Tetrahedron Letters,Vol.23,No.48,pp 5005-5008,1982
Printed in Great Britain

0040-4039/82/485005-04$03.00/0

KETONE METHYLENATION WITH OPTICAL RESOLUTION.
SYNTHESIS OF (+)- AND (-)-HOP ETHER

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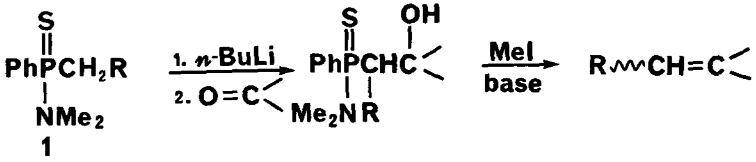
Abstract Chromatographic separations of diastereomeric β-hydroxyphosphinothioic amides made by coupling of a resolved phosphinothioic amide with (±)-ketones have been utilized in the synthesis of (+)- and (-)-hop ether and (+)- and (-)-2,3-diphenyl-3-isopropoxypropene.

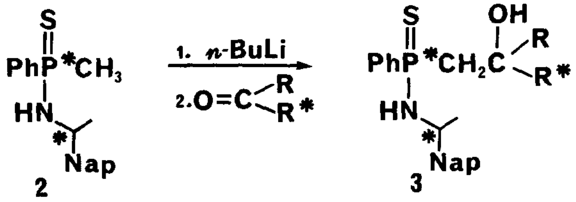
We have recently shown that phosphinothioic amides (1) are highly effective reagents for the alkylidenation of ketones (Scheme 1).[1]

Scheme 1



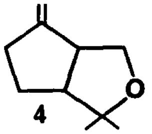
R = H, Me, Bu, CH_2Ph

We now describe a variation of this procedure which couples ketone methylenation with concomitant optical resolution.[2] Our approach relies upon the chromatographic separation of diastereomeric β-hydroxyphosphinothioic amides (3) arising from the coupling of a resolved phosphinothioic amide (2) with a racemic, chiral ketone



Nap = 1-naphthyl

To demonstrate the potential of this method we have synthesized both enantiomers of the iridoid monoterpene hop ether (4),[3] a constituent of the volatile oil of Japanese hops, from ketone (5).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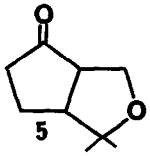
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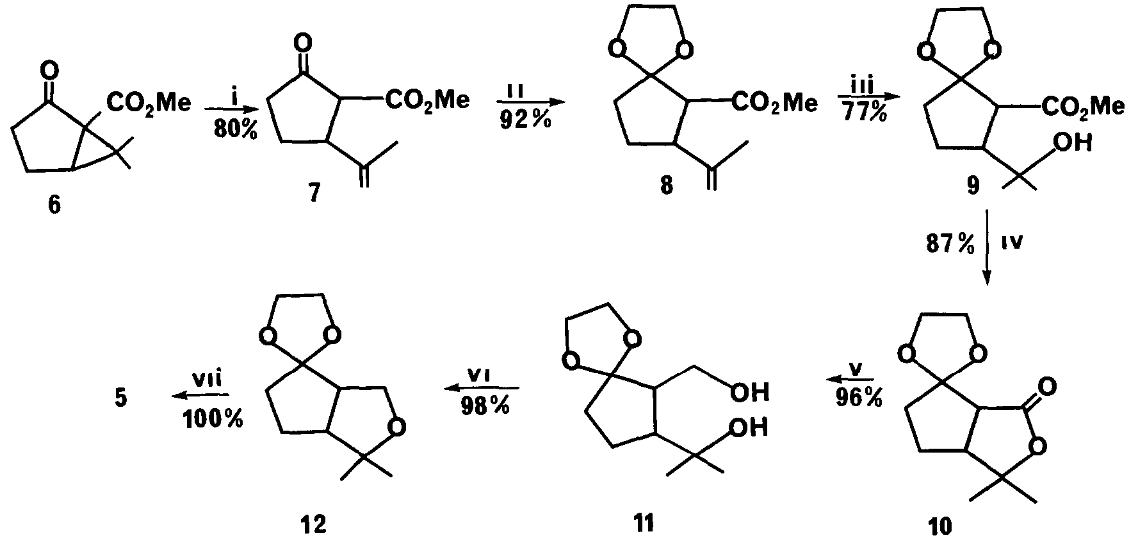
The phosphinothioic amide (2) was prepared by treatment of methylphenylphosphinothioic chloride[1] with (R)-(+)-α-(1-naphthyl)ethylamine [α]$_D^{25}$ +75° (neat), in the presence of triethylamine. The resulting 1 1 mixture of diastereomers of (2) (79% yield) was separated by preparative HPLC The more mobile diastereomer was obtained as an oil, [α]$_D^{25}$ +11 7° (c 1 3, CHCl$_3$) and the less mobile diastereomer was isolated as a crystalline solid, mp 113°C, [α]$_D^{25}$ +47 1 (c 0 9, CHCl$_3$).[4]

The oxa-bicyclo[3.3 0]octanone (5) was synthesized as shown in Scheme 2 The cyclopentanone (7)[5] appeared to be an attractive starting material and was prepared according to the procedure developed by Trost and Vladuchick[5a] with the exception of a practical modification of the final step [(6) ⟶ (7)]. In our hands, thermolytic decomposition of the bicyclo[3.1 0]hexanone (6) under the conditions (hexane solution, column packed with glass helices, 350°C) described by Trost and Vladuchick[5a] afforded a mixture of products from which cyclopentanone (7) could be isolated in low yield We found that refluxing neat cyclopropyl keto ester (6) at atmospheric pressure for 20-30 seconds smoothly and cleanly effected rearrangement to give compound (7) in high yield

The ketone moiety of (7) was protected under standard conditions to give ketal (8) in 92% yield Hydration of (8) by way of an oxymercuration-demercuration reaction[6] gave hydroxy ester (9) which was converted to the lactone (10), mp 80-82°C, by treatment with a slight excess of potassium *t*-butoxide. Reduction with lithium aluminum hydride furnished crystalline diol (11), mp 111-112°C, in 96% yield which underwent cyclization to give the ether (12) upon exposure to *p*-toluenesulfonyl chloride in pyridine Removal of the ketal group of (12) gave 2,2-dimethyl-3-oxabicyclo[3.3.0]octan-6-one (5) which exhibited NMR and IR spectra in accord with the published data.[3a,b,7]

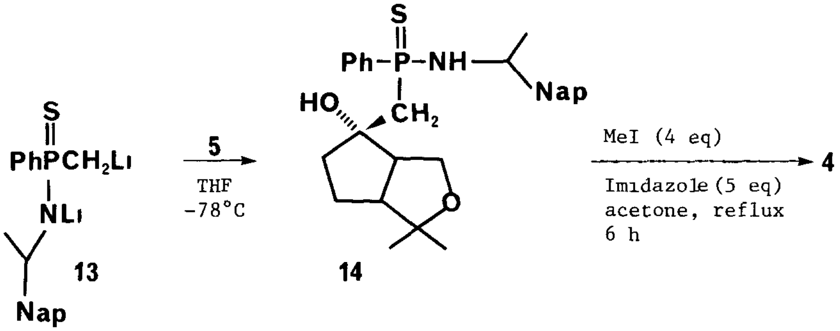
Scheme 2



Reagents and conditions i, reflux, neat, 20-30 sec, ii, HOCH$_2$CH$_2$OH, TsoH, benzene, reflux, iii, Hg(OAc)$_2$, H$_2$O then NaBH$_4$, NaOH, iv, KOt-Bu, THF, v, LiAlH$_4$, Et$_2$O, vi, TsCl, pyridine, vii, TsOH, acetone.

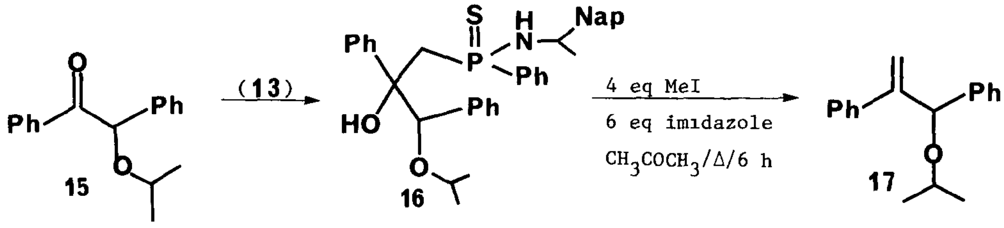
At this point we investigated the methylenation-resolution of ketone (5) using the sulfoximine-based approach that had worked so effectively in our synthesis of (−)-β-panasinsene [8] The addition of (*N*-methylphenylsulfonimidoyl)methyllithium to ketone (5) occurred diastereofaceselectively to give only two diastereomeric adducts which were chromatographically indistinct and could not be separated on a practical scale (analytical HPLC, silica gel, 80% EtOAc/hexane, retention times 2 3 and 2 5 min) However, reductive elimination[9] of crude adducts afforded (±)-hop ether (4) in 71% yield from ketone (5)

Addition of ketone (5) to a solution of the dianion (13), prepared from the less mobile diastereomer of phosphinothioic amide (2) by treatment with 2 molar equivalents of *n*-butyllithium at −78°C, gave a 3 2 mixture of two diastereomeric adducts (14) in 50% combined yield. These were cleanly separated by medium pressure liquid chromatography on silica gel. The more mobile diastereomer was isolated as a crystalline solid, mp 172-173°C, $[\alpha]_D^{25}$ +14.8° (c 1, $CHCl_3$) and the less mobile diastereomer was obtained as an oil, $[\alpha]_D^{25}$ −32.8° (c 1, $CHCl_3$)



Fragmentation of the more mobile diastereomer (+)-(14) by treatment with an excess of methyl iodide and imidazole in refluxing acetone afforded (+)-hop ether (4), $[\alpha]_D^{25}$ +134 6° (c 1, $CDCl_3$) in 62% yield [10] The (+)-hop ether isolated from Japanese hops, $[\alpha]_D^{23}$ +36 7° (c 0 97, $CHCl_3$)[3b] is apparently of low optical purity Similar treatment of the less mobile diastereomer (−)-(18) gave (−)-hop ether $[\alpha]_D^{25}$ −133.4° (c 1, $CDCl_3$) in 61% yield.

In order to further illustrate the synthetic utility of this procedure, a solution of the dianion (13) was treated with benzoin isopropyl ether (15) Only two diastereomeric adducts (16) resulted[11] (66% combined yield) which were readily separated by MPLC on silica gel The more mobile diastereomer (16), mp 172°, $[\alpha]_D^{25}$ −23 2° (c 1, $CHCl_3$), upon fragmentation as described above gave (+)-2,3-diphenyl-3-isopropoxypropene (17), $[\alpha]_D^{25}$ +8.4° (c, 1 2, $CDCl_3$) in 91% yield. The less mobile diastereomer (16), mp 150-151°C, $[\alpha]_D^{25}$ −21.5° (c 1, $CHCl_3$) decomposed under similar conditions to give (−)-(17), $[\alpha]_D^{25}$ −8.4° (c 1.1, $CDCl_3$) in 86% yield



The chromatographic separations described herein were performed using 47 x 450 mm Michel-Miller columns (Ace Glass Company) packed with Silica Gel 60 (E. Merck) Diastereomers **2** (α = 2.41) were separated on a 12 g scale using 10 1 hexane.EtOAc Diastereomers **14** (α = 1 23) were separated on a 1.3 g scale using 12:3 1 hexane EtOAc CH_2Cl_2. Diastereomers **15** (α = 1.42) were separated on a 2.0 g scale using 25 1 hexane EtOAc The α values were determined by analytical HPLC on a silica gel column

Acknowledgement Support for this work by the National Science Foundation is gratefully acknowledged.

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(Received in USA 12 August 1982)