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A Publication
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for the Preparation
of Organic Compounds

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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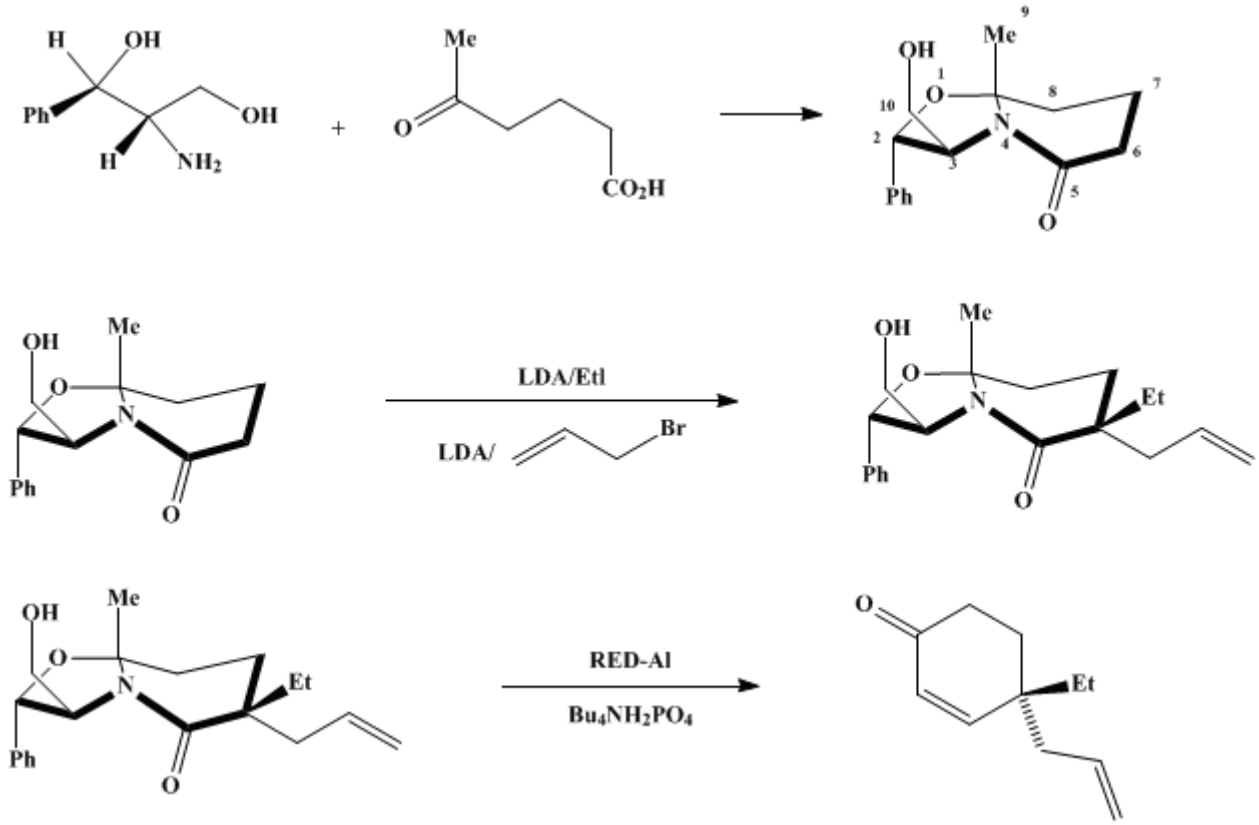
ASYMMETRIC SYNTHESIS OF 4,4-DIALKYLCYCLOHEXENONES FROM CHIRAL BICYCLIC LACTAMS: *(R)*-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE



Submitted by Albert I. Meyers and Daniel Berney[1].
Checked by P. B. Madan, A. Schwartz, and David L. Coffen.

1. Procedure

A. *Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a] pyridine (Bicyclic lactam)*. To a warm solution of (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (32.4 g, 194 mmol) (Note 1) in toluene (800 mL), 5-oxohexanoic acid (25 g, 912 mmol) (Note 2) is added with stirring. The stirred mixture is heated to reflux under argon with azeotropic removal of water for 18 hr. The reaction mixture is cooled, washed with 0.5 *N* hydrochloric acid (100 mL) and with saturated sodium bicarbonate solution (50 mL), dried over magnesium sulfate, and evaporated to dryness. The residue is crystallized from methylene chloride/hexane in the cold. The crystals are collected by filtration and washed with cold ether to give 35.9–37.2 g (71–74% yield) of the bicyclic lactam in two crops (Note 3).

B. *Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,6S,8aR]-5-oxo-5H-oxazolo[3,2-a] pyridine*. In an oven-dried, 500-mL, round-bottomed flask, containing a magnetic stirring bar, is placed 14.4 g (55.2 mmol) of dry bicyclic lactam prepared as described in Part A. The flask is flushed with argon and filled with 150 mL of anhydrous tetrahydrofuran (Note 4) and then sealed with a rubber septum. The air in the flask is further replaced by argon (Note 5). After dissolution of the bicyclic lactam, the flask is cooled in dry ice–acetone and the solution is stirred while preparing lithium diisopropylamide (LDA).

To an oven-dried, 200-mL, conical flask (Note 6) with air replaced by argon, containing 50 mL of

dry tetrahydrofuran (THF) and sealed with a rubber septum, 13.9 g (19.3 mL, 137.4 mmol) of diisopropylamine (Note 7) is added with a syringe. The flask is placed in an ice–water bath. After 15 min, 84 mL (134.4 mmol) of 1.6 *M* butyllithium in hexane (Note 8) is slowly added with a syringe and with gentle swirling of the flask. The solution is kept for 5 min at this temperature.

The lithium diisopropylamide solution prepared as described above is transferred dropwise, via a cannula, into the bicyclic lactam solution. The dry ice–acetone bath is replaced by an ice–water bath, where the reaction mixture is kept for 40 min to complete formation of the lithium enolate. The reaction mixture is cooled again (30 min) with a dry ice–acetone bath. Freshly distilled ethyl iodide (25.8 g, 13.4 mL, 165.4 mmol) (Note 9) is added slowly, via syringe, to the mixture and stirring is continued for 55 min in a dry ice–acetone bath. The cooling bath is replaced by an ice–water bath, and the mixture is stirred for exactly 40 min (Note 10) and is poured immediately into a separatory funnel containing 400 mL of 1.0 *N* hydrochloric acid. The resulting emulsion is extracted once with 400 mL of ether and the organic layer is washed with 200 mL of a 1 : 1 mixture of brine and a saturated solution of sodium bicarbonate. The ether extract is dried over magnesium sulfate and evaporated to dryness in a 500-mL round-bottomed flask. The residue is dissolved in 60 mL of dry toluene and evaporated again using a water bath (60°C for 45 min) to remove all traces of water and toluene. The product (17.2 g, > 100%) is used in the next step without further purification.

The 500-mL flask containing the crude dry product (17.2 g) is filled with argon and dry tetrahydrofuran (150 mL), a magnetic stirring bar is added, the flask is sealed with a rubber septum, and argon is introduced once again. The flask is gently swirled until the viscous oil is totally dissolved and then the flask is immersed in a dry ice–acetone bath.

Another portion of LDA is prepared as described above except that this time 12.6 g of diisopropylamine (17.6 mL, 124.6 mmol) in THF (50 mL) and 78.0 mL (124.8 mmol) of 1.6 *M* butyllithium/hexane are used. The LDA solution is added, through a cannula, to the ethylated bicyclic lactam solution and the mixture is allowed to warm to 0°C; it is kept at this temperature for 3.0 hr (Note 11). The solution is cooled to −75° to −80°C in a dry ice–acetone bath. A solution of 9.4 g of freshly distilled allyl bromide (6.8 mL, 77.6 mmol) (Note 12) in dry THF (50 mL) is prepared in a 100-mL, oven-dried conical flask flushed with argon and sealed with a rubber septum. This solution is cooled in a dry ice–acetone bath and slowly added to the reaction mixture through a cannula (Note 13). After addition of the allyl bromide, the mixture is kept in a dry ice–acetone bath for 2.5 hr; then the bath is replaced by acetone at −50°C, which is allowed to warm to −30°C within a period of 45 min (Note 14). The reaction is terminated by pouring it into 1 *N* hydrochloric acid (as above), extracting with ether, washing with sodium bicarbonate–brine, drying over magnesium sulfate, and evaporating the solvents. The viscous or solid residue is dissolved in methylene chloride (10 mL), and petroleum ether (30–60°C) (140 mL) is added. The product is allowed to crystallize at room temperature for 1 hr, then at −15°C overnight, to give 13.5 g (74%, mp 90–92°C) of a 9 : 1 mixture of diastereoisomers.

This mixture is recrystallized three times with the same mixture of solvents and the product is collected after 1 hr at 0°C to give 8.7 g (47.9%, mp 101–103°C) of a 25 : 1 mixture of diastereoisomers (values based on the 8a-methyl signal integration on NMR spectra) (Note 15).

C. *(R)-4-Ethyl-4-allyl-2-cyclohexen-1-one*. In an oven-dried, 500-mL, round-bottomed flask, containing dry toluene (300 mL) and a magnetic stirring bar, is placed the dialkylated lactam (7.8 g, 23.7 mmol). The solution is cooled in a dry ice–acetone bath and a 1 *M* solution of Red-Al in toluene (55 mL, 55.0 mmol) is slowly added (Note 16). The flask is flushed with argon and sealed with a rubber septum which is connected by a hypodermic needle to a rubber balloon filled with argon. The reaction mixture is allowed to warm to room temperature and stirred for 3 days. The septum is removed, the reaction mixture is cooled to 0°C, and methanol (10 mL) is cautiously added with stirring to destroy excess Red-Al. The solution is poured over 1 *M* aqueous potassium hydroxide (500 mL) in a 2-L separatory funnel and thoroughly shaken with ether (200 mL) until both layers become almost clear. The aqueous layer is extracted twice more with ether (2 × 100 mL), and, after the ethereal layers are combined, the ethereal solution is dried over magnesium sulfate and evaporated to dryness in a 500-mL flask.

The residue is dissolved in ethanol (250 mL), a 1 *M* aqueous solution of tetrabutylammonium

dihydrogen phosphate (80 mL) (Note 17) is added, and the mixture is stirred under reflux for 24 hr. After the solution is cooled, it is partly evaporated on a rotary evaporator with a bath temperature not exceeding 40°C (Note 18) to remove most of the ethanol. Water is added (500 mL) and the solution is extracted twice with chloroform (200 mL). The chloroform extracts are washed with a 1 : 1 mixture of brine and 1 *N* hydrochloric acid and then with brine and saturated sodium bicarbonate solutions. Both aqueous phases are extracted twice with chloroform and the extracts are combined, dried over magnesium sulfate, and evaporated to dryness to give 5.8 g of crude 4,4-disubstituted cyclohexenone. The product is distilled rapidly in a Kugelrohr apparatus at 3.5 mm and 115°C to give 3.0 g (77%) of highly pure cyclohexenone (Note 19).

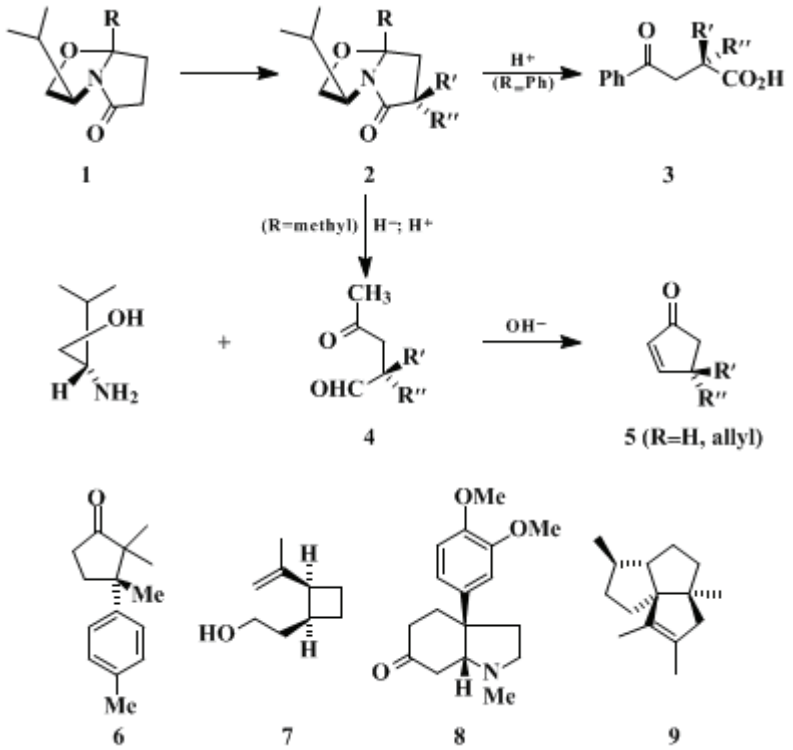
2. Notes

1. The amino diol was purchased from Aldrich Chemical Company, Inc. and was recrystallized before use from methanol/ethyl acetate (the material used had mp 111–113°C).
2. 5-Oxohexanoic acid was purchased from Aldrich Chemical Company, Inc. and was used without further purification.
3. The bicyclic lactam thus prepared has the following physical properties: mp 98–99°C; $[\alpha]_D^{21}$ + 13.54° (EtOH, c 1.55); IR (KBr) cm^{-1}: 3360, 2950, 1625, 1500, 1395; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.75 (dd, $C_{10}H$, J = 11.3, 8.5), 3.90 (dd, $C_{10}H$, J = 11.3, 1.9), 4.07 (dt, C_3H, J = 8.5, 1.9), 4.79 (d, C_2H, J = 8.6), 4.89 (br s, 1 H, OH), 7.38 (s, 5 H, phenyl) and unresolved signals.
4. THF was distilled from a blue solution of benzophenone ketyl obtained by refluxing THF in the presence of a sodium dispersion in paraffin and benzophenone.
5. All reactions were done under argon atmosphere. The argon was introduced through hypodermic needles at a pressure below 50 mm across the rubber septum. An exhaust line was also provided to remove air or excess pressure.
6. A conical flask was used in order to allow efficient transfer of the LDA solution.
7. Commercial diisopropylamine wa distilled over calcium hydride and stored over potassium hydroxide or Linde 4A molecular sieves.
8. 1.6 *M* Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc.
9. Ethyl iodide was distilled over anhydrous potassium carbonate and stored in the refrigerator over copper turnings.
10. If the reaction mixture is kept for longer than 40 min in the ice-water bath, undesirable amounts of the diethylated product are produced.
11. This is the minimum time to allow complete enolate formation.
12. Allyl bromide was distilled over anhydrous potassium carbonate and stored in the refrigerator over Linde 4A molecular sieves.
13. The allyl bromide solution was allowed to cool efficiently by dripping it against the cold walls of the flask. It is important that allyl bromide reach the reaction mixture at the lowest possible temperature in order to obtain an optimal stereo-selective alkylation. The cannula was protected against heat exchange with air by coating it with a fine rubber tubing.
14. Dry ice was removed, leaving only acetone in the Dewar vessel. The temperature was then adjusted to −50°C by adding warm (room temperature) acetone; the temperature was allowed to rise slowly to −30°C by adding small portions of acetone.
15. The physical properties for the dialkylated bicyclic lactam are as follows: $[\alpha]_D^{21}$ +38.89° (EtOH, c 1.77); IR (KBr) cm^{-1}: 3250, 2490, 1600, 1450, 1370, 1330, 1070, 890, 750; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.91 (t, 3 H, $C_{12}H$, J = 7.3), 1.57 (s, 3 H, C_9H); 2.42 (ddd, 2 H, $C_{13}H$, J = 63.6, 13.4, 7.4), 3.65 (br, 1 H, OH), 3.75 (dd, $C_{10}H$, J = 11.3, 8.8), 3.90 (dd, $C_{10}H$, J = 11.2, 2.5), 4.13 (dt, C_3H, J = 8.8, 2.5), 4.78 (d, C_2H, J = 8.5), 5.11–5.16 (m, 2 H, $C_{15}H$), 5.73–5.88 (m, $C_{14}H$), 7.37 (s, 5 H, phenyl) and unresolved signals. Anal. calcd. for $C_{20}H_{27}NO_3$: C, 72.91: H, 8.26; N, 4.25. Found: C, 72.77; H, 8.25; N, 4.24.
16. 1 *M* Red-Al is prepared, by diluting to 100 mL with toluene, 29.5 mL of commercially available 3.4 *M* Red-Al solution in toluene (Aldrich Chemical Company, Inc.; the checkers used Vitride brand supplied by Hexcel Corp.). Before use, this solution should be warmed to room temperature since it tends to separate into two layers at low temperatures. The first milliliter of Red-Al produces a vigorous evolution of gas; therefore, the flask should be kept open until the Red-Al addition is complete. Then the reaction vessel is sealed as described.
17. 1 *M* Tetrabutylammonium dihydrogen phosphate aqueous solution was purchased from Aldrich Chemical Company, Inc.

18. The product has a high vapor pressure and can easily be lost by evaporation. Thus, the yields will vary because of this property. The more caution exerted in the evaporation and distillation step, the higher will be the yield of product.
19. If the distillation is performed slowly, a substantial amount of the product may polymerize, resulting in lower yield. The physical data are as follows: $[\alpha]_D^{21}$ −23.12° (EtOH, c, 1.67); IR (film) cm^{-1}: 2960, 1680, 1450, 1380, 1210; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.95 (t, 3 H, C_8H, J = 7.6), 1.49–1.57 (m, 2 H, C_3H), 1.87 (t, 2H, C_5H, J = 6.8), 2.23 (d, 2 H, C_9H, J = 6.6), 2.45 (t, 2 H, C_6H, J = 6.8), 5.07–5.14 (m, $C_{11}H$), 5.65–5.82 (m, $C_{10}H$), 5.94 (d, C_2H, J = 10.3), 6.71 (d, C_3H, J = 10.3). Anal. calcd. for $C_{11}H_{16}O$: C, 80.45; H, 9.82. Found: C, 79.67; H, 10.05. By GLC analysis, the product is 93–95% pure with 5–7% of diethylcyclohexenone detectable by GLC–MS.

3. Discussion

Chiral bicyclic lactams such as those described here are useful in reaching a variety of chiral quaternary carbon derivatives. Thus, **1** can be doubly alkylated to the bicyclic lactam **2** in high diastereoselectivity. Acidic hydrolysis leads to α,α-substituted γ-keto acids **3**,[2] whereas reduction and hydrolysis furnish the chiral keto aldehydes **4**. Base-catalyzed aldolization affords chiral cyclopentenones **5**.[3] In addition, several total syntheses of natural products have been accomplished, further demonstrating the synthetic usefulness of these bicyclic lactams **1**. Thus, (−)-α-cuparenone **(6)**,[4] (−)-grandisol **(7)**,[5] (+)-mesembrine **(8)**,[6] and (−)-silphiperfol-6-ene (**9**)[7] have been prepared in high enantiomeric excess.



To reach chiral cyclohexenones, we have found that the bicyclic lactam **10**, derived from 5-oxohexanoic acid and the commercially available amino diol, gave excellent results. A number of examples were obtained (Table I).[8]

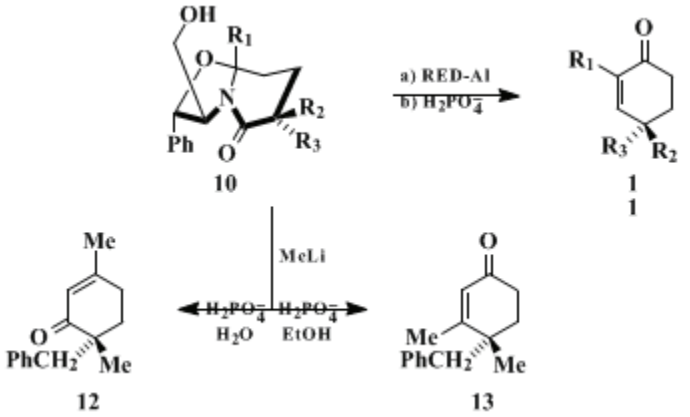
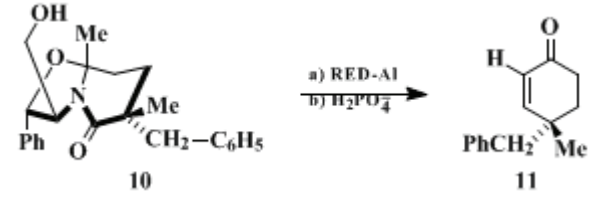
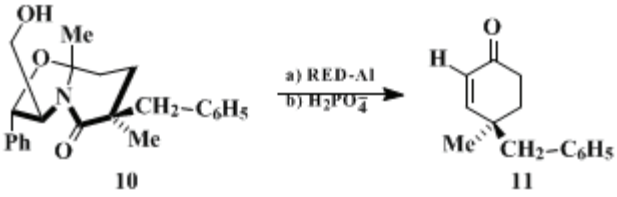
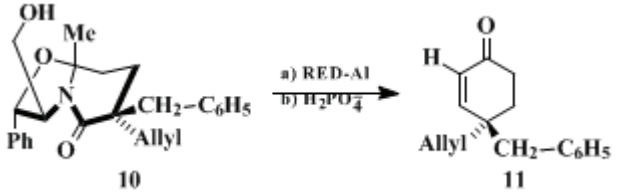
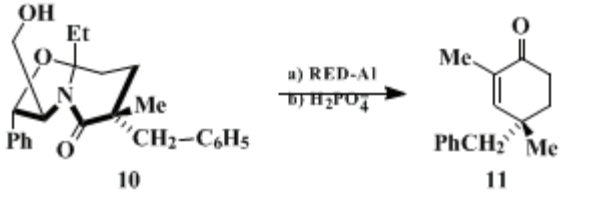
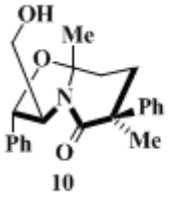
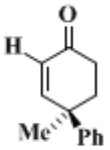


TABLE I
CHIRAL 4,4-DIALKYLCYCLOHEXENONES(**11**)[a]

10			**11**				
R_1	R_2	R_3	R_1	R_2	R_3	Yield(%)	$[\alpha]_D$
Me	Me	$PhCH_2$	H	ME	$PhCH_2$		−65.6°
						53	
Me	$PhCH_2$	Me	H	$PhCH_2$	Me		+64.8°
						68	
Me	$PhCH_2$	Allyl	H	$PhCH_2$	Allyl		+48.9°
						47	
Et	Me	$PhCH_2Me$	Me	$PhCH_2$			−39.7°
						66	

Me	Ph	Me	H	Ph	Me		a) RED-Al b) H_3PO_4		+122.2°

10 11

[a]Yields refer to reduction and hydrolysis of **10** to **11**. All products are 99% optically pure (see [8]).

Furthermore, in place of reduction of **10** it was possible to add organolithium reagents such that the resulting alkyl carbinolamine, after hydrolysis, gave either **12** or **13** depending on hydrolysis conditions.[6] In summary, these bicyclic lactams have provided a route to a variety of chiral, nonracemic cyclohexenones and cyclopentenones containing quaternary stereocenters.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 457
- Org. Syn. Coll. Vol. 9, 530

References and Notes

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

petroleum ether

benzophenone ketyl

brine

Red-Al

Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine (Bicyclic lactam)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

Allyl bromide (106-95-6)

allyl (1981-80-2)

copper turnings (7440-50-8)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Ethyl iodide (75-03-6)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

5-oxohexanoic acid (3128-06-1)

tetrabutylammonium dihydrogen phosphate (5574-97-0)

(R)-4-Ethyl-4-allyl-2-cyclohexen-1-one (122444-62-6)

(1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol

Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,6S,8aR]-5-oxo-5H-oxazolo[3,2-a] pyridine