Registry No.—1-Ethoxycyclopropanol, 13837-45-1; *p*-(dimethylamino)bromobenzene, 586-77-6; 5-bromocoumarin, 66826-78-6; *p*-(methoxy)bromobenzene, 104-92-7; *p*-(methyl)bromobenzene, 106-38-7; bromobenzene, 108-86-1.

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Preparation of Optically Pure *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine and Its Antipode

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O-Benzyl-L-serine derivatives are useful in peptide synthesis. The currently available methods for preparing these compounds are laborious and not convenient for large-scale preparation. Okawa[1] prepared *O*-benzyl-L-serine via bromination of methyl acrylate and resolved the racemate of the *N*-acetyl derivative by acylase. The other method is benzylation of N-*tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia[2] or in sodium hydride–dimethylformamide.[3] The acylase method can obtain optically pure *O*-benzyl-L-serine but the amino-protecting group should be introduced again for peptide synthesis. The enzyme, however, is not cheap and is hard to obtain. The second method, benzylation of *N-tert*-butyloxycarbonyl-L-serine, is only around 50% in yield and racemization might occur in the benzylation process.

The direct resolution of *N-tert*-butyloxycarbonyl derivatives of racemic amino acids would be a better way of preparing optically pure protected amino acids rather than incorporating the protecting group onto optically active amino acids or derivatives.

We present here a new method for the preparation of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode. Both enantiomers appeared optically pure and the yields are higher than the published values.

Starting from methyl acrylate, *O*-benzyl-DL-serine obtained[1] was converted to *N-tert*-butyloxycarbonyl derivative[4] and then methylated by diazomethane.[5] The butyloxycarbonyl group might be introduced to the amino acid methyl ester prepared by thionyl chloride in methanol. The racemic acyl amino acid methyl ester was then hydrolyzed under papain catalysis to afford the L acid in 72% yield; its antipode was recovered in 81% yield from the unreacted D ester by mild alkaline treatment.

The same approach to other amino acids including threonine derivative, which has two optical centers, is under investigation.

Experimental Section

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Dicyclohexylammonium Salt.** *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine (mp 90–91 °C, from ether/*n*-hexane) (5.9 g, 20 mmol) prepared from *O*-benzyl-DL-serine was dissolved in ether (100 mL). The ethereal solution of diazomethane[7] was dropped in until the solution remained pale yellow. The mixture was then washed twice with 20-mL portions of 1 N $NaHCO_3$, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to dryness. The oily ester (6.0 g, 98%) obtained was dissolved in 10 mL of dimethylformamide and then added to a phosphate buffer solution (0.05 M, pH 6.0) containing 5 mmol of β-mercaptoethanol, 5 mmol of EDTA and 500 mg of crude papain. The mixture was kept at 35 °C with stirring and the pH was maintained at 6.0 by addition of 1 N NaOH. After 4 h and with no decrease in pH, the mixture was extracted twice with 50-mL portions of ether to recover the unreacted ester. The aqueous solution was then acidified to pH 3.0 with 3 N HCl and extracted three times with 50-mL portions of ethyl acetate. The combined ethyl acetate was washed with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure to give a colorless oil. The oil was dissolved in 30 mL of ether/*n*-hexane (1:1 v/v) followed by addition of dicylcohexylamine (1.6 mL). The precipitates formed after cooling were collected by filtration to give the title compound (3.4 g, 72%): mp 135–136 °C; R_f 0.78 (system A), 0.20 (system B); $[\alpha]^{25}_D$ +25.0 (*c* 2, MeOH) [lit.[7] mp 135.5–136 °C, $[\alpha]^{25}_D$ +24.3 (*c* 2.94, MeOH)].

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 8.92; N, 6.03.

***N-tert*-Butyloxycarbonyl-*O*-benzyl-D-serine Dicyclohexylammonium Salt.** The unreacted ester obtained above in ether was washed with water, dried, and evaporated to give an oil (3.4 g, 11 mmol), which was further digested with papain (50 mg) in the same way as described above (in 100 mL of solution) for 4 h and the unreacted ester was isolated again (2.5 g, 8.1 mmol): R_f 0.88 (system B); $[\alpha]^{25}_D$ +2.5 (C 2, MeOH). It was hydrolyzed by stirring in a mixture of dioxane–1 N NaOH (1:1 v/v) (30 mL) with 1.5 equiv of alkali for 20 min. The solution was then acidified and followed by extraction to prepare the dicyclohexylammonium salt of *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine (3.8 g, 8 mmol): mp 133–134 °C; $[\alpha]^{25}_D$ −24.2 (*c* 2, MeOH) [lit.[7] mp 130–131 °C; $[\alpha]^{25}_D$ −23.6 (*c* 2.28, MeOH)]; TLC data were the same as for the L isomer.

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 9.11; N, 6.06.

The Steric Purity. An aliquot of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode obtained by the above procedure were dissolved in 5 mL of 2 N HCl–AcOH, respectively. After 1 h at room temperature, the reaction mixture was evaporated under reduced pressure at 25 °C to yield a residue which was then diluted to 5 mL with 1 N HCl for optical rotation determination. The samples showed the same optical rotation in absolute value, respectively, as a sample of *O*-benzyl-L-serine[1] similarly treated, $[\alpha]^{25}_D$ =7.4 (*c* 2, 1 N HCl).

Registry No.—*N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine dicyclohexylammonium salt, 30200-52-3; *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine, 53317-22-9; *O*-benzyl-DL-serine, 5445-44-3; dicyclohexylamine, 101-83-7; *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine dicyclohexylammonium salt, 10342-02-6.

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Synthesis of β-Dihydrothebaine

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The 6,14-*endo*-etheno and 6,14-*endo*-ethanotetrahydrooripavines are among the most potent analgesics known.[1]

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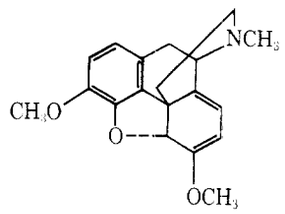
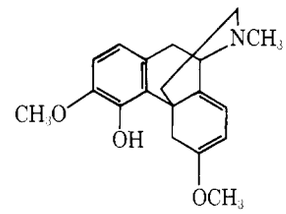
They were discovered by Bentley and co-workers during a study of the Diels–Alder reaction of thebaine with various dienophiles. β-Dihydrothebaine (2) is a diene related to thebaine which could thus give Diels–Alder products of interest as potential analgesic intermediates. Earlier attempts to pursue this approach were limited because compound 2 was not readily available.[2b,3] In spite of the report by Schmid and Karrer[4] that β-dihydrothebaine (2) can be prepared from



thebaine 1



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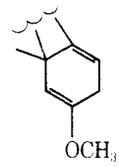

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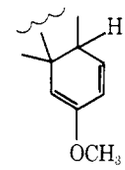

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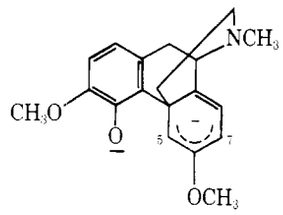

5

thebaine (1) in 42% yield by reduction with $LiAlH_4$ in C_6H_6/ether, it has been pointed out on several occasions that 2 is still essentially inaccessible.[2,3,5,6] Bentley and co-workers[6] reexamined the reaction and noted that the reaction was "capricious and slow and considerable amounts of thebaine were found in solution after 48 h reflux". Furthermore, these authors studied the reaction utilizing mixtures of $LiAlH_4$/$AlCl_3$ and found that ratios of 1:1, 1:3, or 1:4 of the reagents, respectively, gave mainly a rearranged product neodihydrothebaine, whereas ratios of 4:1 or 3:1 yielded thebainone-A enol methyl ether 4 as the major product with traces of neodihydrothebaine and β-DHT (2). Bentley, Robinson, and Wain[5a] had earlier carried out the reduction of thebaine with Na/liquid NH_3 and found it to form the unconjugated diene, φ-DHT (3) in 95% yield with no trace of 2. This was confirmed by Birch and Fitton[3] who also reported that the isomerization of 3 to 2 cannot be accomplished by the usual basic reagents.

We have found that the reaction of thebaine with K/liquid NH_3 gives a 1:1 mixture of 2 and 3 in 95% yield. The procedure is reproducible and provides pure β-DHT (2), mp 167–168 °C (lit.[4] 170–171 °C), after one crystallization (isolated yield 34%). A comparative study of various amounts of K and other metals is shown in Table I. It was also observed that treatment of φ-DHT (3) with K/liquid NH_3 in the presence of a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$[7] gave a 1:1 mixture of 2 and 3 in 79% yield. These results suggest that an intermediate dianion 5 is formed which is protonated either at C_5 or C_7. However, in our hands attempts to increase the yield of 2 by modification of quenching conditions were not successful. On occasion enriched mixtures of 2 were obtained but the results were not reproducible.

Table I. Reaction of Thebaine with Alkali Metals in Liquid NH_3

no.	elements	equiv	% thebaine converted	% 2	% 3
1	K	1.0	50[a]	50	50
2	K	2.3	95	50	50
3	Ca	2.3	50[a]	0	100
4	Li	2.3	62	0	100
5	$K/FeCl_3$[b]	2.3	95	0	100
6	Na[c]	2.3	95	0	100
7	Na[d]	2.3	95	25	75

[a] 50% of unreacted thebaine recovered. [b] A few crystals of $FeCl_3$ were added to liquid NH_3 followed by K metal. [c] Following the literature[5a] conditions Na metal was added over 35 min and after stirring for another 10 min the reaction was quenched. [d] Reaction was carried out as described for K metal.

Experimental Section

The following general procedure, as described below using potassium, was used for the reduction of thebaine with various alkali metals. The results are summarized in Table I.

Reaction of Thebaine (1) with K/Liquid NH_3. The apparatus consisted of a 1-L, three-neck flask fitted with a mechanical stirrer, a reflux condenser which was in turn fitted with a KOH drying tube, and a ground glass stopper. The flask was insulated with a heating mantle. Approximately 600 mL of liquid NH_3 was introduced into the flask followed by the addition of 44.0 g (0.141 mol) of thebaine. The sand-colored mixture was stirred and 12.6 g (0.322 mol, 2.3 equiv) of K was added in small pieces over a period of 80 min. As the K was added the resulting mixture became orange in color, which eventually turned dark red. The reaction mixture was stirred for 1 h and quenched by the addition of 24 mL of C_2H_5OH (200 proof). Stirring was then continued for 0.5 h and the NH_3 was allowed to evaporate overnight. Then 500 g of crushed ice followed by 150 mL of H_2O was added slowly. The resultant green solution was treated with solid CO_2 until the mixture was acidic. Ether (2 L) was added and the layers were separated. The ether layer was washed with 4 × 250 mL of H_2O, dried, and concentrated to yield a tan powder. Analysis by NMR ($CDCl_3$) showed it to be a 1:1 mixture of 2 [olefin protons: δ 5.73 (d, 1 H, 4.80 (d, 1 H)] and 3 [olefin protons: δ 6.10 (s, 1 H), 5.57 (t, 1 H)]. The mixture was boiled in 250 mL of ligroin (bp 63–75 °C) and then EtOAc was added until the solution was complete. After filtration while hot, the filtrate was allowed to stand at room temperature overnight and typically 15 g (34%) of 2, mp 167–168 °C dec (lit.[4] 170–171 °C) (free of 3 by NMR), was obtained. The filtrate on concentration and crystallization gave pure 3, mp 150–152 °C (lit.[5a] 154 °C).

Reaction of φ-DHT (3) with K/Liquid NH_3. In a 100-mL three-neck flask, equipped as described above, approximately 65 mL of liquid NH_3 and a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ were added to the flask followed by the slow addition of 750 mg (19.2 mmol, 3 equiv) of K in small portions: the resulting solution, which was steel-gray in color, was then stirred for approximately 0.5 h. After addition of 2.0 g (6.4 mmol) of 3 the reaction mixture (red color) was stirred for 2 h and then quenched by the careful addition of 10 mL of ether followed by 10 mL of H_2O/ether mixture. The NH_3 was allowed to evaporate and an additional quantity of H_2O/ether mixture and an excess of NH_4Cl was added. The ether layer was separated and the aqueous layer was extracted once with ether. The combined ether extract was washed with H_2O, dried, and evaporated to leave 1.58 g (79%) of a red resin, identified as a 1:1 mixture of 2 and 3 (NMR).

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Registry No.—1, 115-37-7; 2, 63944-52-5; 3, 6878-93-9.

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Synthesis of *dl*-α-Lipoic Acid from a Butadiene Telomer

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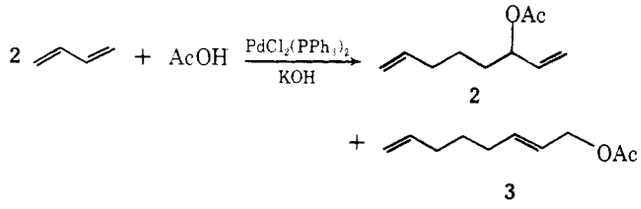
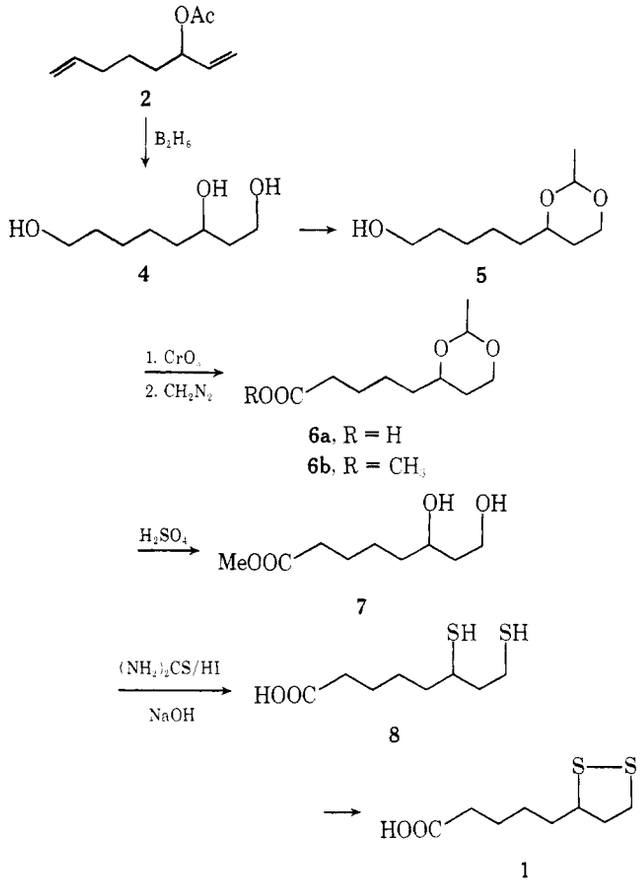
α-Lipoic acid has been recognized as a cofactor involved in the biochemical decarboxylation of α-keto acids and as a growth factor for a variety of microorganisms.[1] This naturally occurring sulfur containing vitamin was isolated by Reed et al.[2] from liver in 1951 and identified as 1,2-dithiolane-3-valeric acid (1). Because of its important physiological properties, numerous synthetic studies of this acid have been carried out.[1]

In designing an efficient synthesis of *dl*-α-lipoic acid, two problems have to be considered. The first one is the selection of proper building blocks for the eight-carbon chain, and there are still many possibilites. In the first synthesis by Bullock et al.,[3] ethylene and adipic acid half ester acid chloride were used as building blocks of the eight-carbon chain. In another synthesis by Braude et al.,[4] 6-heptenoic acid was subjected to Prins reaction. Other starting materials were 2-hydroxyethylanisole[5] and 2-acetoxyethylcyclohexanone[6] which were cleaved to give the eight-carbon chain with necessary functional groups. The second problem in the α-lipoic acid synthesis is the method of forming the dithiolane system. For this purpose, usually 1,3-diols, tosylates, and halides were converted to the dithiols by the reaction of sulfur compounds such as sodium disulfide,[7] thioacetic acid,[8] benzylmercaptane,[8] and thiourea.[3-5]

We now wish to report a new simple synthetic method for *dl*-α-lipoic acid using a butadiene telomer as a very suitable starting material, offering a new solution to the first problem mentioned above. Palladium-catalyzed telomerization of butadiene with various nucleophiles affords a number of useful telomers. In our continuous effort to utilize these telomers in organic synthesis, we have already synthesized a number of natural products starting from various butadiene telomers. In the present synthesis of *dl*-α-lipoic acid, we used 3-acetoxy-1,7-octadiene (**2**), a telomer obtained easily with 1-acetoxy-2,7-octadiene (**3**) from butadiene and acetic acid.[9,10] The ester **3** can be rearranged to **2** with the palladium catalyst.



We have already utilized these easily available telomers for simple syntheses of 2,15-hexadecanedione,[11,12] 1-octen-3-ol (Matsutake alcohol),[13,14] and diplodialide.[15] The compound **2** has the eight-carbon chain necessary for *dl*-α-lipoic acid synthesis. In addition, its functional groups, namely two double bonds and one acetoxy group, are located at the right positions and very suitable for conversion to *dl*-α-lipoic acid. The synthesis has been carried out by the following sequence of reactions.



The first step of the synthesis is hydroboration of two terminal double bonds. At first the reaction was carried out with 9-borabicyclo[3.3.1]nonane. Although the hydroboration proceeded smoothly with this hydroborane, the separation of cyclooctanediol, formed by the oxidation of the reagent, from desired 1,3,8-octanetriol (**4**) was not easy. Therefore the hydroboration of **2** was carried out using B_2H_6 to give the triol **4** which is very soluble in water. The triol was isolated using a continuous extractor. Then in order to differentiate one hydroxy group from the 1,3-diol system, the latter was protected by six-membered acetal formation using paracetaldehyde to afford **5** in 64% yield from **2**. The oxidation of the unprotected terminal alcohol was carried out with Jones reagent to give carboxylic acid **6a** in 73% yield. Although the oxidation was carried out under acidic conditions, the protecting group of the 1,3-diols was not attacked. The carboxylic acid was methylated with diazomethane in order to avoid lactone formation in the next step. The protecting group was removed by heating with sulfuric acid in dry methanol to give methyl 6,8-dihydroxyoctanoate (**7**) in 92% yield. The ester **7** is a known compound and the conversion of the ester to *dl*-α-lipoic acid has been carried out already. Following the method of the literature,[3] the ester was treated with thiourea in hydroiodic acid and 6,8-dimercaptooctanoic acid (**8**) was isolated in 80% yield. The final step is the oxidative ring closure to form the dithiolane ring by bubbling oxygen in the presence of ferric chloride. By this way, *dl*-α-lipoic acid was obtained as a yellow crystalline compound which was identified by its melting point and spectral data.

Experimental Section

All boiling points and melting points were uncorrected. IR spectra were recorded as neat films on a JASCO IR-2 spectrometer. NMR spectra were recorded in CCl_4 on a HITACHI R-24 A, (60 MHz) with Me_4Si as an internal standard.

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