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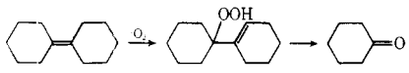
(11) See, for example, the decomposition of the hydroperoxide **8** (from **7**) to



7 8

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(12) For experimental details, see J. A. Turner and W. Herz, *J. Org. Chem.*, in press.
(13) **Note Added in Proof.** Since hexamethylbenzene is a difficultly separable impurity in commercial HMDB, the hexamethylbenzene which we isolated may have been material originally present in the starting material.

Enzymatic and Chemical Resolution of 1-Octyn-4-ol

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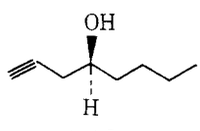
The alcohol 1-octyn-4-ol (I) is an intermediate in certain syntheses of prostaglandin analogues.[1] As such, it was important to have the racemate[2] resolved for stereospecific synthesis. Usually alcohols are converted to the half-phthalates and then resolved using such bases as brucine, dehydroabietylamine, or α-methylbenzylamine. In our hands these reagents were ineffective in this particular case. The enzymatic method of resolution is as old as the chemical method but organic chemists seldom avail themselves of this process.[3] In this note we would like to show that this method may be just as available to the chemist as the more popular chemical procedures.

We screened ten cultures in shaker flasks before finding one which selectively cleaved the benzoate of this alcohol. This culture, *Rhizopus nigricans* (Lederle culture R70), was then grown in a 30-L fermentor and the harvested cells were resuspended in distilled water and incubated with substrate. Using this technique, a free alcohol having a specific rotation of (−) 27 ± 2° (EtOAc) was obtained. This oil was reacted with (−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) chloride and the resultant ester examined by NMR in the methoxy region at δ 3.44 and 3.54 and found to be better than 95% optically pure.[4]

The (−)-I obtained by microbiological transformation was converted to the crystalline half-phthalate (−)-α-methylbenzylamine (MBA) salt. With the aid of these seed crystals a chemical resolution of (±)-I was achieved.



(−)-I

The unreacted benzoate of 1-octyn-4-ol recovered directly from our transformation work, while exhibiting good positive rotation, was not obtained optically pure. The optically pure positive rotamer was obtained, however, by processing the filtrates from the recrystallizations of (−)-MBA half-phthalate of (−)-I. These filtrates were stripped of (−)-MBA by HCl extraction and then treated with (+)-MBA. Repeated recrystallizations and careful manipulation of solvent composition finally yielded the pure salt (+)-MBA half-phthalate of (+)-I. When both enantiomorphs of 1-octyn-4-ol were obtained, a number of derivatives were made as shown in Table I. This table shows that the diastereoisomeric MBA salts, which are to be fractionally crystallized away from each other, melt only 9 °C apart, which may account in part for some of the difficulties of this resolution.

To assign absolute configuration we carried out the Horeau test[5] on (−)-1-octyn-4-ol and recovered excess (+)-(*S*)-α-phenylbutyric acid. If we assume that the butyl group is larger than the propargyl group as suggested by Landor et al.,[6] then (−)-I should have the *S* configuration. Hence, this material falls in line with the negative rotamers of 1-octyn-3-ol[7] and 1-hexyn-3-ol,[5] both of which are of the *S* configuration. Mindful of the difficulties which Pappo et al.[8] had with the assignment of (−)-1-octyn-3-ol using the Horeau method, we reduced (−)-I to 4-octanol. This sweet-smelling oil failed to give a Horeau response. Indeed the material showed no specific rotation. There is no doubt about its optical activity since the benzoate had a specific rotation of −3° and the phthalate gave a value of −4°. Table II gives CD values on (+)-I, the phthalate of (+)-I, and the phthalate of (+)-4-octanol. There is no reversal of Cotton effect in replacing the ethynyl group by an ethyl group; consequently (+)-4-octanol is likely to have the *S* configuration.

Experimental Section

TLC was carried out on silica gel thin layers with fluorescent indicator supplied by Brinkmann. IR spectra were taken either in KBr pellets or as smears between salt plates using an Infracord spectrophotometer. Mass spectra were run on a high-resolution direct inlet AEI MS9 instrument. NMR spectra were made using a Varian HA-100 instrument. Melting points were taken in capillaries and are uncorrected. CD spectra were supplied by Professor K. Nakanishi of Columbia University and were recorded on a Jasco spectropolarimeter.

Flask Screening Procedure. About 5 mL of sterile medium was used to wash out an agar slant of each culture using a sterile pipet. The inoculum wash was then divided between two Erlenmeyer flasks each containing 50 mL of medium which consisted of 2% edamine, 0.72% corn steep liquor, and 2% dextrose in water with pH adjusted to 6.8. The flasks were set on a rotary shaker at 28 °C for 72 h at which time 50 mg of the benzoate of (±)-I in 0.1 mL of acetone was aded to one of the flasks and the fermentations were continued. Samples of 5-mL volume were taken at 16 and 40 h after substrate addition. The samples were extracted with $CHCl_3$. The extracts were dried, concentrated to dryness, and reconstituted to 0.1 mL with MeOH. Approximately 25 μL of the reconstituted samples was applied to thin layers and developed using 90:10 hexane–EtOAc. The spots were visualized by UV scanning and by H_2SO_4 charring and compared with control spots. By this procedure it was found that *Rhizopus nigricans* (Lederle culture R70) transformed the negative benzoate rotamer to the free alcohol.

Thirty-Liter Tank Conversion of Substrate by R70. Two Erlenmeyer flasks of the previously described medium were inoculated from a slant of culture R70 and grown for 3 days and then used to inoculate a 1-L bottle of the same medium. This second stage inoculum was grown for 1 day and then added to a 30-L fermentor. After 24 h of growth in the tank at 25 °C with aeration and agitation, 8.5 g of the benzoate of (±)-I in 25 mL of acetone was added. The tank was harvested 9.5 h later. The cells were filtered off using cheese cloth and set aside for further work. The filtrate was extracted with ⅕ volume of EtOAc which yielded 6.4 g of an oil. Chromatography of this oil over adsorbent silica yielded 1 g of the benzoate of I, $[\alpha]^{25}_D$ +21 ± 1° (*c* 1.65, EtOAc), and 250 mg of 1-octyn-4-ol, $[\alpha]^{25}_D$ −10 ± 1° (*c* 1.65, EtOAc). The cells from the above procedure were washed with H_2O and then resuspended in 15 L of H_2O with 15.0 g of substrate in 5 mL of acetone added. After agitating overnight without air supply, the cells were again removed using cheese cloth. Extraction of the filtrate with EtOAc yielded 7.0 g of an oil which when subjected to adsorbent silica chromatography yielded 1.8 g of I, $[\alpha]^{25}_D$ −18 ± 2° (*c* 1.60, EtOAc).

About 120 mg of this preparation was distilled in a Kugelrohr apparatus at 75 °C under 250-μm pressure to get 66 mg of a mobile, colorless oil: $[\alpha]^{25}_D$ −27 ± 2° (*c* 0.41, EtOAc); ^1H NMR ($CDCl_3$) δ 0.92 (3 H, t, terminal CH_3), 1.41 [6 H, m, $-(CH_2)_3CH_3$], 1.91 (1 H, t, $-C{\equiv}CH$), 2.28 (2 H, m, $HC{\equiv}CCH_2$), 3.66 (1 H, m, >CHOH); IR

Table I. Physical Constants of Compounds Derived from 1-Octyn-4-ol (I)

Registry no.	Compd	Mp, °C	$[\alpha]^{25}_D$ in EtOAc, deg
56085-20-2	(−)-1-Octyn-4-ol (I)	Oil	−27 ± 2
61303-39-7	(+)-I	Oil	+25 ± 1
56085-18-8	Half-phthalate of (−)-I	48–49	−53.4 ± 1
61586-58-1	Half-phthalate of (+)-I	48–49	+53 ± 1
56007-93-3	Half-phthalate of (±)-I	67–68	0
56085-19-9	Salt (−)-MBA half-phthalate of (−)-I	121–122	−45 ± 1
61586-59-2	Salt (+)-MBA half-phthalate of (+)-I	121–122	+44 ± 1
61586-60-5	Salt (−)-MBA half-phthalate of (+)-I	112.5–113.5	−24 ± 1
61559-27-1	Salt (+)-MBA half-phthalate of (−)-I	112.5–113.5	+23 ± 1

Table II. CD Data on (+)-I and Derivatives

Phthalate of (+)-4-octanol	$\Delta\epsilon_{238}$ +1.25 × 10^{-1}
Phthalate of (+)-1-octyn-4-ol	$\Delta\epsilon_{240}$ +2.76
(+)-1-Octyn-4-ol	$\Delta\epsilon_{222}$ +2.6 × 10^{-3}

(smear) 3300, 2920, sh 2850, 2135, 1050, 852 cm^{-1}; mass spectrum M^+ *m/e* 126.

Despite several attempts microanalytical values on this material were consistently low. Anal. Calcd for $C_8H_{14}O$: C, 76.40; H, 11.18. Found: C, 75.51; H, 11.41 (e.g.).

Use of Mosher's MTPA Reagent to Test for Optical Purity.[3,6] About 100 mg of (−)-I in 0.2 mL of pyridine was reacted with 0.2 mL of (−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) chloride for 1 h at room temperature. The reaction mixture was worked up by standard methods to give 132 mg of an oily product. NMR in C_6D_6 showed a strong methoxy signal (these signals appear as unresolved quartets due to long-range coupling with $-CF_3$ group) at δ 3.54 with the smallest hint of a signal at δ 3.44. Based on this result (−)-I was better than 95% optically pure.

Anal. Calcd for $C_{18}H_{21}O_3F_3$: C, 63.15; H, 6.14. Found: C, 62.72; H, 6.39.

Half-Phthalate (−)-I. This derivative of (−)-I was prepared using phthalic anhydride and dry pyridine to get a crystalline product: mp 48–49 °C: $[\alpha]^{25}_D$ 53.4 ± 1° (*c* 1.11, EtOAc); ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, terminal CH_3), 1.36 [4 H, m, $(CH_2)_2CH_3$], 1.76 [2 H, m, $CH_3(CH_2)_2CH_2CHOH-$], 1.92 (1 H, t, HC≡C–), 2.57 (2 H, m, $HCCCH_2-$), 5.11 (1 H, m, –CHOH–), 7.36 (3 H, m, 3 aromatic H), 7.84 (1 H, m, aromatic H ortho to –COOH), 12.59 (1 H, s, exchanges, COOH).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.15; H, 6.61. Found: C, 69.83; H, 6.72

The (−)-MBA salt of this half-phthalate was prepared and recrystallized from ether–hexane to get a material, mp 121–122 °C, $[\alpha]^{25}_D$ −45 ± 1° (*c* 1.0, EtOAc).

Anal. Calcd for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39, N, 3.54. Found: C, 73.14; H, 7.75; N, 3.74.

Chemical Resolution of Half-Phthalate of (±)-I. A solution of 22 g of (−)-MBA in 150 mL of hexane was added to a solution of 50 g of the half-phthalate of (±)-I in 150 mL of EtOAc. The resultant solution was seeded with the MBA salt of the half-phthalate of (−)-I and left in the refrigerator for 3 days. The crystals were recovered and recrystallized with seeding three more times from EtOAc–hexane to get 11 g of crystals, $[\alpha]^{25}_D$ −39 ± 1°. Three such batches were combined and recrystallized from 400 mL of 1:1 EtOAc–hexane without seeding. After two such recrystallizations 27 g of material was obtained, mp 121–122 °C, $[\alpha]^{25}_D$ −45 ± 1° (*c* 1.0, EtOAc). About 7 g of this material were taken up in 100 mL of 2 N HCl and the solution extracted with 200 mL of ether. The ether solution was dried and concentrated to 4.0 g of an oil which crystallized in the refrigerator, mp 48–49 °C, $[\alpha]^{25}_D$ −53 ± 1° (*c* 1.0, EtOAc). When 1 g of this half-phthalate was stirred for 4 h in 80 mL of 8% KOH, 380 mg of (−)-I was obtained. Distillation of this oil in the Kugelrohr at 75 °C under 250-μm pressure gave a material with $[\alpha]^{25}_D$ −24.6 ± 1° (*c* 1.09, EtOAc). The material was better than 99% pure by GLC.

Preparation of (+)-I. Filtrates from crystallization of (−)-MBA salt of the half-phthalate of (−)-I were combined and extracted with HCl. The solvent phase was dried and taken to an oil and 50 g of this oil was reconstituted in 150 mL of EtOAc.

A solution of 20 g of (+)-MBA in 180 mL of hexane was added and the solution refrigerated for 7 days. The product was recrystallized seven times to give a low yield of material, mp 121–122 °C, $[\alpha]^{25}_D$ +44 ± 1° (*c* 1.22, EtOAc). The NMR of this material was identical with that of the diastereoisomeric salt already described. When the (+)-MBA was removed in the usual fashion, crystals of the half-phthalate of (+)-I were obtained, mp 48–49 °C $[\alpha]^{25}_D$ +53° (*c* 0.97, EtOAc). The free alcohol (+)-I was obtained as described before, $[\alpha]^{25}_D$ +25 ± 1° (*c* 0.88, EtOAc).

Catalytic Reduction of (−)-I. About 148 mg of (−)-I were reduced in 10 mL of EtOAc with H_2 at atomospheric pressure in the presence of 15 mg of 10% Pd/C catalyst. The resultant oil had $[\alpha]^{25}_D$ 0° (*c* 1.0, EtOAc); ^1H NMR ($CDCl_3$) δ 0.91 (6 H, m, 2 terminal CH_3), 1.38 (10 H, m, 5 methylenes), 2.78 (1 H, s, exchanges OH), 3.64 (1 H, m, –CHOH–).

The benzoate of this octanol was prepared and shown to have $[\alpha]^{25}_D$ −3° (*c* 0.98, EtOAc).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.68; H, 9.46. Found: C, 76.70; H, 9.65.

Catalytic Reduction of Half-Phthalate of (+)-I. This reduction was carried out as described for (−)-I to yield a crystalline product, mp 52.5–53.5 °C, $[\alpha]^{25}_D$ +4 ± 2° (*c* 0.78, EtOAc).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.46; H, 8.06

Horeau Method on (−)-I. A solution of 70 mg of (−)-I and 0.3 mL of (±)-α-phenylbutyric anhydride in 3 mL of dry pyridine was left overnight at room temperature. Workup of the reaction in the prescribed manner[9] yielded 210 mg of an oil which crystallized overnight, $[\alpha]^{25}_D$ +2 + 0.1° (*c* 6.5 benzene). TLC and NMR data showed the material to be α-phenylbutyric acid. When the Horeau method was applied to (−)-4-octanol, the recovered acid was essentially optically inactive.

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Registry No.—(±)-I, 56007-85-3; (±)-I benzoate, 61284-53-5; (−)-I benzoate, 61303-38-6; (−)-I MTPA ester, 61559-28-2; (−)-MTPA, 20445-33-4; (−)-MBA, 2627-86-3; (+)-MBA, 3886-69-9; phthalic anhydride, 85-44-9; (−)-4-octanol, 61559-29-3; (−)-4-octanol benzoate, 61559-30-6; (+)-4-octanol phthalate, 61559-31-7.

References and Notes

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