The isopropyl ester is a surprisingly stable and versatile protecting group for sulfonic acids. It is stable to a wide variety of acidic and basic conditions that are commonly used to modify carbohydrate protecting groups, yet may be easily cleaved by treatment with boiling methanolic ammonia.[18] (The crude sulfonate resulting from this reaction is a mixture of ammonium and isopropylammonium salts, indicating that, in accord with the stability of this sulfonate toward base (see below), deprotection most likely occurs through an S_N2 displacement and not elimination.) The isopropyl sulfonate survived conditions required for the removal of carbohydrate isopropylidene and anomeric methoxy protecting groups, as well as basic conditions such as boiling Et_3N. A bulkier sulfonate ester, neopentyl mesylate,[16] was readily alkylated, but could not be deprotected with ammonia.

By taking advantage of the alkylation of isopropyl mesylate anions and the subsequent deprotections described above we have been able to synthesize the sulfonate analogues of ribose 5-phosphate, (three steps from the iodide **1a**, 51% overall yield); glucose 6-phosphate, (four steps from the iodide **4**, 51% overall yield); and uridine 5-phosphate (three steps from the iodide **5**, 43% overall yield). The biological activity of these phosphate analogues is currently being studied.

We have also found that complex alcohols can be used in place of the isopropyl protecting group. The anion of the relatively hindered 3-*O*-mesylate of 1,2:5,6-diacetone allose **6** could be alkylated using the iodide **1a** (49%) (Scheme II). Thus, we were able to synthesize a disaccharide **7** linked by a sulfonate group, simply by alkylating the α-lithio anion of a carbohydrate mesylate. The alkylation of mesylates should therefore provide easy access to disaccharides or oligosaccharides linked by a sulfonate backbone in analogy to the oligonucleotide backbone of ribonucleic acids. We are also currently using this methodology to synthesize and design analogues of phosphatidic acid, as well as a variety of isosteric and uncharged phospholipid analogues, to be used as potential phospholipase inhibitors and to probe the processing and recognition of phospholipids in vivo. The results of these efforts will be communicated shortly.

Acknowledgment. We wish to thank the Eli Lilly and Procter & Gamble companies for financial support and Profs. A. I. Meyers and W. R. Roush for helpful discussions.

Supplementary Material Available: Experimental data and NMR spectra for the compounds in this paper (14 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of 4,4-Disubstituted 1-Naphthalenones. Diastereoselectivity as a Function of Metal Alkoxides

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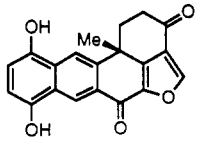
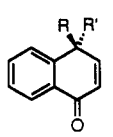
Summary: Chiral tricyclic lactam (**5**) was sequentionally metalated (LDA or LDA/zirconocene halides) and alkylated to give quaternary alkylation products (**8**) in 6–54:1 diastereomeric ratio. Reduction and hydrolysis furnish the title compound in three steps with >99% enantiomeric purity.

During the course of reaching biologically significant molecules via asymmetric synthetic routes, we were interested in the recently isolated antimicrobial,[2] halenoquinol **1**, which possesses the elements of a 4,4-disubstituted naphthalenone, **2**.[3] Since there are no known routes



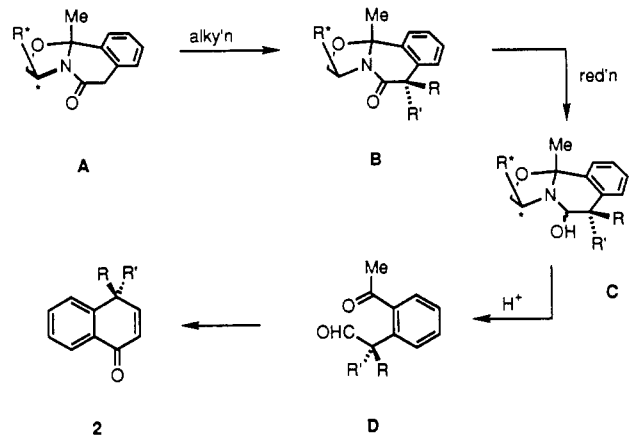
(+)-1



2

to reach these systems with absolute stereochemistry at the quaternary center,[4] we embarked on a study to initially obtain a general route to **2** and ultimately employ these as pivotal intermediates to pursue the asymmetric total synthesis of **1**. We now can report in preliminary form that our initial goal has been reached. Based on our previous reports utilizing chiral bicyclic lactams to reach a number of enantiomerically pure cyclopentenones and cyclohexenones and their application to asymmetric total syntheses,[5] we envisioned a route to chiral naphthalenones.

Scheme I



(1) Feodor Lynen Forschungsstipendium of the Alexander von Humboldt-Stiftung, 1989–1990.

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(3) The absolute configuration and the enantioselective total synthesis of (+)-1 starting from optically pure Wieland–Mischer ketone has been reported. CD spectrum and absolute configuration: Harada, N.; Uda, H.; Kobayashi, M.; Shimiqu, N.; Kitagawa, I. *J. Am. Chem. Soc.* **1989**, *111*, 5668. Total synthesis: Harada, N.; Sugioka, T.; Ando, Y.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1988**, *110*, 8483.

(4) **2** (R = Me, R′ = allyl) is known in racemic form: Miller, B.; Saidi, M. R. *J. Am. Chem. Soc.* **1976**, *98*, 2227, and racemic **2** (R = Me, R′ = Et) is also known: Carlin, R. B.; Sivara-Makrishnan, K. P. *J. Org. Chem.* **1970**, *35*, 3368.

(5) Meyers, A. I.; Bienz, S. *J. Org. Chem.* **1990**, *55*, 791 and earlier papers cited.

0022-3263/90/1955-4233$02.50/0

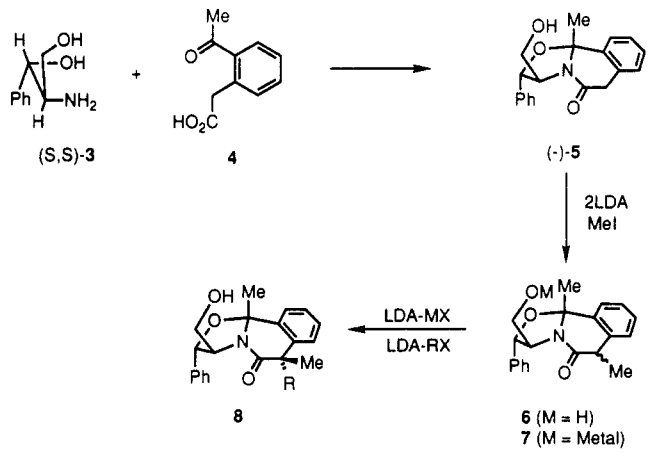
Table I. Diastereoselective Alkylation of 7

entry	RX	M	8, α/β[a]	8, yield,[b] %
a	$PhCH_2Br$	Li	1.2	44
b	allyl Br	Li	3.2	55
c	EtI	Li	4.0	30
d	$H_2C{=}CH_2(CH_2)_3CH_2I$	Li	14.8	64
e	$TBDMSO(CH_2)_2CH_2I$	Li	53.7	65
f	$PhCH_2Br$	Cp_2ZrCl	6.3	61
g	allyl Br	Cp_2ZrCl	12.6	72
h	EtI	Cp_2ZrCl	21.5	52

[a] Determined by ^1H NMR of HPLC. [b] Yields are for pure diastereomer after flash chromatography.

In Scheme I, the four-step process to naphthalenones (2) is presented starting from the general structure depicting a chiral tricyclic lactam (A). We anticipated that the sequential alkylation to B would proceed with useful levels of diastereoselectivity and, after reduction to the carbinolamine (C), hydrolysis would afford the keto aldehyde (D) possessing a stereocenter at the quaternary carbon. Aldolization of the latter should furnish the desired chiral 4,4-disubstituted naphthalenones (2).

This scheme was indeed implemented, although not without some hurdles which provided us with some interesting insights into asymmetric enolate alkylations. The synthetic route to the chiral naphthalenones utilizes the chiral amino diol 3[6] as the key stereochemical element in constructing the tricyclic lactam, 5. This was accomplished by heating a solution of 3 and the keto acid 4[7] in toluene (TsOH, 18 h, reflux) and furnished (-)-5 in 60% yield (mp 91 °C, $[\alpha]_D$ +166.7° (c 1.14, CH_2Cl_2)). This chiral lactam was treated with 2.0 equiv of LDA (THF, -78 °C, 1 h) to remove sequentially, the hydroxyl proton and generate the lithium enolate. Addition of methyl iodide gave, after quenching with saturated NH_4Cl, the monomethyl derivative 6, which was recovered after aqueous quench and ether extraction to be used directly in the next alkylation step. Addition of LDA (3.0 equiv, -78 °C THF, 1 h) to



6 followed by introduction of a variety of alkyl halides gave the α,α'-dialkyl derivative 8 and since this was the critical stereochemical step, careful monitoring of the α/β ratios were performed by either HPLC or ^1H NMR which gave cleanly visible ratios of diastereomers (Table I). As seen, the lithioalkoxide lactam enolate gave rather poor diastereoselectivity with allyl, benzyl, and ethyl halides, and although the reactions went well, the overall yields of pure diastereomer were moderate (entries a–c). However,

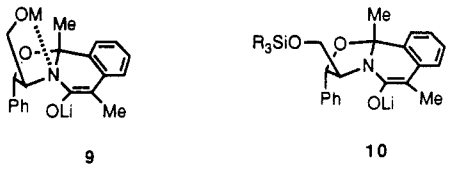
Table II. Diastereoselective Alkylation of 7 with Benzyl Bromide as a Function of Various Metal Alkoxides

entry	MX[a]	7 (M)	α/β
a	-	Li	1.2
b	$ZnBr_2$	ZnBr	2.9
c	CH_3MgI[b]	MgI	3.7
d	$Ti(i\text{-}PrO)_3Cl$	$Ti(i\text{-}PrO)_3$	5.1
e	Cp_2ZrCl_2	Cp_2ZrCl	6.3
f	$t\text{-}BuMe_2SiCl$	$t\text{-}BuMe_2Si$	0.31[c]

[a] Added to the lithio alkoxide of 6, prior to metalation to form the enolate. [b] Methylmagnesium iodide was used to deprotonate the hydroxyl group in 6. [c] Use of trimethyl silyl group gave ratios of 0.22 when alkylations were carried out at -100 °C.

halides derived from longer chain alkyl groups, and presumably slower to react, gave respectable diastereoselective ratios as well as improved yields of pure diastereomer (entries c, d). The diastereomers of 8 are readily separated via flash chromatography, and the stereochemical assignments were made by X-ray crystallographic analysis.[8] The major product in all cases in the table was that derived from α entry of the alkyl halide.[9,10]

This disappointing stereochemical results prompted us to utilize a more bulky metal ion system on the hydroxymethyl group in the hope that it would retard alkylation from the β-face by complexing this large group to the nitrogen lone pair.[9] As it turned out, addition of zirconocene dichloride[11] to the lithioalkoxide 7 (M = Li) gave not only improved yields of pure diastereomers, but significant increases in diastereoselectivity (Table I, entries f–h; compare with entries a–c). To further convince ourselves that the zirconocene moiety indeed acts as a β-face blocking group, we introduced a number of other metals to assess the diastereomeric ratios as a function of size. Thus, we treated monomethyl lactam 6 with LDA, followed by addition of metal salts (Table II), and added LDA–benzyl bromide to form, after workup, 8 (R = $PhCH_2$). We were surprised to learn that although the size of the metal alkoxides did follow a reasonable correlation with α/β ratios, the silicon substituent exhibited a reversal of stereochemistry. We currently favor the explanation of these events by presenting 9 and 10 as the enolates involved in the alkylation. The noncomplexing silicon group



may be turned totally away from the ring system due to dipole–dipole repulsion to allow easier access to β-face alkylation. On the other hand, the bulky metal groups are complexed to the unshared lone pair, thus providing an

(6) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663.

(7) Prepared on 10-g scale from 1-indanone and MeLi–$CeCl_3$ (-78 °C, THF, 3 h) to give the carbinol (90%), dehydration (p-$TsOHCH_2Cl_2$, room temperature, 2 h), ozonolysis (-78 °C, CH_2Cl_2, Zn–HOAc) to the keto aldehyde (88%), and Jones oxidation (75%) to 4, mp 162–164 °C.

(8) Full X-ray crystallographic details are given in the supplementary material. Attempts to assign the stereochemistry of the quaternary center was very difficult since the two methyl singlets in 8 (R = $PhCH_2$) were very close (1.65, 1.75 ppm), and NOE effects were difficult to assess due to their proximity. Other NOE signals gave enhancements too small to be reliable.

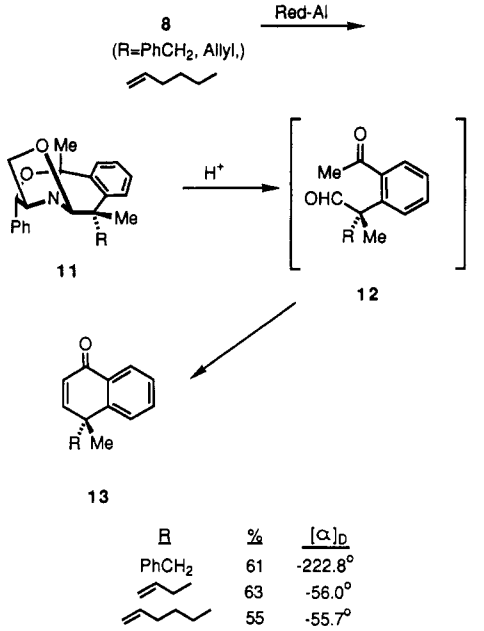
(9) Previous studies on related chiral bicyclic lactams gave generally high α (endo) alkylations. The reasons for this selectivity is still under investigation, see, however, a recent discussion of this matter: (a) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509. (b) Matassa, V. G.; Jenkins, P. R.; Kumin, A.; Danm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* **1989**, *29*, 321.

(10) Since the nitrogen atom is almost planar in 6, as seen from the X-ray study, it hardly seems reasonable to discuss the alkylation in terms of "endo–exo". Thus, we use the more traditional facial diastereoselectivity terms, α and β.

(11) Aldrich Chemical Co.; Milwaukee, WI.

"umbrella" over the ring. It should also be noted that although the nitrogen hybridization in **8** is virtually that of sp^2 (C–N–C angle of 0.1 Å off the plane), nitrogen is known to be highly pyramidalized in amide enolates.[12] Because of this the *N*-lone pair in the amide enolate makes a very good Lewis base (or electron donor).

With reasonable diastereoselectivity achieved using either the dilithiated lactam (for slow reacting alkyl halides) or the zirconated-lithio lactams (for more reactive halides) we proceeded to our goal by reducing the pure dialkylated lactams **8** (Red-Al (Aldrich), toluene, −78 °C, 48 h) to the carbinolamine, which indicated by spectral analysis that it existed as the oxazolidine **11**, presumably formed by intramolecular trapping of the iminium ion by the pendant hydroxy group.[13] The crude material (after ether extraction and concentration) was subjected directly to an ethanolic solution of aqueous 1.0 M $Bu_4NH_2PO_4$ and heated to reflux (48 h).[5] The keto aldehyde **12**, expected to have formed during the hydrolytic removal of the chiral auxiliary, was not observed, and only the desired naphthalenone **13** was isolated. In this fashion, three examples of **13** were formed in ~60% overall yield (from **8**) presumably due to conditions which were proper to effect the aldol cyclization. The products were considered to be optically pure by virtue of the diastereomeric purity of the precursors, **8**.



R	%	$[\alpha]_D$
$PhCH_2$	61	-222.8°
	63	-56.0°
	55	-55.7°

In summary, this preliminary report on our efforts to reach **1** has culminated in an efficient route to chiral, nonracemic, 4,4-dialkylnaphthalenones **13**, which contain the salient stereochemical feature necessary to proceed.

Acknowledgment. Financial support for this study was provided by the National Institutes of Health for which we are grateful.

Supplementary Material Available: Complete X-ray parameters for **8** (R = PhCH) (6 pages). Ordering information is given on any current masthead page.

(12) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. Laube, T.; Dunitz, J. D.; Seebach, D. *Hlev. Chim. Acta* **1985**, *68*, 1373. We have recently determined the X-ray structure of a bicyclic lactam lithio enolate related to those in this paper and also find a high degree of pyramidialization for nitrogen: Lefker, B. A.; Williard, P. G.; Meyers, A. I., unpublished results.

(13) This oxazolidine–iminium ion equilibrium has been noted in other related systems, cf.: Bienz, S.; Busacca, C.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905.

Addition of Zinc Homoenolates to Acetylenic Esters: A Formal [3 + 2] Cycloaddition

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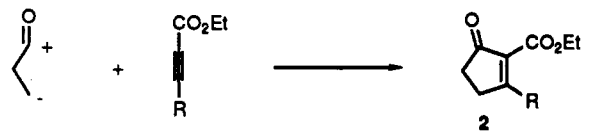
Summary: Addition of zinc homoenolates to acetylenic esters results in conjugate addition followed by intramolecular acylation of the intermediate allenolate to produce 2-carbalkoxycyclopentenones, formally a [3 + 2] cycloaddition, in a single operation.

Homoenolate reagents have recently proven to be highly versatile reagents in the formation of new carbon–carbon bonds. Methods utilizing homoenolates in acylations, nucleophilic additions, and metal-catalyzed coupling reactions have been reported.[1-3] More recently, conjugate additions of zinc homoenolates in the presence of catalytic copper(I) have been performed on various electrophiles. While Kuwajima and Nakamura[2a,f] and independently

Scheme I



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