



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

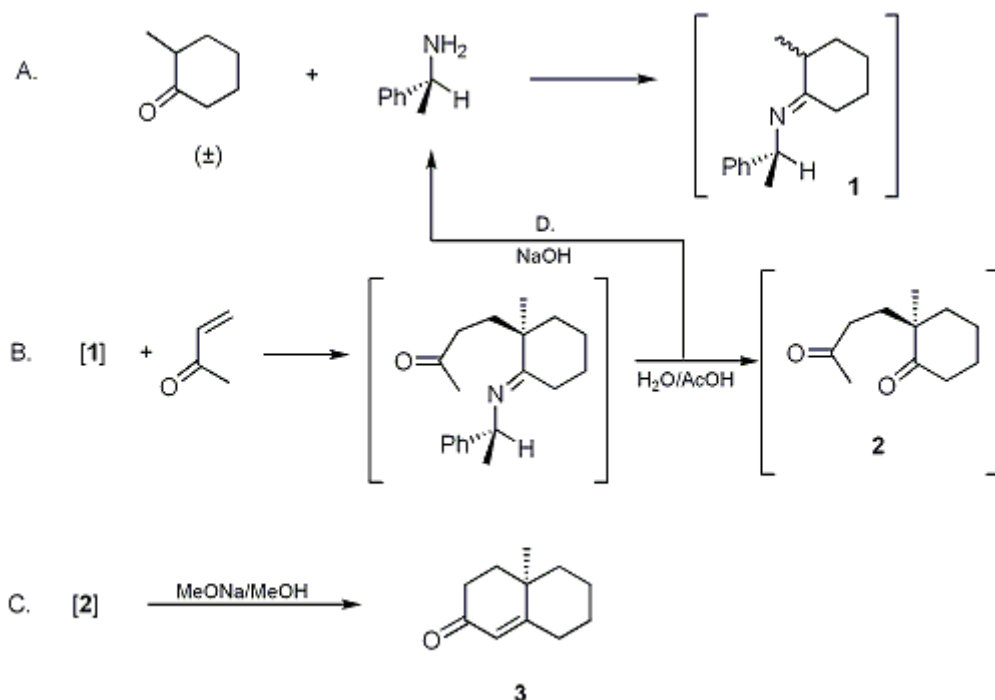
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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(R)-(-)-10-METHYL-1(9)-OCTAL-2-ONE

[2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4a-methyl-, (R)-]



Submitted by G. Revial and M. Pfau¹.

Checked by Graham N. Maw and Robert K. Boeckman, Jr..

1. Procedure

A. *Imines (1)*. In a 1000-mL, round-bottomed flask, fitted with a toluene-filled Dean-Stark water separator, 100.0 g (0.825 mol) of (S)-(-)- α -methylbenzylamine (Note 1), 92.5 g (0.825 mol) of 2-methylcyclohexanone (Note 2) and 100 mL of toluene are heated at reflux temperature under a nitrogen atmosphere. After 24 hr, ca. 15 mL of water (ca. 100% theor.) has been removed azeotropically.

B. *(R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone (2)*. The solution of imines **1** is cooled in an ice bath and 72.5 mL (61.0 g, 0.870 mol, ca. 1.05 equiv) of freshly distilled methyl vinyl ketone (Note 3) is added with a syringe, with magnetic stirring, under a nitrogen atmosphere. The flask is then heated at ca. 40°C for 24 hr.

The slightly yellow solution is cooled in an ice bath and 60 mL of glacial acetic acid (ca. 1 mol) and 50 mL of water are added. Hydrolysis is achieved by stirring the heterogeneous mixture at room temperature for 2 hr. The now clear solution is poured into a 2000-mL separatory funnel containing 100 mL of brine and 160 mL of water and is extracted five times with a 50:50 mixture of ether-petroleum ether (35–60°C) (1000-mL total amount). The organic phase is washed efficiently with 20 mL of 10% hydrochloric acid, 20 mL of water, and two 10-mL portions of brine.

The aqueous layer is kept for recovery of the amine (see D below).

The pale yellow organic layer is dried over a small amount of anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator at ca. 40°C and the crude diketone **2** (ca. 145 g) is used directly for the next step.

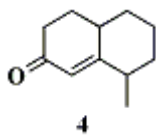
C. *(R)-(-)-10-Methyl-1(9)-octal-2-one (3)*. Dry methanol (600 mL) is added to the crude diketone **2**

contained in a 2000-mL, round-bottomed flask and a rubber septum is fitted. The solution is stirred at room temperature for 15 min under a slight stream of **nitrogen** to remove traces of **oxygen**. A 25 wt. % solution of **sodium methoxide** in **methanol** (Note 4) is then introduced dropwise with a syringe, under stirring, until a slightly red color develops (Note 5). At this point, 15 mL (ca. 0.07 mol) of the **sodium methoxide** solution is added and the mixture is heated at 60°C for 10 hr under a **nitrogen** atmosphere. The solution is cooled and the now deep red solution is neutralized with glacial **acetic acid** (ca. 4.5 mL) until the color turns yellow. **Methanol** is removed with a rotary evaporator until a thick paste (**sodium acetate**) results; this is dissolved with 200 mL of water. Extraction is effected in a 2000-mL separatory funnel using four portions of a 50:50 mixture (1000 mL total amount) of **ether**-petroleum ether (35–60°C). The pale orange organic phase is washed twice with 40 mL of water, then twice with 20 mL of brine. The organic layer is dried over a small amount of anhydrous **magnesium sulfate** and filtered. The solvents are removed with a rotary evaporator at ca. 40°C and the red oily residue of crude octalone **3** is distilled under reduced pressure to afford ca. 110 g of a colorless oil, bp 70°C (2 mm) (Note 6). The oil is purified by recrystallization at a low temperature with an apparatus designed for this purpose.² The oil is dissolved with stirring in a 1000-mL, round-bottomed flask with 370 mL of **pentane** under a **nitrogen** atmosphere. The flask is then cautiously cooled in a Dewar flask containing liquid **nitrogen** until the solution is solid. The Dewar flask is removed and the temperature is allowed to rise, while magnetic stirring is resumed. When a crystalline mass in suspension appears suddenly (Note 7), an acetone bath adjusted to about –10°C is installed. When only a few crystals remain in suspension, the bath temperature is slowly lowered to –35°C, inducing crystallization. After the mixture has been kept at –35°C for 15 min, magnetic stirring is stopped and efficient filtration is performed through the filter stick. Still at –35°C, the compound is washed with 40 mL of **pentane**. The solution is stirred vigorously for 5 min and filtered as before. The washing operation is repeated two more times. The flask is warmed to room temperature and the oil is distilled as before, bp 70°C (2 mm), to afford 60–65 g (44–48% overall yield from **2-methylcyclohexanone**) of methyloctalone **3** [$[\alpha]_D^{20}$ >99% chemical purity, capillary GLC (Note 6)], $[\alpha]_D^{20}$ –210° (**ethanol**, *c* 1.00), optical purity 96% (Note 8).

D. *Recovery of (S)-(-)- α -methylbenzylamine.* The aqueous layer (see above, *B*, 3rd paragraph) contained in a 1000-mL flask is cooled in an ice bath under a **nitrogen** atmosphere. An aqueous 10% **sodium hydroxide** solution is added with stirring until a pH of 12–14 (Note 9) is reached. The mixture is transferred to a 2000-mL separatory funnel and extracted three times with **ether** (1000-mL total amount). The organic phase is washed twice with 100 mL of water and twice with 30 mL of brine, then dried over **potassium carbonate** and filtered. The solution is concentrated at room temperature with a rotary evaporator and distilled under reduced pressure to afford 85–90 g (85–90% yield) of the amine, bp 70°C (15 mm), the specific rotation of which is the same as that of the original starting material.

2. Notes

1. (S)-(-)- α -Methylbenzylamine (95.8% optical purity) and its (R)-(+)-enantiomer (93.4% optical purity) were purchased from Aldrich Chemical Company, Inc. and used without further purification. **CAUTION: These amines are toxic.** Air must be excluded to prevent formation of carbonates.
2. **2-Methylcyclohexanone** was purchased from Aldrich Chemical Company, Inc., and used without further purification.
3. **Methyl vinyl ketone**, purchased from Aldrich Chemical Company, Inc., is dried over anhydrous **potassium carbonate** for 0.5 hr. The now slightly-colored oil is filtered and distilled under a **nitrogen** atmosphere at reduced pressure, bp 55°C (260 mm). *The colorless center of the distillate is collected over a few milligrams (ca. 0.05% concentration) of hydroquinone.*
4. A 25 wt % solution of **sodium methoxide** in **methanol** (4.6 M) was purchased from Aldrich Chemical Company, Inc.
5. Any **acetic acid** present is thus neutralized (a few drops are usually sufficient). Confirm that a basic pH has been reached by testing a drop of the solution, removed by syringe.
6. Although a TLC test (silica gel Merck 60 F₂₅₄, **ethyl acetate**/hexane 20:80 elution, UV and chromic-sulfuric acid visualization) of this oil reveals only one spot (*R_f* 0.6), capillary GLC (Hewlett-Packard HP-5, 25 m × 0.2 mm × 0.5 μ m, 200°C) shows in addition to methyloctalone **3** (retention time, 10.9 min), an 8% impurity (retention time, 11.7 min) which is probably the regioisomer **4**.



A chemically pure sample of methylcyclohex-2-en-1-one **3**, $[\alpha]_D^{20} -190^\circ$ (ethanol, c 1.00) is obtained by preparative GLC (3 m \times $\frac{1}{4}$ " , 5% carbowax 20 M on Aeropak 30, 180°C, retention time 12.4 min) of a distillate sample. The impurity has a 13.2-min retention time under these conditions. A good approximation of the reaction ee is calculated as follows, taking into account the optical purity of the starting amine (95.8%) and the $[\alpha]_D^{20} -219^\circ$ (ethanol, c 1.00) value (Note 8) for optically pure methylcyclohex-2-en-1-one **3**: ee = $100 \times 190 \times 100 / 95.8 \times 219 \cong 91\%$.

7. If no crystalline mass is formed but instead an emulsion of the two liquid phases appears, the entire solidification must be repeated (liquid nitrogen cooling).

8. Chiral capillary GLC (OV-1701 + trimeb/2), 25 m \times 0.3 mm, He, 65 kPa, 130°C: (R)-(-)-**3**, 58.3 min (98%); (S)-(+)-**3**, 62.0 min (2%). Optically pure methylcyclohex-2-en-1-one **3** is obtained by recrystallizing a sample of the purified compound several times until a constant $[\alpha]_D^{20} -219^\circ$ (ethanol, c 1.00 or methanol, c 1.10) is observed. As chiral capillary GLC shows only (R)-(-)-**3**, the $[\alpha]_D^{20} -219^\circ$ (methanol, c 1.1) value from the literature³ is confirmed.

9. If a pH lower than 12 is used, recovery of the amine is poor.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

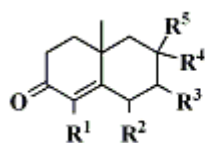
Optically active methylcyclohex-2-en-1-one **3** (or its enantiomer) has been obtained by resolution^{3,4} and by asymmetric synthesis.⁵ Both enantiomers are also available commercially. The synthesis described here is by far the most simple and gives the best yield. It is an application of the general method reported for the enantioselective elaboration of quaternary carbon centers through Michael-type alkylation of chiral imines.^{6 7 8 9 10 11 12 13 14}

This general method has the following advantages: very simple procedures, very mild conditions involving moderate reaction temperatures and no acids, bases, catalysts, etc., allowing the use of labile reactants, excellent regio- and enantioselectivities as well as high chemical yields, and creation of useful chiral building blocks with quaternary carbon centers involving functionalized chains, allowing one to devise syntheses of natural compounds of various types (terpenes, steroids, alkaloids, etc.). As both optically active amines are commercially available, targets with either desired absolute configuration can be synthesized. Easy recovery of the auxiliary chiral moiety is possible.

Racemic methylcyclohex-2-en-1-one **3** has been used as a starting material for many transformations as well as for syntheses of racemic natural compounds. In the following examples, the absolute configuration of the methylcyclohex-2-en-1-one that would be required to obtain the natural enantiomer is indicated in parentheses: β -gorgonene¹⁵ (S), widdrol^{16,17} (R), thujopsene^{16,18} (R), 7-hydroxycostal^{19,20} (R), β -selinene^{21,22} (R), costol, costal and costic acid²¹ (R), norketoagarofuran^{23,24} (R), β -eudesmol^{21,22,23,25} (R), taxane model²⁶ (S), polygodial²⁷ (S), warburganal²⁷ (S).

(R)-Methylcyclohex-2-en-1-one **3** itself has been used to synthesize a pasmalinine model,²⁸ a subunit of penitrem D,²⁹ and several biologically active decalin derivatives.³⁰

The following key-intermediates have been prepared by a procedure similar to the one described above, generally with excellent chemical and optical yields :



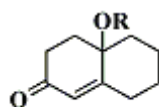
5: $R^1 = \text{Me}; R^2 = R^3 = R^4 = \text{H}$ (R and S)²³

6: $R^1 = R^3 = R^4 = \text{H}; R^2 = \text{Me}$ (S,S)²³

7: $R^1 = R^2 = R^4 = \text{H}; R^3 = \text{C}(\text{=CH}_2)\text{Me}$ (R,R and 7 R, 10 S)²⁴

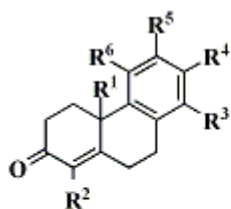
8: $R^1 = \text{Me}; R^2 = R^4 = \text{H}; R^3 = \text{C}(\text{=CH}_2)\text{Me}$ (R,R)²⁵

9: $R^1 = R^2 = R^3 = \text{H}; R^4 = \text{O}(\text{CH}_2)_4\text{O}$ (R)²⁶



$R = \text{Me}$ ²⁵

$R = \text{CH}_2\text{Ph}$ (R)²⁸



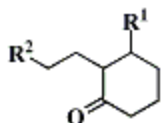
$R^1 = \text{Me}; R^2 = R^3 = R^4 = R^5 = R^6 = \text{H}$ (R)²⁹

11: $R^1 = \text{Me}; R^2 = R^4 = R^5 = \text{H}; R^3 = (\text{CH}_2)_2\text{COOH}; R^6 = \text{OMe}$ (S)²⁹

12: $R^1 = \text{Me}; R^2 = R^4 = R^5 = R^6 = \text{H}; R^3 = \text{OMe}$ (S)³⁰

13: $R^1 = R^2 = \text{Me}; R^3 = R^4 = R^6 = \text{H}; R^5 = \text{OMe}$ (R and S)³¹

14: $R^1 = R^2 = \text{Me}; R^3 = R^5 = \text{H}; R^4 = \text{OMe}$ (S)³²



16: $R^1 = \text{Me}; R^2 = \text{COOMe}$ (R)^{33,34}

17: $R^1 = \text{Et}; R^2 = \text{COOMe}$ (S)³⁴

$R^1 = \text{Me}$ (R) or OMe (S); $R^2 = \text{CN}$ ³⁵

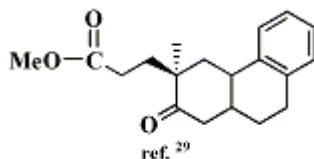
$R^1 = \text{OMe}$ or $\text{OCH}_2\text{Ph}; R^2 = \text{COOMe}$ (R)²⁸

$R^1 = R^2 = \text{COMe}$ (S)³⁶

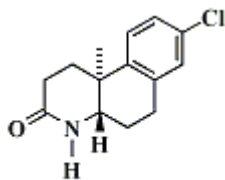
$R^1 = \text{COOEt}; R^2 = \text{COOMe}$ (S),³⁷

COOEt (R)³⁶ (S),³⁷

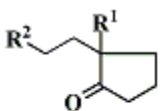
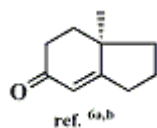
COO-t-Bu (S),³⁷ CN (S) (18),³⁸



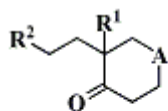
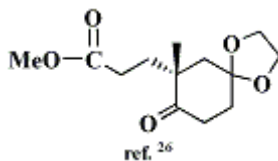
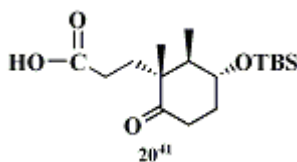
ref. 29



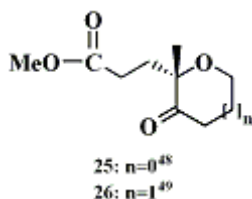
19 (R and S)



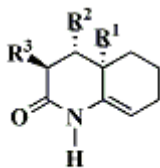
$R^1 = \text{Me}; R^2 = \text{COOMe(R)}^{6a,b}$
 21: $R^1 = \text{Et}; R^2 = \text{COOMe(S)}^{42}$
 $R^1 = \text{CH}_2\text{COOMe}; R^2 = \text{SO}_2\text{Ph(S)}^{43}$
 $R^1 = \text{COOMe}; R^2 = \text{CN(S)}^{38}$
 COOMe^{37}
 COOEt^{37} $\text{COO-t-Bu(S)}^{(22)^{37}}$



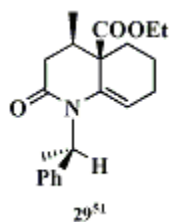
$A = \text{NMe}; R^1 = R^2 = \text{COOMe or CN(S)}^{45}$
 24: $A = \text{NBn}; R^1 = \text{Me}; R^2 = \text{COMe(R and S)}^{46}$
 $A = \text{S}; R^1 = \text{Me or allyl (R and S), Pr(S)}; R^2 = \text{COOMe}^{47}$



The use of substituted acrylic acid derivatives shows that besides the high enantioselectivity usually observed, the process is also highly diastereoselective, leading to compounds such as **27-32**.

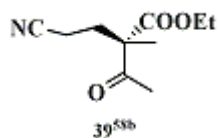
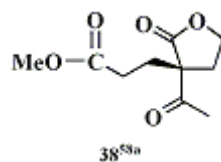
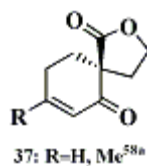
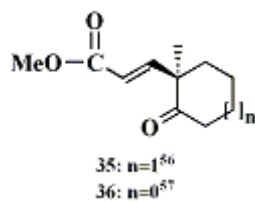


27: $R^1=R^2=\text{Me}; R^3=\text{H}^{50}$
 28: $R^1=R^2=\text{Me}; R^3=\text{H}^{50}$

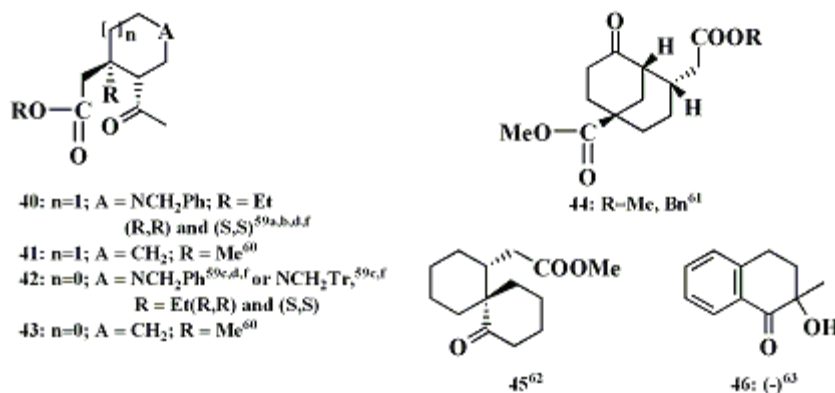


An acetylenic electrophile such as methyl propiolate leads to unsaturated compounds **35** and **36**.

Linear β -ketoesters and lactones lead to compounds such as **37-39**.



Compounds **40-45** arise from an analogous but intramolecular reaction. A special application of the chiral imine procedure, i.e., the use of an oxaziridine rather than an electrophilic olefin, yielding compound **46**, has been reported.



Several of these chiral non racemic compounds were used for the synthesis of biologically active products. Thus, (R)- and (S)-dimethyloctalones **5** lead respectively to natural and ent-geosmin.³¹ The (R)-enantiomer is also a precursor for the formal synthesis of isocostic and 3-isocostic acid³² while the (S)-enantiomer would lead to tuberiferine³³ and was actually used to synthesize (-)-TMD, a specific inhibitor of the cholesterol biosynthesis.³⁴ (S,S)-Dimethyloctalone **6** (a natural compound) leads to a natural octalin³¹ and would lead to α -vetispirore³⁵ while the (R,R)-enantiomer would lead to frullanolide.³⁶ Compound **7** (R,R) is a precursor for the formal synthesis of muzigadial²⁷ while the (S,S)-enantiomer would lead to polygodial²⁷ and warburganal.²⁷ (+)- α -Cyperone **8** has been widely used as a starting material for the synthesis of many other sesquiterpenes³⁷ and was in particular converted to ent-allohedycaryol.³⁸ Compound **9** was transformed into a C_2 -symmetric chiral dione³⁹ while compound **10** was the starting material for the synthesis of (-)-polywood.³⁴ Tricyclic compounds **11** and **12** were used respectively to synthesize a ring C aromatic steroid⁴⁰ and a key [ABC] steroid intermediate⁴¹ while compounds **13** were transformed into isosteres of aphidicolin as potential antiherpes agents.⁴² Methoxyketone **14** was converted to a precursor of bruceantin⁴³ and compound **15** was used for the preparation of a 14-hydroxymorphinan derivative.⁴⁴ (R)-Ketoester **16** is a key building block for the synthesis of (+)-cassiol,⁴⁵ a potent antiulcerogenic agent, tridensone,⁴⁶ and (-)-19-noraspido-permidine,⁴⁷ while **17** led to (+)-aspido-permidine.⁴⁸ Compound **18** was converted to (-)-nitramine.^{49,14} Lactams **19** show potent inhibition of the recombinant human type-1 steroid 5α -reductase. Compound **20** was used to perform the first synthesis of (+)-petasine and (+)-isopetasine, potent anti-inflammatory and spasmolytic agents.⁵⁰ Ketoester **21** is an intermediate for the formal total synthesis of vallesamidine.⁵¹ Ketodiester **22** or **23** led to the marine antibiotic (-)-malyngolide.⁵² Aza-heterocycles **24** were used to synthesize substituted isoquinoline derivatives which were evaluated as potential inhibitors of 2,3-oxidosqualene lanosterol cyclase⁵³ while oxo-heterocycles **25** and **26** have been used respectively for the synthesis of the mycotoxin, (-)-vertinolide⁵⁴ and of a subunit of marine polyethers toxins⁵⁵ as well as to advanced intermediates for the synthesis of the anti-fertility agent, zoapatanol.⁵⁶ Compounds **32** and **34** lead to precursors of *Vinca* and *Hunteria* alkaloids.⁵⁷ Ethylenic compounds **35** and **36** were used respectively for the total synthesis of both riccardiphenols A and B⁵⁸ and isocuparene.⁵⁹ Acyclic compound **39** was converted to a nipecotic acid derivative.⁶⁰ (R,R)-**40** is a common intermediate in the total synthesis of (-)-ajmalicine and (-)-tetrahydroalstonine^{61,62,63} as well as of (+)-yohimbine,^{64,62,63} (-)-ochroposinine,⁶³ and (-)-emetine^{62,63} while (S,S)-**40** leads to (-)-(10R)-hydroxydihydroquinine.^{61,62,63}

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

silica gel

petroleum ether

brine

(S)-(-)- α -methylbenzylamine

β -gorgonene

widdrol

thujopsene

7-hydroxycostal

β -selinene

costol

costal

costic acid

norketoagarofuran

β -eudesmol

polygodial

warburganal

penitrem D

isocostic and 3-isocostic acid

tuberiferine

(-)-TMD

octalin

α -vetispirene

frullanolide

muzigadial

(+)- α -Cyperone

ent-allohedycaryol

bruceantin

(+)-cassiol

tridensone

(-)-19-noraspidospermidine

(+)-aspidospermidine

(-)-nitramine

5 α -reductase

(+)-petasine

(+)-isopetasine

vallesamidine

(-)-malyngolide

2,3-oxidosqualene lanosterol cyclase

mycotoxin

(-)-vertinolide

zoapatanol

isocuparene

(-)-ajmalicine

(-)-tetrahydroalstonine

(-)-ochroposinine

(-)-emetine

(-)-(10R)-hydroxydihydroquinine

[ethanol \(64-17-5\)](#)

[potassium carbonate \(584-08-7\)](#)

[hydrochloric acid \(7647-01-0\)](#)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

toluene (108-88-3)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

2-methylcyclohexanone (583-60-8)

oxaziridine

methyl propiolate (922-67-8)

(R)-(-)-10-METHYL-1(9)-OCTAL-2-ONE,
2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4a-methyl-, (R)- (63975-59-7)

(R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone (91306-30-8)

(+)-yohimbine