolyzed as described above for (±)-cyclohepten-3-ol: yield 79%; bp 70–72 °C (2 mm).

(*R*)-Cycloocten-3-ol. The racemic alcohol was converted to the camphanate ester as described by Crabbé et al.[6] which was resolved by four recrystallizations from hexane: mp 86–91 °C; $[\alpha]^{25}_D$ −39.2° (*c* 1.31, CH_2Cl_2). The NMR spectrum showed absorption at δ 0.93 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 5.37 (m, 1 H), 5.54 (m, 1 H), and 5.65 (m, 1 H) [lit.[6] mp 99–100 °C; $[\alpha]^{25}_D$ −69° (*c* 2.5, CH_2Cl_2)]. The *R* alcohol **11a** was prepared by reduction with $LiAlH_4$ of the camphanate ester in THF: yield 87%; $[\alpha]^{25}_D$ −21.5° (*c* 1.75, CH_2Cl_2)[lit.[6] for *R* enantiomer $[\alpha]_D$ −48° (*c* 0.8, CH_2Cl_2)].

Acetylation of the alcohol was carried out in the usual manner to yield (*R*)-cycloocten-3-yl acetate (**11b**), $[\alpha]^{25}_D$ −50.5° (*c* 5.08, *n*-hexane).

Ruthenium Tetraoxide Oxidation of 11b. The oxidation was carried out as described for **4b** to give (*R*)-dimethyl 2-acetoxyoctanedicarboxylate ((+)-**10**): 66% yield; $[\alpha]^{25}_D$ +9.7° (*c* 4.66, $CHCl_3$).

Ruthenium Tetraoxide Oxidation of 9b. The acetate **9b** was prepared from **9a** in the usual manner; $[\alpha]^{25}_D$ −51.4° (*c* 4.51, $CHCl_3$). The RuO_4 oxidation was run on 106 mg of **9b** as described for **4b** to give (−)-**10**: 47% yield; $[\alpha]^{25}_D$ −17.4° (*c* 2.97, $CHCl_3$).

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Acknowledgment. We express our appreciation to Dr. U. Weiss for valuable discussions.

Registry No. (*S*)-(−)-**2a**, 65915-63-1; (*S*)-(−)-**2b**, 84580-10-9; (*S*)-(−)-**3**, 84499-95-6; (±)-**4a**, 79605-67-7; (*S*)-(−)-**4a**, 84580-11-0; (*S*)-(−)-**4a** camphanate, 84520-47-8; (*S*)-(−)-**4b**, 78341-38-5; **5**, 6786-30-7; (*S*)-(−)-**6a**, 84499-96-7; (*S*)-(−)-**6b**, 84499-97-8; (*S*)-(−)-**7**, 55095-00-6; **8**, 829-14-1; (*S*)-(−)-**9a**, 84499-98-9; (*S*)-(−)-**9b**, 84499-99-0; (*R*)-(+)-**10**, 84500-00-5; (*S*)-(−)-**10**, 84500-01-6; (±)-**11a**, 62249-35-8; (*R*)-(−)-**11a**, 62210-83-7; (*R*)-(−)-**11a** camphanate, 84580-12-1; (*R*)-(−)-**11b**, 84580-13-2; benzocyclohepten-3-one, 826-73-3.

Alkylation of Allylic Derivatives. 4.[1] On the Mechanism of Alkylation of Allylic *N*-Phenylcarbamates with Lithium Dialkylcuprates

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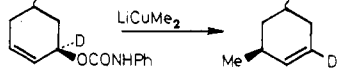
Alkylation of allylic *N*-phenylcarbamates by deprotonation, complexation with CuI in THF, and addition of 1 equiv of RLi results in syn γ-alkylation in both cyclic and acyclic systems. This procedure gives higher stereo- and regiospecificity than when allylic *N*-phenylcarbamates are reacted with 3 equiv of ethereal $LiCuR_2$. A mechanism is presented which incorporates an intramolecular oxidative addition leading to a σ-allyl complex (**3**) which undergoes reductive elimination to give the syn γ-alkylation product.

Gallina and Ciattini[3] recently reported that alkylation of allylic *N*-phenylcarbamates with lithium dimethylcuprate gives exclusive γ-alkylation in both cyclic and acyclic systems. Moreover, in the 5-phenyl-2-cyclohexenyl system (**1**), the reaction results in exclusive syn γ-alkylation as illustrated by eq 1. This regio- and stereochemistry



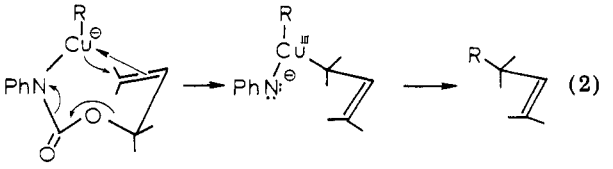
(1)

1-OCONHPh

is in striking contrast to that observed for alkylation of other allylic carboxylates with dialkylcuprates. In general, little if any regiospecificity is observed with allylic esters;[1,3-5] a copper(III) π-allyl complex common to α- and γ-alkylation products is thought to be involved.[1,6] Also, usually stereochemistry favoring anti γ-alkylation and α-alkylation with inversion is observed in both cyclic[3,4,5b] and acyclic systems.[7]

Two or more equivalents of $LiCuMe_2$ are required for alkylation of allylic *N*-phenylcarbamates in ether. With 1 equiv a yellow precipitate (presumed to be CuMe)[3] is formed, and only starting carbamate is recovered on quenching. From this it was concluded that the unique regio- and stereochemistry results from a concerted syn γ-alkylation of the lithium carbamate, whereas alkylations of other carboxylates involve allylic ion-pair intermediates.[3]

An alternate interpretation is that the carbamate is converted to a mixed cuprate (**2**) which undergoes a cyclic intramolecular oxidative addition of the γ carbon to the copper to give a copper(III) σ-allyl complex (**3**). Reductive elimination converts the latter to the syn γ-alkylation product as illustrated in eq 2. This mechanistic pathway



(2)

2 **3**

parallels that proposed earlier for alkylation of allylic carboxylates with mixed cuprates (e.g., RCu(CN)Li).[6] The major difference is that in the present case the oxidative addition step (**2** → **3**) is intramolecular instead of intermolecular, and this requires syn γ bonding. We now report evidence that supports this cyclic mechanism, and we also

Table I. Regiochemistry of Alkylation of α- and γ-D-*cis*-5-Methyl-2-cyclohexenyl *N*-Phenylcarbamate (*cis*-4-OCONHPh)

cis-4 OCONHPh	method[a]	% 1-D-5[b]	% 3-D-5	% yield[c]
α-D	A	98	2	79
α-D	B	52	48	88
α-D	C	>99		66
α-D	D	>99		70
γ-D	D		>99	68

[a] Method A: three equiv of 0.1 M ethereal $LiCuMe_2$ was added slowly to 4-OCONHPh in ether at 0 °C and stirred 10 h at 25 °C. Method B: same as above except 0.4 M ethereal $LiCuMe_2$ was added rapidly. Method C: 1 equiv of 0.4 M ethereal $LiCuMe_2$ was added to 4-OCONHPh in THF at 0 °C and stirred 10 h at 25 °C. Method D: the lithium anion of carbamate was complexed with 1 equiv of CuI in THF followed by addition of 1 equiv of MeLi at 0 °C and stirring at 25 °C. [b] This isomer results from γ-alkylation of α-D-4-OCONHPh and α-alkylation of γ-D-4-OCONHPh. [c] GC yield; 1,5-cyclooctadiene was used as an internal standard.

(1) Previous paper in this series is Goering, H. L.; Seitz, E. P., Jr.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304.
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(4) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854.
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