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(8) The starting material, **6**, yields no glycine under these conditions.
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(11) Photoaffinity labeling with nitrenes will probably lead to imidate esters analogous to those formed with carbenes; the mode of hydrolysis of these compounds remains to be established.

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## Synthesis of *d*-Biotin via Dehydrobiotin

*Sir:*

The synthesis[1] of *d*-biotin (**6**) reported here avoids the problem of diastereomer formation by maintaining two of the three chiral carbons in a prochiral form until a late stage. Its success also depends on several other critical features: (1) a new carbon–carbon bond-forming reaction leading to an $\alpha$-nitro ketone; (2) easy resolution of $\alpha$-nitro ketone **3** or its precursor acid **2a**; and (3) a virtually stereospecific, economic catalytic hydrogenation of a derivative of dehydrobiotin **5b.**

The bulk of the molecule is rapidly assembled by sequential treatment of adipaldehydic acid methyl ester[2] (**1**) in dimethylformamide with nitromethane (1.4 equiv), magnesium sulfate (1.6 equiv), piperidine (1.1 equiv), and thioglycolic acid (1.0 equiv) at 3 °C. Acidification with 2 N sulfuric acid and extraction with toluene gives 6-carboxymethylthio-7-nitroheptanoic acid methyl ester (**2a**) as an oil, characterized as its dicyclohexylamine (DCA) salt, **2b**, mp 100–105 °C,[3] in 90% yield. A salt of the *S* enantiomer of **2a**, appropriate to the synthesis of *d*-biotin, is obtained by its treatment with (+)-$\alpha$-methylbenzylamine ((+)-$\alpha$-MBA) in ethyl acetate followed by dilution with ether. Two recrystallizations from ethyl acetate give **2c** in 30% yield (from *dl*-**2a**) with >97% ee,[4] mp 88–89 °C, $[\alpha]^{25}_{365}$ 155.0° (*c* 1.55, $CHCl_3$).

The final carbon–carbon bond is formed by first converting **2c** to enantiomerically pure **2b**.[5] Treatment of **2b** with phenol, thionyl chloride, and a catalytic amount of pyridine overnight at room temperature yields the oily phenyl ester **2d** in 95% crude yield. Mixing of this oil with (−)-$\alpha$-methylbenzylamine in ethyl acetate at 3 °C gives crude 5-(2,5-dihydro-4-hydroxy-3-nitrothien-2-yl)pentanoic acid methyl ester (−)-$\alpha$-MBA salt (**3a**),[6,10] which is purified by acidification followed by reprecipitation with (−)-$\alpha$-MBA to give **3a** in 75% yield, mp 138–139 °C, $[\alpha]^{25}_{589}$ −252° (*c* 0.595, 95% ethanol, >97% ee[11]). Alternatively, the racemic nitro ketone obtained analogously (characterized as *dl*-**3b**, mp 157–159 °C dec, UV max 348 nm ($\epsilon$ 15 800)) may be resolved by treatment of an ether solution with (−)-$\alpha$-MBA (0.5 equiv) to give crude **3a** in 40% yield (based on *dl*-**3b**).

Construction of the remaining heterocyclic ring commences by the low-pressure hydrogenation of the nitro group over 10% Pd/C in ~8:1 mixture of acetic acid and 3 N hydrochloric acid. The reaction is complete in 3 h at room temperature. The uncharacterized amino ketone hydrochloride is reacted with aqueous potassium cyanate at pH 5–6. Treatment with sodium hydroxide and then acidification leads to hexahydro-6a-hydroxy-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic acid (**4**) (*dl*-**4**, mp 192–200 °C). Dehydration of **4** takes place in acetic acid by continuous stripping at 55 °C, yielding 2,3,4,6-tetrahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic acid (**5a**)[12] (mp 210–214 °C, $[\alpha]^{25}_{589}$ −76.5° (*c* 1.00, 0.1 N NaOH)). Acid-catalyzed reaction with refluxing methanol for 8 h adds methanol to the double bond and produces a mixture of methoxybiotin methyl esters. After neutralization with sodium bicarbonate and removal of methanol, the mixture is treated with acetic anhydride for 6 h at 110 °C. Filtration of an ether solution of the crude product through silica gel and recrystallization from 2-propanol gives enantiomerically pure 1,3-diacetyl-2,3,4,6-tetrahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic acid methyl ester (**5b**)[13] (mp 89 °C, $[\alpha]^{25}_{389}$ −113° (*c* 1.00, $CH_2Cl_2$)) in 42% yield from **3a**.

In striking contrast to many other sulfur-containing compounds including dehydrobiotin (**5a**), **5b** is an excellent substrate for catalytic hydrogenation.[14] The reduction is carried out in a 5–8% solution in acetic anhydride at 550 psi of hydrogen pressure, 85 °C, 6 h, and a 10% loading of 5% Pd/C to give, after crystallization from 2-propanol, enantiomerically pure *N,N*-diacetylbiotin methyl ester (mp 71–71.5 °C, $[\alpha]^{25}_{589}$ −66.8° (*c* 1.00, $CH_2Cl_2$)). The palladium catalyst can be recycled a number of times. Basic hydrolysis of this substance in aqueous methanol and recrystallization from water give pure *d*-biotin (mp 228–228.5 °C, $[\alpha]^{25}_{289}$ +91.3° (*c* 1.00, 0.1 N NaOH)) in 85% yield (from (**5b**)). The yield of *d*-biotin can be made quantitative by using more catalyst and hydrogen pressures of >3000 psi.

The above reduction justifies our planar strategy and completes a synthesis which is ~90% stereoselective. The overall yield is 7.2% optically pure *d*-biotin from adipic acid half-aldehyde.

## References and Notes

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(2) Several methods are available for the formation of the aldehyde. (a) Rosenmund on the acid chloride of the half ester of adipic acid: A. I. Rachlin, H. Gurien, and D. P. Wagner, *Org. Synth.*, **51**, 8 (1971). (b) $\epsilon$-Caprolactone opened with methanol and oxidized with pyridinium chlorochromate: E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975). (c) Same as (b) but gas phase oxidation with copper and air: D. Valentine, Jr., private communication.

(3) All compounds have the expected analytical and spectral properties. We thank the staff of the Physical Chemistry Department for this data. We also thank the personnel of the Kilo Laboratory and the High Pressure Laboratory for providing intermediates and running the large number of hydrogenations and Mr. W. P. May and Mr. J. Vermeulen for skillful technical assistance.

(4) The enantomeric excess was determined by use of a NMR shift reagent on the (+)-$\alpha$-methylbenzyl amide.

(5) DCA as opposed to (+)-$\alpha$-methylbenzylamine leads to a cleaner product and a higher yield.

(6) $\alpha$-Nitro ketones have been prepared from acyl cyanides,[7] but the combination of only moderate yields[8] and the difficult preparation of the starting materials[9] makes this approach unsuitable. (−)-MBA was used in this cyclization to avoid the isolation of any of the wrong isomer if racemization should occur.

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(10) In acyclic cases we have used a modified procedure in which the phenyl ester is added to a cold (0–10 °C) suspension of the potassium salt of nitromethane (>2 equiv) in $Me_2SO$ followed by warming to room temperature to obtain $\alpha$-nitro ketones in 50–70% yields (not optimized). Another solution to this problem has been reported recently. The reaction requires extremely basic conditions not compatible with our substrate and use inconveniently low temperatures: D. Seebach and F. Lehr, *Angew. Chem.*, **88**, 540 (1976).

(11) The enantiomeric excess is determined by ring opening to **2a**, amide formation, and then NMR.[4]

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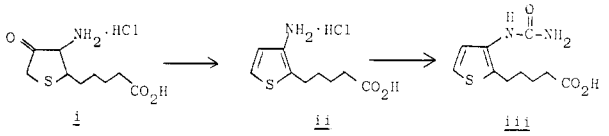

the amino ketone undergoes dehydration, i.e. aromatization, when heated with mineral acid. The product ii gives the substituted urea upon treatment with cyanate.

(13) The enantiomeric purity is determined by differential scanning calorimetry. As little as 0.3% of the racemic material can be easily detected since its melting range is totally resolved from that of the pure enantiomer.

(14) Precedents for the reduction of acetyl imidazolones are found in R. Duschinsky and L. A. Dolan, *J. Am. Chem. Soc.*, **70**, 657 (1948), and G. Guillerm, J. C. Tabel, and A. Marquet, *J. Org. Chem.*, **42**, 3776 (1977).

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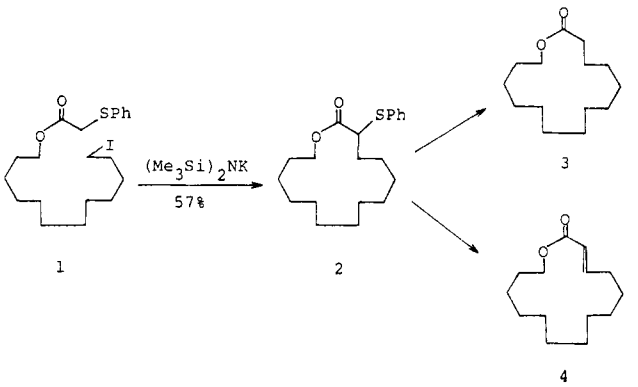
## A New Synthetic Method for Medium- and Large-Membered Lactones by Intramolecular Alkylation of $\omega$-Haloalkyl Phenylthioacetates, and Its Application to the Syntheses of Recifeiolide and 9-Decanolide Using Butadiene Telomers Obtained by Palladium Catalyzed Telomerization

*Sir:*

Synthesis of macrolides is a current problem of intensive investigation.[1] The most crucial problem inherent in the macrolide synthesis is the efficient method of cyclization which is easy to be operated and gives high yields of lactones. The most widely used method is intramolecular esterification of $\omega$-hydroxy acids, and various methods for activation of acid derivatives have been devised for this purpose.[2-8] Recently a new approach to this problem by intramolecular carbon–carbon bond formation has attracted attention, and a few acceptable methods are now known.[9]

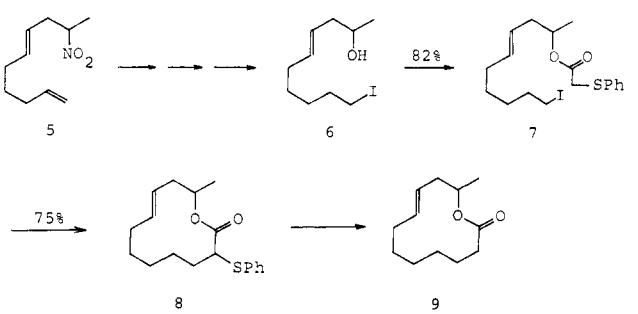
In this paper, we report a new method of lactone formation by carbon–carbon bond formation based on intramolecular alkylation of a carbanion generated from phenylthioacetate such as **1**. Subsequent oxidative or reductive removal of the phenylthio group leads to unsaturated and saturated lactones. The present method of alkylation is rapid and irreversible, and hence requires short reaction time.

At first, a 15-membered lactone was synthesized. The ester **1** was readily prepared by the acylation of 12-iodododecanol



with phenylthioacetyl chloride in dichloromethane. The ester **1** (253 mg, 0.53 mmol) in THF (10 mL) was added slowly over 2.5 h at 65 °C under a nitrogen atmosphere to potassium hexamethyldisilazane (0.8 mmol) in THF (25 mL). The reaction mixture was stirred for 20 min and quenched. The 15-membered lactone **2** was isolated as an oil in 57% yield after chromatographic purification (silica gel): IR (film) 1730 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 4.0 (2 H, m, $-CH_2O$), 3.5 (1 H, m, PhSCH). Similarly, a 13-membered lactone was prepared by the cyclization of 10-tosyldecyl phenylthioacetate in 49% yield by using sodium hydride in HMPA. The reductive elimination of phenylthio group from **2** by treatment with an excess of Raney nickel (W-2) in boiling ethanol gave 14-tetradecanolide (**3**) in 92% yield: IR 1735 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 2.25 (2 H, m, $CH_2CO$), 4.0 (2 H, m, $CH_2OCO$); mass spectrum *m/e* 226 ($M^+$). The oxidation of **2** with sodium periodate[10] and heating in toluene produced 2-tetradecen-14-olide (**4**) in 71% yield: IR 1720 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 6.8 (1 H, dt, $J$ = 7 and 16 Hz, olefinic), 5.65 (1 H, d, $J$ = 16 Hz, olefinic), 4.1 (2 H, t, $J$ = 4 Hz, $CH_2O$); mass spectrum *m/e* 224 ($M^+$).

Then we prepared 10- and 12-membered lactones, which are generally regarded to be cyclized less efficiently than 15-membered lactones.[2d] As a 12-membered lactone, we selected the naturally occurring recifeiolide (**9**) as a target. Several known syntheses of this lactone were achieved by the internal esterification of 11-hydroxy-*trans*-8-dodecenoic acid.[11,12] We have reported the facile synthesis of this acid



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