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Synthesis of Cacalol

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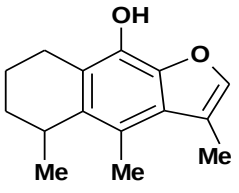
Abstract

The sesquiterpene cacalol, isolated from the root of *Cacalia deposita A, Gray*, exhibits important biological activities (anti-inflamatory, anti-hyperglycemic, anti-microbial etc) and therefore several routes have been developed to achieve the synthesis of cacalol. The applications of several organic reactions have been observed during the synthesis of cacalol. The synthesis of optical active cacalol has also been accomplished.

Keywords: cacalol, cyclodehydration, demethoxylation, cyclization, ring enlargement

1. Introduction

In the northern region of Mexico and in the southwest region of united states, the *plant Psacalium decompositum (Gray*) has been traditionally used as medicinal remedy. The Mexican population have utilized both roots and rizones of *Psacallium decompositum* against pains, rheumatism, renal as well as anti-diabatic remedy (Martinez, 1989). Phytochemical studies reveal that *Psacalllium decompositum* contains various sesquiterpenes such as cacalol, cacalone, maturin etc (Romo & Joseph-Nathan, 1964; Correa & Romo, 1966). Cacalol **1** and Cacalone **2** are the most abundant constituents of *Psacallium decompositum*. The petroleum ether extracts of the ground roots and rhizomes of Psacallium decompositum afford cacalol 1 and cacalone **2**. The interesting biological activities of cacalol have encouraged organic chemists to develop several routes for cacalol. The biological activities and synthetic details of each approach are described below.



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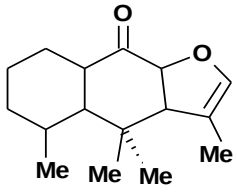

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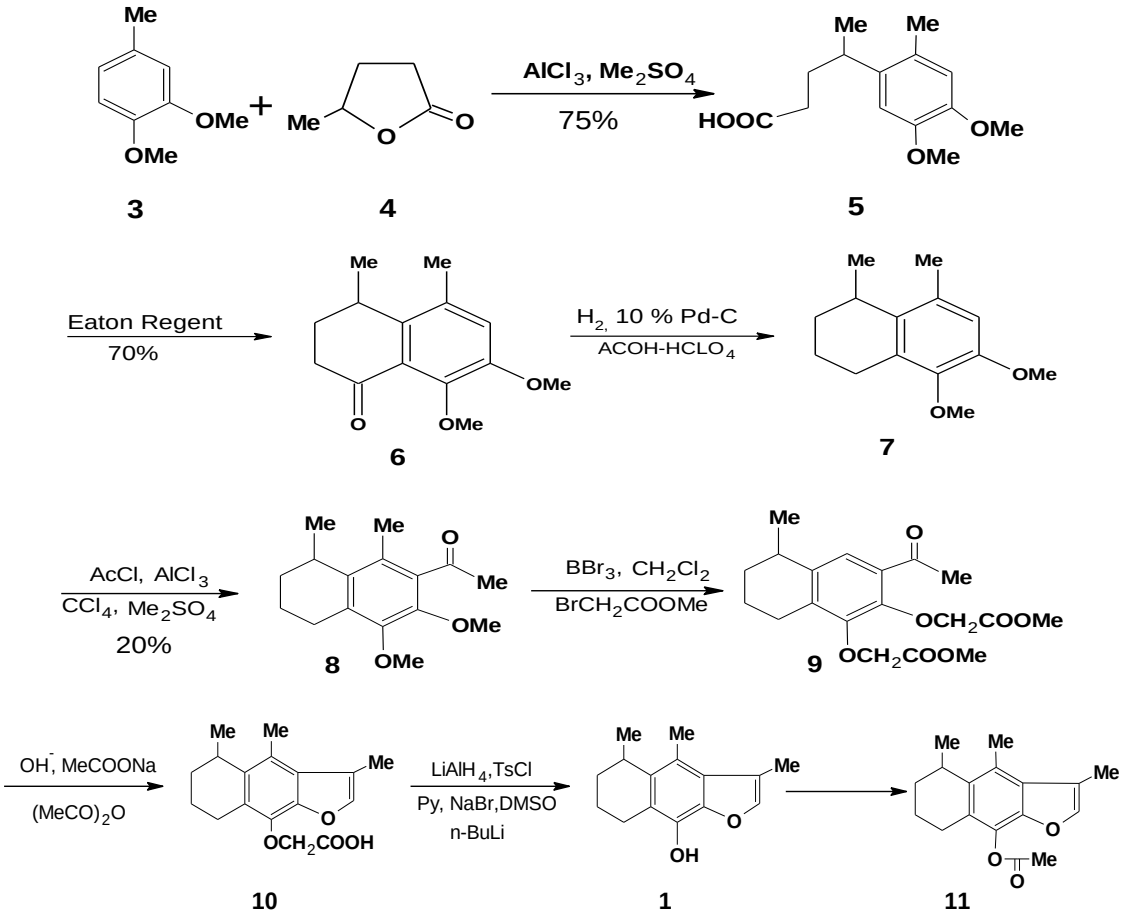
Biological Activities

Cacalol is a sesquiterpene natural product which exhibits antihyperglycemic (Inman etal., 1999), anti-inflamatory (Jiminez-Estrada etal., 2006), antioxidant (Shindo etal., 2004) and anticancer properties (Rostro-Alonso etal., 2024) properties.

Synthetic Approaches

1. **Synthesis Of Cacalol by Inouye, Uchida and Kakisawa**

The synthesis of cacalol **1** developed by Japanese scientists (Inouye etal., 1975) is noteworthy which has established its correct structure. The synthetic details are described below: Friedel-Crafts reaction (Berliner, 1949) between cresolmethyl ether **3** and valerolactone **4** followed by methylation with dimethyl sulfate afford the acid **5 (Scheme 1).**



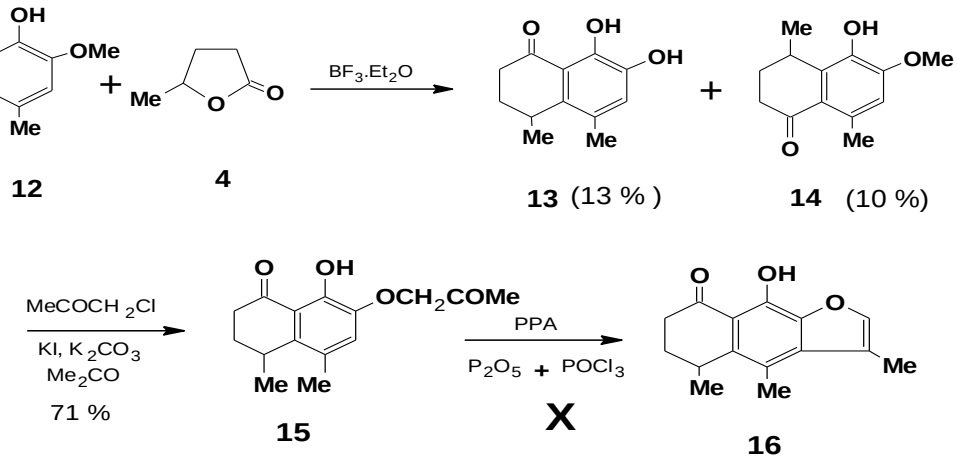
Scheme 1. Synthesis of cacalol **1**

The cyclization of the acid **5** with Eaton's reagent (Eaton etal.,1973) yields the tetralone **6.** The cyclization attempted with polyphosphoric acid (PPA) produces 8-hydroxy-1-tetralone in 28% yield. The hydrogenolysis (10% Pd-C, acetic acid and perchloric acid) of the tetralone **6** affords dimethoxy tetralin **7** which is converted to acetyl derivative **8** by Friedel-Crafts acetylation (AcCl, $AlCi_3$, CCl_4, 70°C), followed by the methylation with dimethyl sulfate. Demethyltion of the acetyl derivative **8** with boron tribromide and alkylation of the resulting product with bromoacetate respectively yield the compound **9.** Alkaline hydrolysis of **9** and the cyclization of the resulting product with sodium acetate in acetic anhydride respectively provide the furan compound **10** whose transformation into cacalol 1 is achieved (van der Gen etal., 1973) by successive treatment with lithium aluminium hydride, tosyl chloride in pyridine, sodium bromide in dimethyl sulfoxide and finally with n-butyl lithium. The cacalol **1** fails to crystallize even after repeated chromatographic purification. Its identity is confirmed by preparing its acetate **11** (mp. 119-120°C) and comparing its IR spectrum with an authentic specimen (Romo & Joseph-Nathan, 1964). The acetate **11** can easily be converted into cacalol 1 by alkaline hydrolysis.

The present synthesis of cacalol shows the importance of Eaton's reagent in the cyclization of the acid **5.** PPA fails to afford the desired ketone **6**. The furan ring has been constructed tactfully. The yield of some of the intermediates has not been mentioned. Therefore it is very difficult to know the correct overall yield of cacalol obtained. The structure of cacalol been confirmed by the above mentioned synthesis.

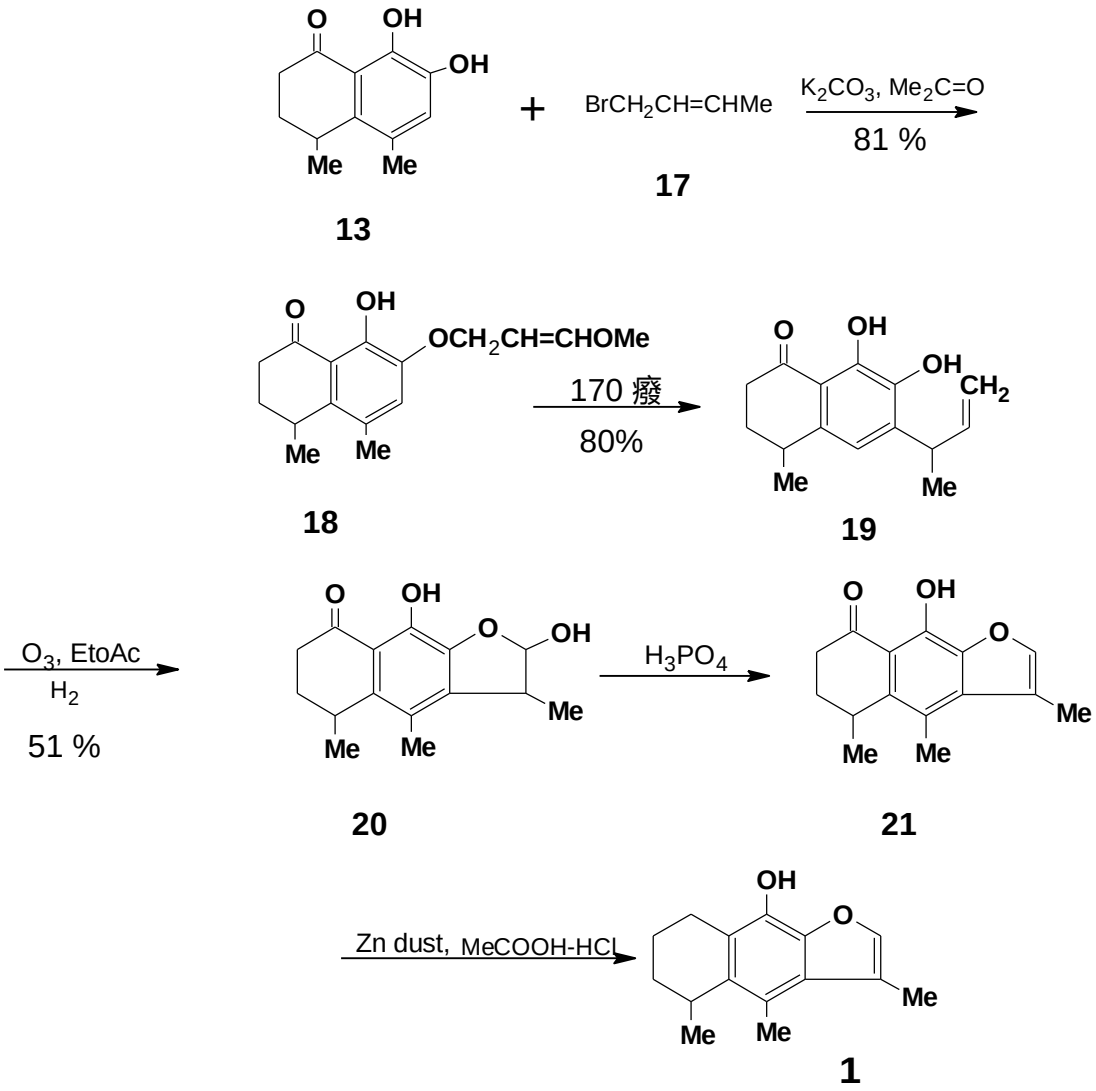
2. Synthesis Of Cacalol by Yuste and Walls

The **scheme 2** describes another approach (Yuste & Walls, 1976) to achieve the total synthesis of cacalol **1.**



Scheme 2. Synthesis intermediate 16

The Friedel-Crafts condensation (Berliner, 1949) between γ-valerolactone **4** and 2- methoxy-4-methyl phenol **12** in boron trifluoride etherate leads the formation of 7,8-dihydroxy-4,5-dimethyl-1-tetralone **13** (13%) and 4,8-dimethyl-5-hydroxy-6-methoxy-1-tetralone **14** (10%). The tetralone **13** is converted into the ketoether **15** (71%) by boiling with chloroacetone, potassium iodide and potassium carbonate in dry acetone. The cyclodehydration of the ketoether **15** with polyphosphoric acid (PPA) fails to afford the expected compound **16**. The cyclodehydration attempted with phosphorous oxychloride and phosphorous pentoxide also does not afford the desired compound **16**. Due to the difficulties in the cyclization of the keoether **15** to **16** the synthesis of cacalol could not be accomplished. It is worthwhile to mention that the cyclization could have been tried with other acids. Therefore an alternative route **(Scheme 3)** has been sought.

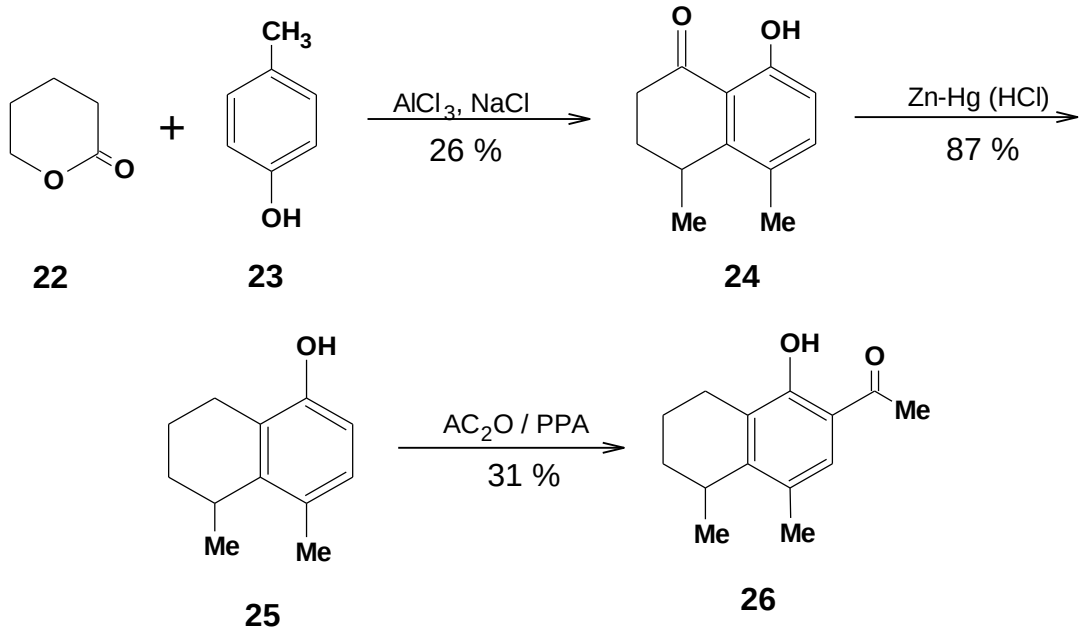


Scheme 3. An alternative route for the synthesis of cacalol **1**

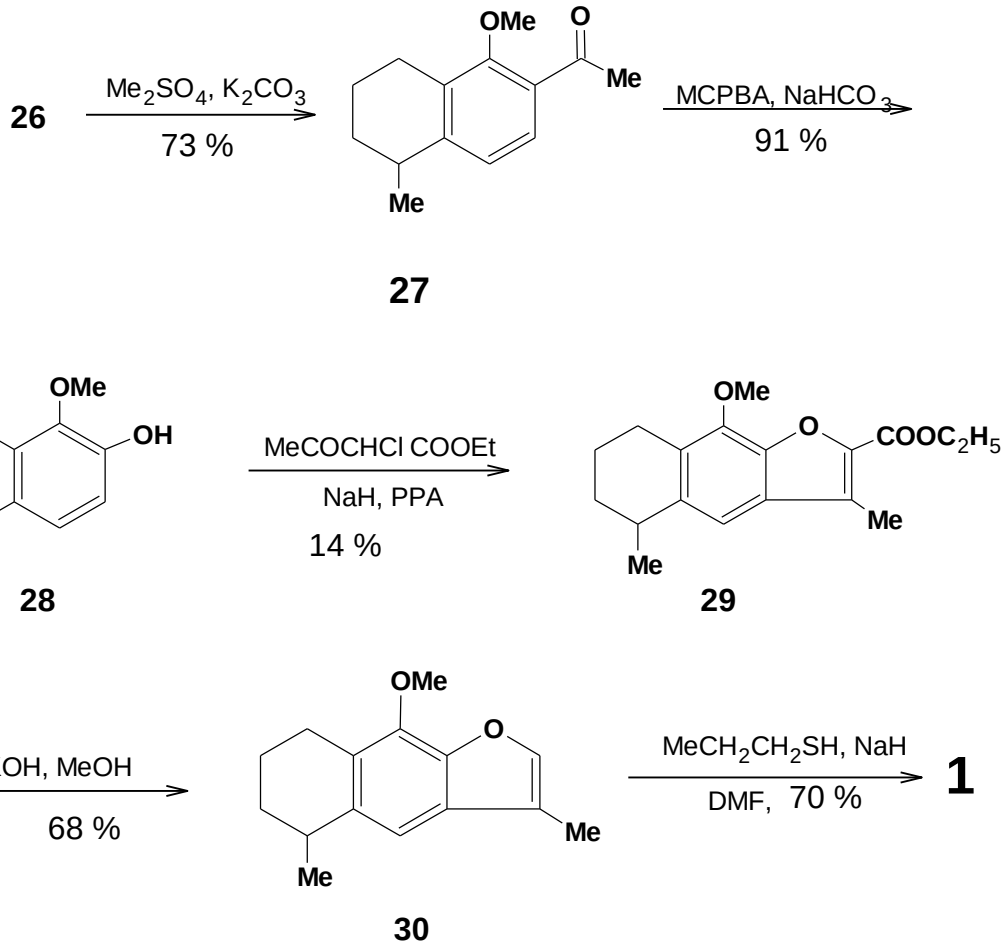
The tetralone **13** in acetone is heated with 1-bromobut-2-ene **17** and potassium carbonate to obtain the allyl ether **18**. The Claisen rearrangement (Rhoads and Raulins, 1975; Ganem, 1996) of **18**, effected by heating at 170ºC, yields 2-allyl phenol **19**. Ozonolysis of **19** in ethyl acetate followed by catalytic hydrogenation of the ozonide (Pd-C at 0-5ºC) in ethyl acetate affords the compound **20** which on heating with phosphoric acid affords the compound **21.** The transformation of the compound **21** to cacalol **1** is achieved by heating with zinc, acetic acid and hydrochloric acid. The resulting cacalol fails to crystallize and thus its identity is confirmed by preparing its acetate (m.p. 115º C) and by comparing with an authentic specimen. The transformation of **21** to cacalol **1** can be also realized by Clemmensen reduction (Martin, 1942).

3. Synthesis Of Cacalol by Huffman and Pandian

The synthetic approach of cacalol (Huffman & Pandian, 1979) describes the preparation of 6-acetyl tetrahydronaphthalene **26 (Scheme 4)** and its transformation into cacalol **1**. **(Scheme 5).** The Friedel-Crafts reaction (Berliner, 1949) of δ-valerolactone **22** and p-cresol **23** with aluminium chloride and preheated NaCl (140ºC) yields the tetralone **24** which is converted into the dimethyl phenol **25** by Clemmensen reduction (Martin, 1942). The direct acetylation of phenol **25** with acetic anhydride and PPA affords acetyl tetrahydronaphthalene **26**. This method of acetylation has proved superior to the classical Fries rearrangement (Blatt, 1942). The transformation of the acetynaphthalene **26** to cacalol **1** is described in **Scheme 5.**



Scheme 4. Synthetic of 6-acetyl tetrahydronaphthalene **26**

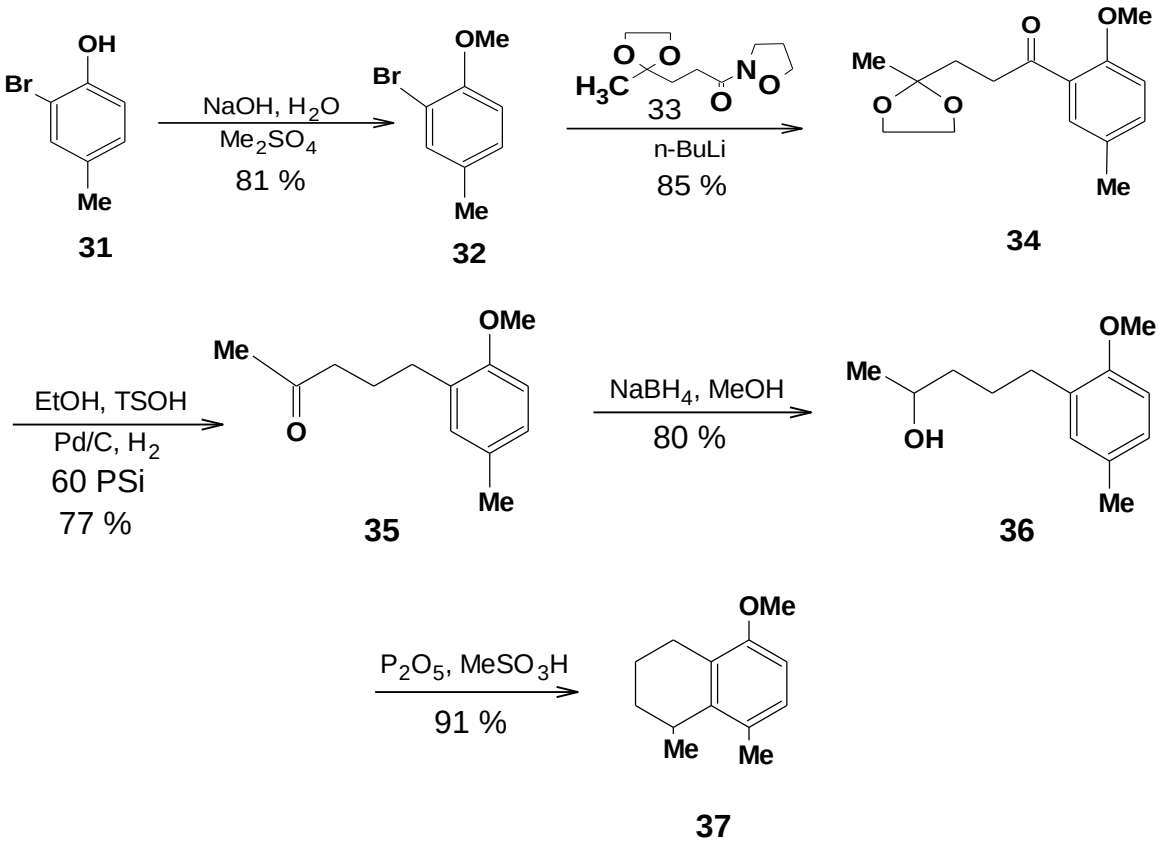


Scheme 5. Transformation of 6-acetyl tetrahydronaphthalene 26 to cacalol 1

The treatment of **26** with dimethyl sulfate and anhydrous potassium carbonate produces the compound **27.** Baeyer-Villiger oxidation (Krow, 1993) of **27** with m-chloroperbenzoic acid (MCPBA) at 0ºC for over one week furnishes the acetate which on alkaline hydrolysis yields phenol **28.** The transformation of the phenol **28** to naphthofuran carboxylic ester **29** has been achieved in 14% yield by alkylation with ethyl 2-chloroester followed by the cyclization with PPA. The transformation of **29** to cacalol methyl ether **30** is achieved by the alkaline hydrolysis of **29** at room temperature followed by pyrolytic decarboxylation in the presence of copper powder (Spencer etal., 1971). The cacalol methyl ether is cleaved by using sodium thiopropoxde in dimethylformamide (Sher and Berchtold, 1977) to give cacalol **1**. The infrared spectra of synthetic cacalol and the derived acetate **11** have been found identical with those of natural cacalol and cacalol acetate respectively. The synthesis involves many steps but it introduces a new method of acetylation which constitutes an alternative of Fries rearrangement. It is difficult to understand the reason for selecting sodium thiophenoxide instead of the commercially available boron tribromide for demethoxylation. The method for construction of furan ring is interesting but the yield is poor.

4. Synthesis of Cacalol by Garofalo, Litvak,Wang, Dubenko, Cooper and Bierer

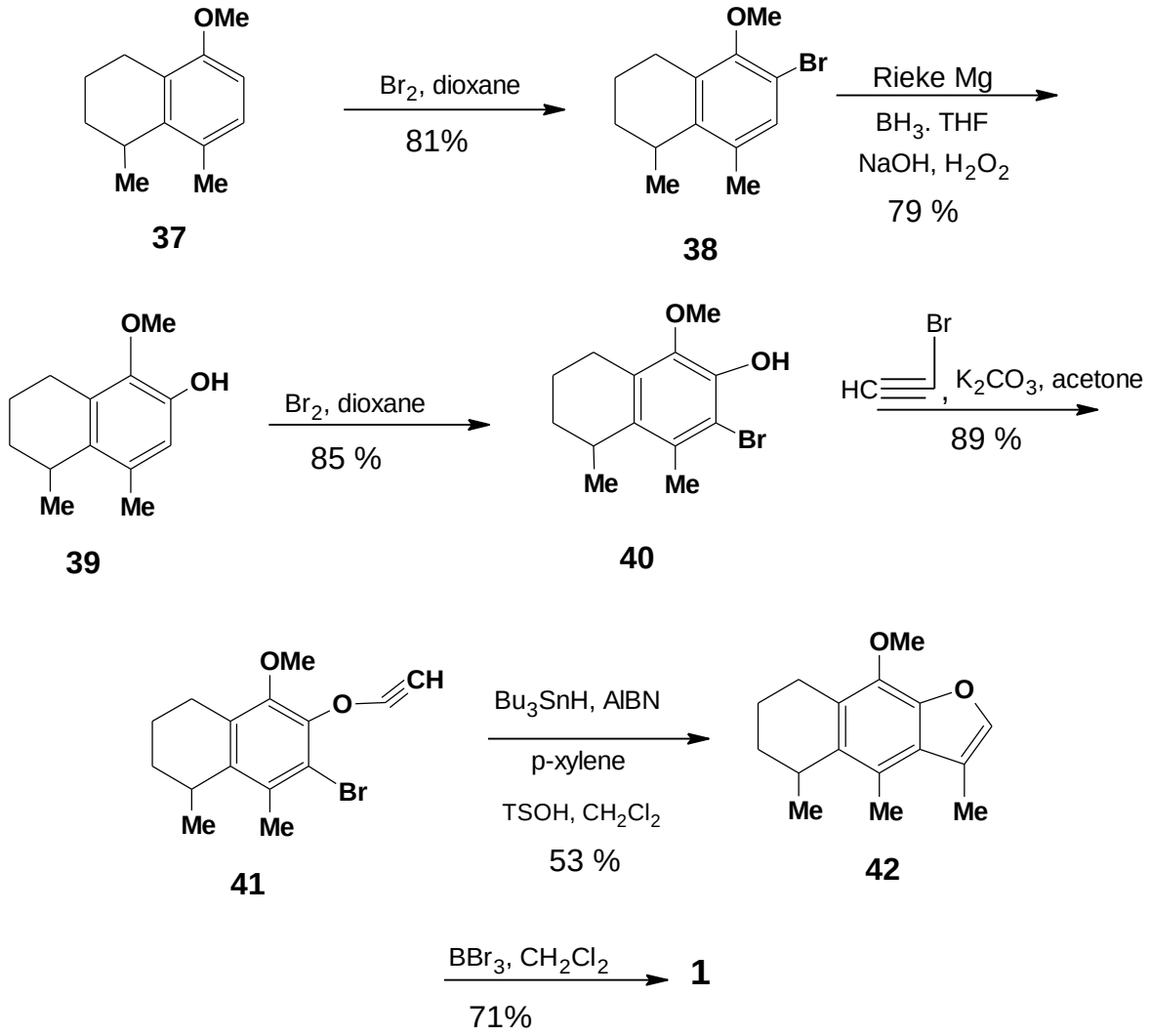
The synthesis of cacalol **1** developed by Bierer and collaborators (Garofalo etal., 1999) illustrates the synthesis of the tetralin **37 (Scheme 6)** and its transformation to the cacalol 1 (**Scheme 7).** In order to achieve the synthesis of the tetralin **37**, the phenol **31** is methylated to obtain the compound **32** which on lithiation with t-butyllihium followed by condensation with isoxazolidine **33 (Scheme 8)** yields methylanisole **34**. It is noteworthy that lithiation attempted with *n*-butylithium or *sec*-butyllithium does not give satisfactory result. Benzylic decarbonylation of **34** with 10% Pd-C in ethanol and p-toluenesulfonic acid causes deprotection to yield the pentanone **35**. Metal hydride reduction of the pentanone **35** affords alcohol **36** which is cyclized with phosphorous pentoxide and methanesulphonic acid to furnish the tetralin **37** whose transformation into cacalol 1 is described in **Scheme 7.**



Scheme 6. Synthesis of the tetralin **37**

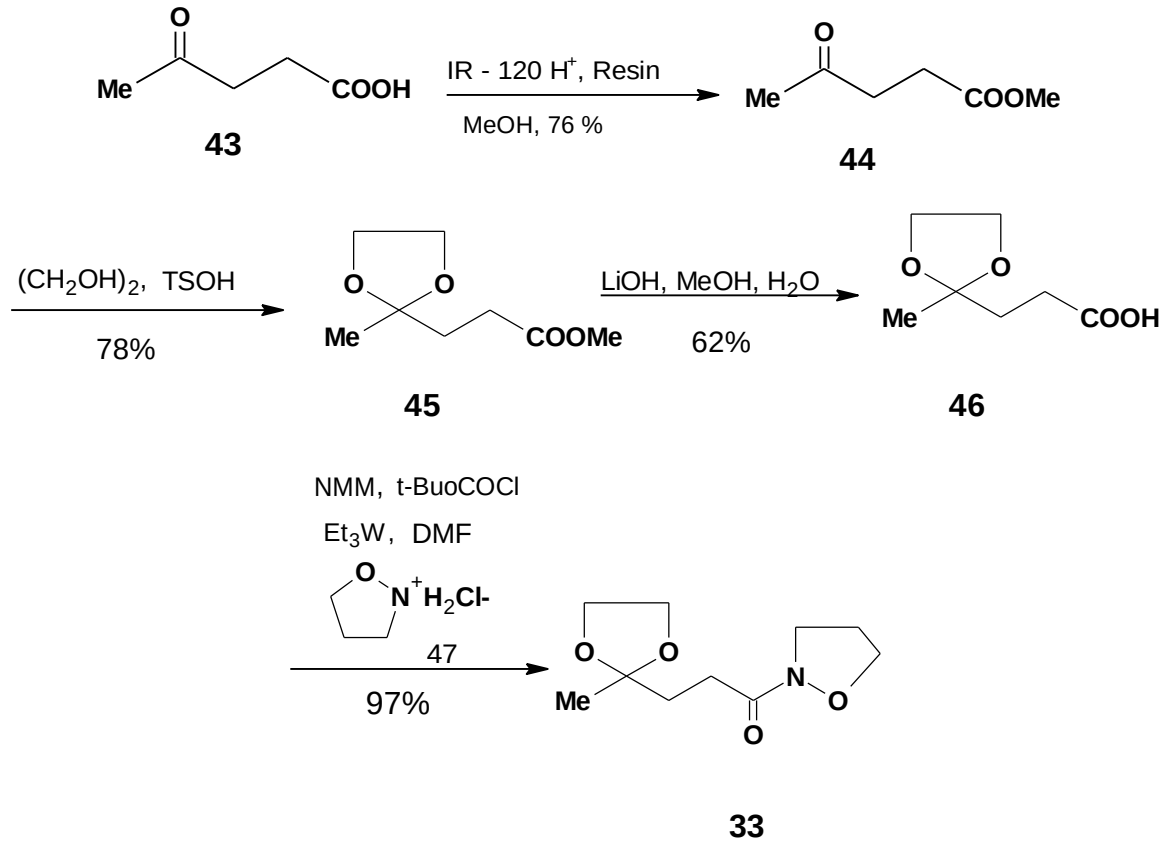
Regioselective bromination of **37** yields **38** which is made to react with Rieke magnesium to form the Grignard reagent. Transmetalation of the Grignard reagent with BH_3. THF and oxidation with alkaline peroxide afford the tetraol **39.** Bromination of **39** with already mentioned reagent yields **40** which on alkylation with propargyl bromide leads the formation of the product **41.** Radical cyclization of **41** with *tributyl*-stanic hydride (Bu_3SnH) and azo-bis-isobutyronitrile (AIBN) in p-xylene (Tsukazaki & Snieckus, 1992) produces a mixture of *exo* and *endo*- cyclic double bond isomer. The exo isomer is isomerized to the desired endo by exposure **42** to *p*-toluenesulfonic acid in dichloromethane. Demethylation

of **42** with boron tribromide in dichloromethane affords cacalol **1** in 7% overall yield from the phenol **31**.



Scheme 7. Transformation of the tetralin **37** to cacalol 1

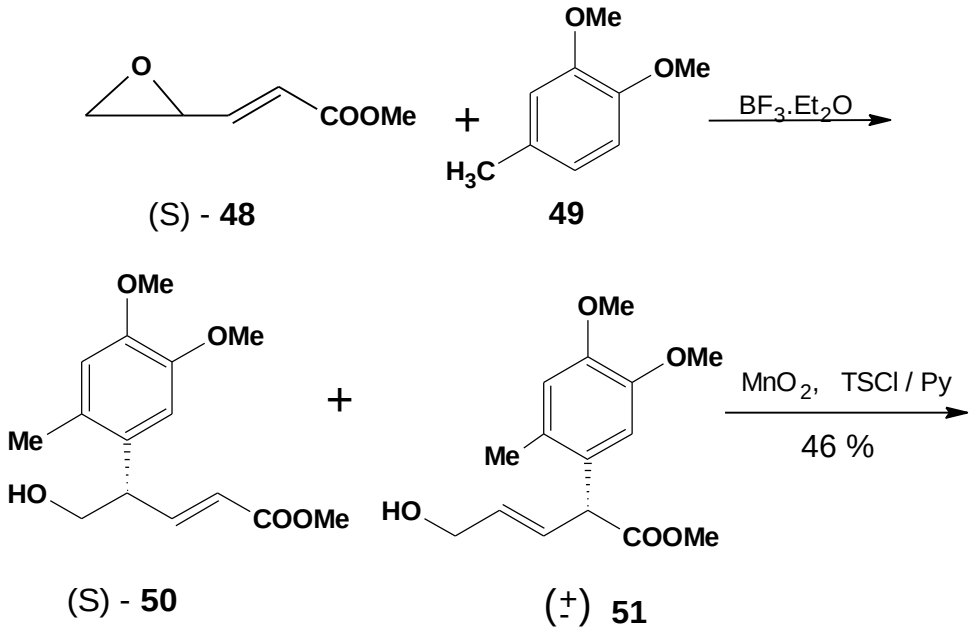
The Scheme **8** describes the synthesis of isoxazolidine **33** which has proved useful for the synthesis of tetralin **37** (**Scheme 6).** Esterification of levulinic acid **43** gives the ester **44** which on ketalization with standard reagent produces the compound **45**. The acid **46,** obtained by careful hydrolysis of **45**, is treated with isobutyl chloroformate in *N*-methylmorpholine followed by the adition of isoxazolidine hydrochloride **47** (Cupps etal., 1985) in DMF to yield the isoxazolidine **33.** The above mentioned approach (Garofalo etal., 1999) describes a novel approach for the synthesis of cacalol. The synthesis involves many steps and thus fails to be attractive. The synthetic approach (Garofalo etal., 1999) also describes other methods for the synthesis of tetrlin **37.** The incorporation of the furan ring onto the tetralol **39** has been achieved by the well-known approaches.

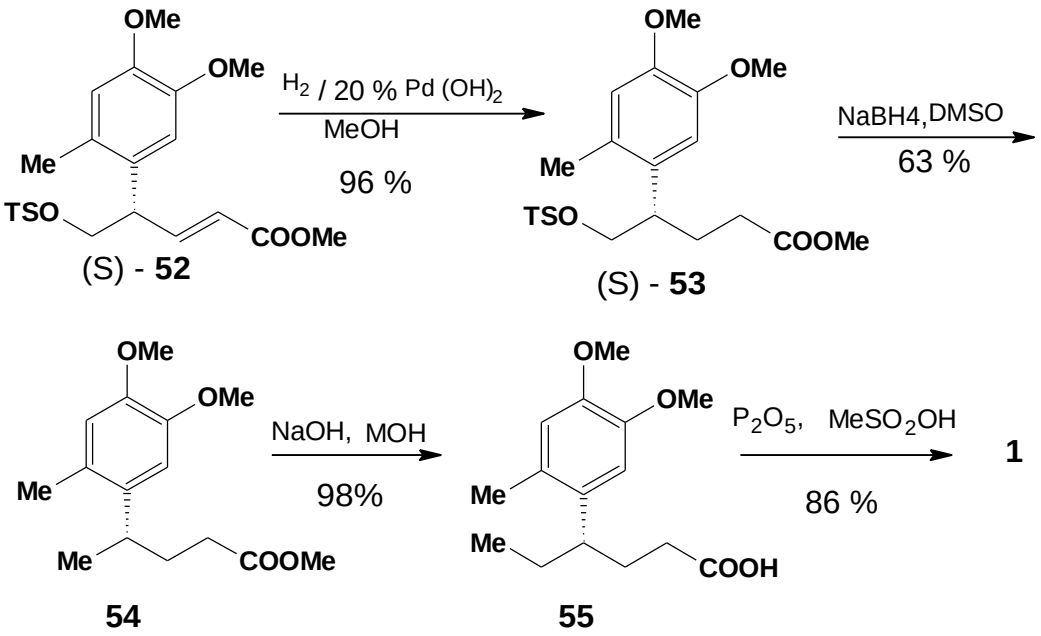


Scheme 8. Synthesis of isoxazolidine **33**

5. **Synthesis of (S) (+)-Cacalol by Tanikawa, ONO and AKITA**

The synthesis of the optically active cacalol **1** was first developed by Akita and collaborators (Tanikawa etal., 2005). The synthetic details are described in **Scheme 9.**

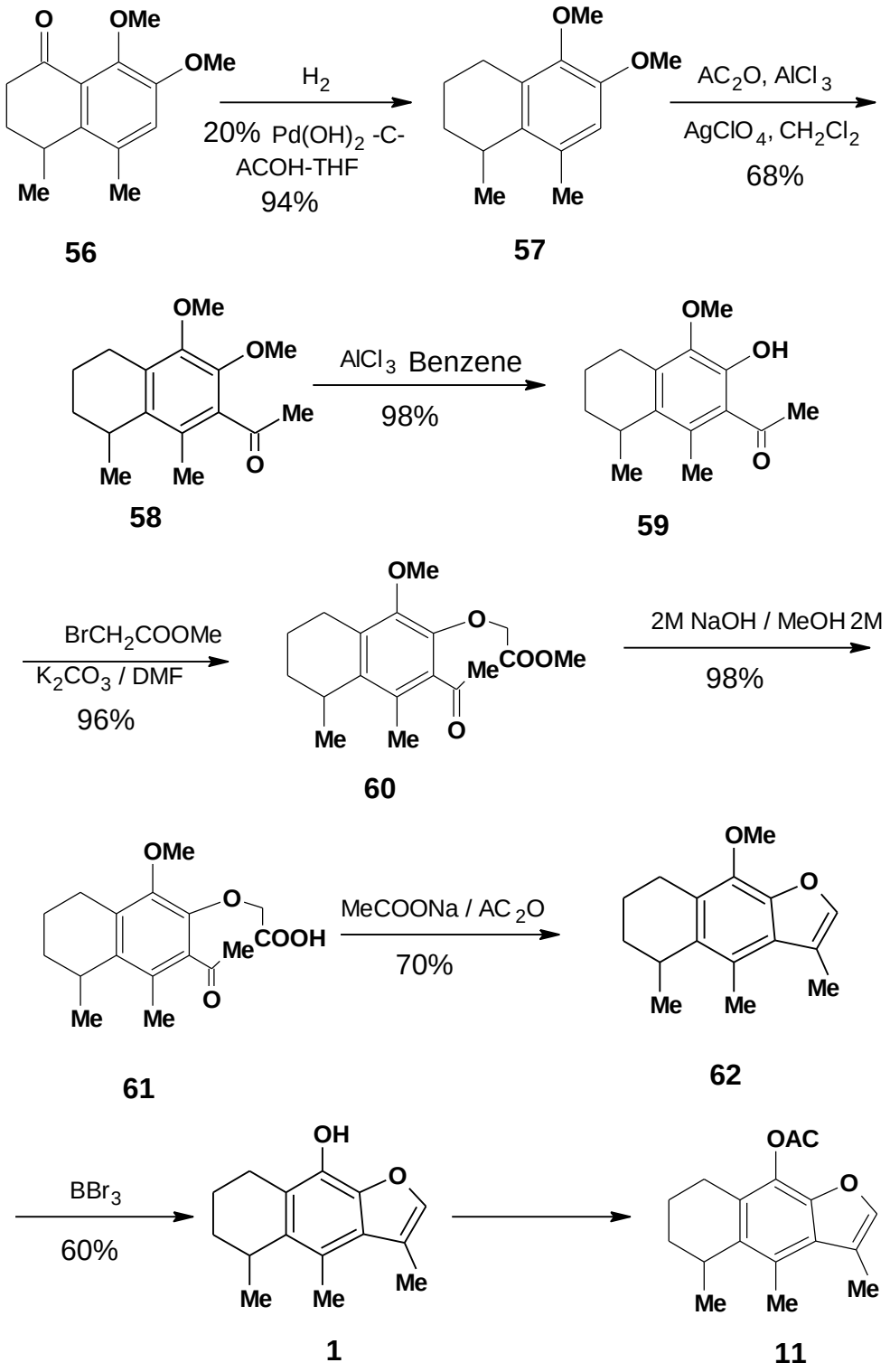




Scheme 9. Synthesis of the optically active cacalol **1** from 4,5-epoxy-2 **48**

The optically active 4,5-epoxy-2 **48** is made to react with 3,4-dimethoxy-toluene **49** to yield a mixture of **50** and racemic ester **51 (Scheme 9).** Oxidation yields pure **50** whose tosylate **52** on hydrogenation in methanol affords **53.** Metal hydride reduction produces the ester **54** which on alkaline hydrolysis yields the acid **55 i**n quantitative yield. The cyclization of the acid **55** to cacalol **1** is described in **Scheme 10.**

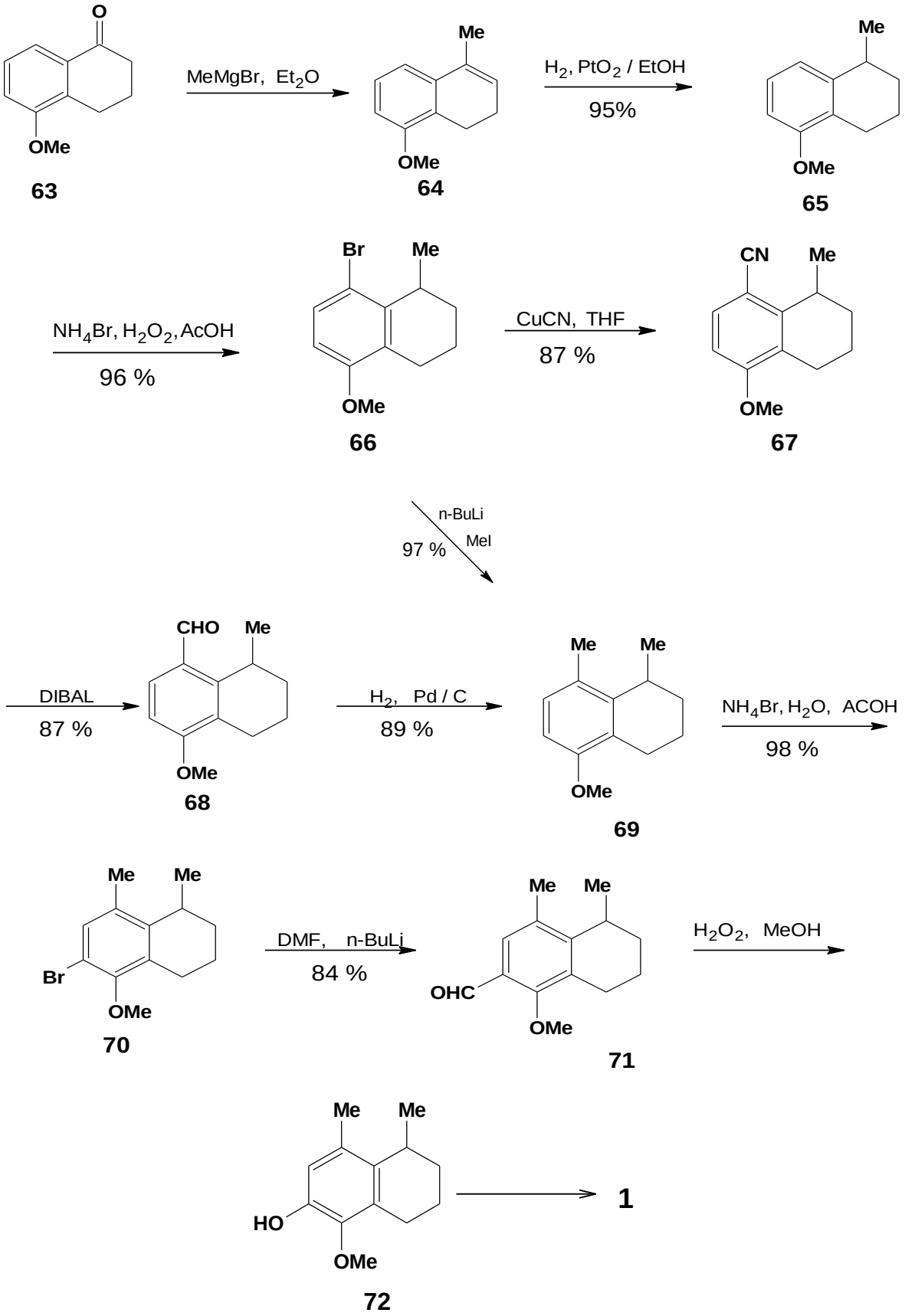
The cyclization of the acid **55** with phosphorous pentoxide in methane sulfonic acid yields the tetralone **56** which is converted to tetralin **57** by hydrogenolysis. Acetylation of **57** following the method of Mukaiyama (Mukaiyama etal., 1991) furnishes **58.** $AlCl_3$–mediated selective demethylation (Akita etal., 1981) leads the formation of the product **59** which on methoxy carbonylation produces the ester **60** whose conversion into acid **61** is achieved by alkaline hydrolysis. Treatment of the acid **61** with sodium acetate and acetic anhydride produces furotetralin **62** which undergoes demethylation with boron tribromide to furnish synthetic cacalol (S)**1** whose (S) acetate **11** is obtained by acetylation.



Scheme 10. Synthesis of cacalol 1 from tetralone 56

6. Synthesis of Cacalol by Banerjee, Melean, Mora, Cabrera and Laya

A formal total synthesis of cacalol **1** has been developed by Banerjee and collaborators (Banerjee etal., 2007). The synthetic route has been depicted in **Scheme 11.**

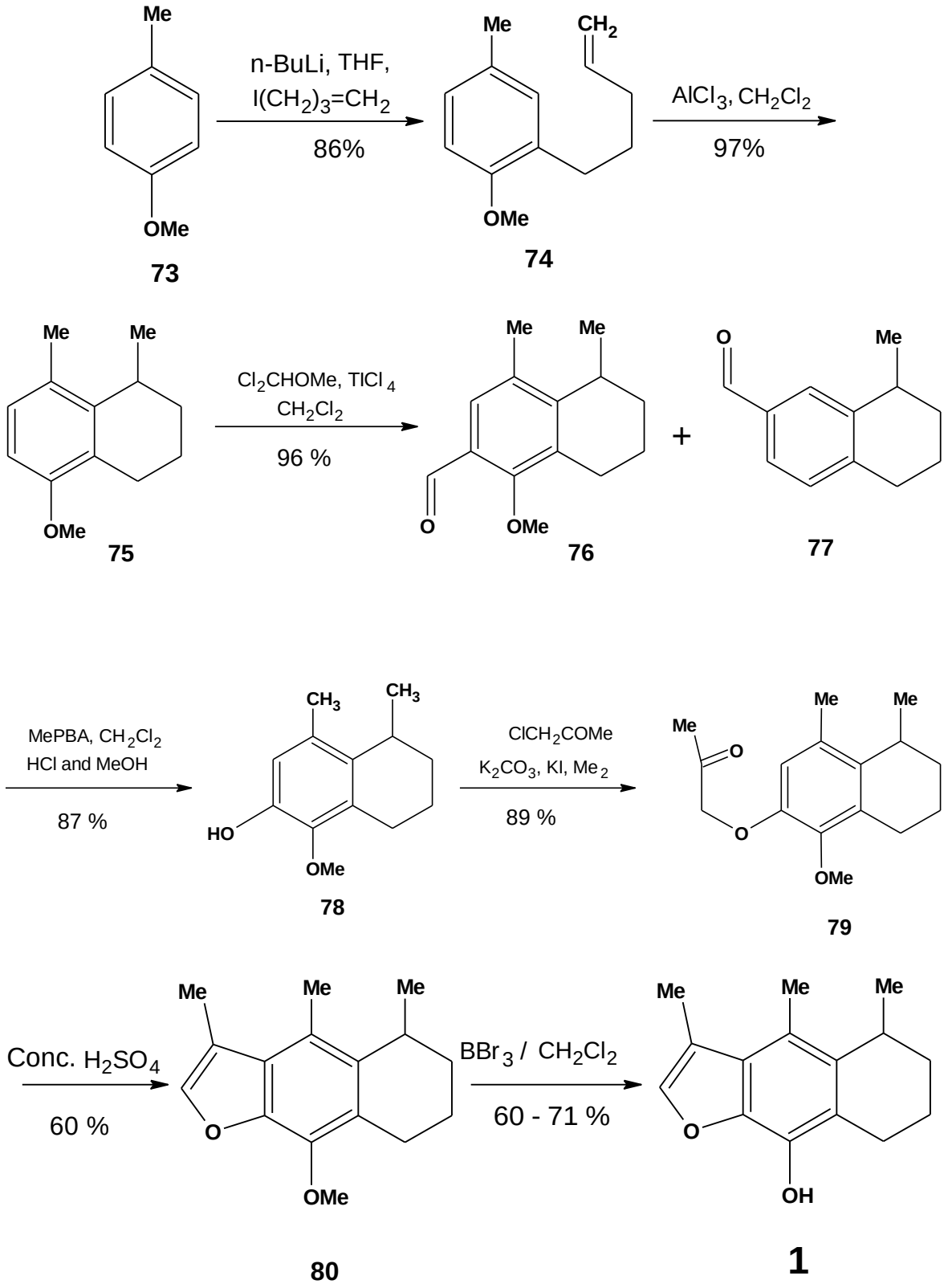


Scheme 11. Transformation of the 5-methoxy tetralone 63 to tetraol 72. Whose transformation to cacalol 1 has been reported por (Garofalo etal., 1999)

The commercially available 5-methoxy-1-tetralone **63** is treated with methylmagnesium bromide. The resulting product on acid hydrolysis yields the reported dihydronaphthalene **64** (Poon &Banerjee, 2006) which on catalytic hydrogenation over PtO_2 in ethanol affords tetralin **65** (Harrowven & Dainty, 1997). Bromination of **65** with ammonium bromide and hydrogen peroxide (Krishna Mohan etal., 2004) yields bromotetralin **66** whose conversion to cyanotetralin **67** has been achieved by treatment with cuprous cyanide. Reduction with diisobutylaluminium hydride (DIBAL) affords aldehyde **68** which on catalytic hydrogenation yields dimethyltetralin **69 .** The dimethyltetralin **69** has also been achieved by the treatment of the bromotetralin **66** with n-BuLi in hexane followed by the reaction with methyl iodide. The metalation procedure not only shortens (two steps) the reaction sequence but also considerably improves the yield of the dimethyltetralin **69.** In order to achieve the conversion of the tetralin **69** into cacalol**,** the tetralin is brominated by the already mentioned procedure (Krishna Mohan etal., 2004). The resulting compound **70** on treatment with dimethylformamide in presence of n-BuLi in hexane produces aldehyde **71** which with hydrogen peroxide in acidic methanol (Matsumoto etal., 1984) undergoes rearrangement to the already reported tetraol **72** (Garofalo etal., 1999). As the transformation of tetraol **72** to cacalol **1** in has been already been reported (Garofalo etal., 1999), an alternative approach for the synthesis of tetraol **72** constitutes a formal total synthesis of cacalol.

7. Synthesis of Cacalol by Kedrowski, Hoppe

A simple synthesis of cacalol **1** has been developed by Kedrowski and Hoppe (Kedrowski & Hoppe, 2008). The synthesis proceeds in seven steps affording an overall yield 21-25%. The synthetic details are described in **Scheme 12.** The *ortho*-lithiation of 4-methylanisole **73** and alkylation of the resulting product with 5-iodo- -1-pentane (Padwa & Kamigata, 1977) afford alkene **74** which on intramolecular Friedel-Crafts alkylation by treatment with chromium chloride in methylene chloride form the reported tetralin **75** (Banerjee etal., 2007; Garofalo etal., 1999). Formylation with α,α-dichloromethyl methyl ether and titanium tetrachloride furnishes a mixture of regioisomeric aldehydes **76** and **77** in proportion 14:1 as determined by ^{1}NMR and GCMS analyses. These aldehydes for having the same mobility on silica gel are inseparable by flash chromatography. Baeyer-Villiger oxidation (Krow, 1993) of the mixture of aldehydes yields the already reported phenol **78** (Hoffman & Pandian, 1979, Banerjee etal., 2007). The phenol **78** on alkylation with chloroacetone affords the ketone **79** which on treatment with sulfuric acid undergoes cyclodehydration yielding the cacalol methyl ether **80.** Finally the cleavage of methyl ether of **80** with boron tribromide affords (±)-cacalol.



Scheme 12. A short synthesis of cacalol 1 from 4-methylanisole **73**

The approach is interesting because it describes a short steps synthesis of the tetralone **75** .The yield obtained is superior compared to other published methods. The attractive aspects of the present synthesis are two-step annulation of **73** to afford **75**, a two-step oxygenation **75** to give **78** and two-step annulation of **78** to yield **80.**

8. Conclusions

The present review describes several approaches for the synthesis of cacalol. The applications of several important organic reactions e.g. Clemmensen reduction, Fries rearrangement, Friedel -Crafts ortho-lithiation, Baeyer Villiger oxidation, etc can be observed during the realization of the synthesis of cacalol. The importance of Eaton's reagent (phosphorous pentoxide and methane sulfonic acid) for cyclization has been mentioned. The acetylation by the method of Mukaiyama is noteworthy.

Acknowledgments

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Authors contributions

Dr. Ajoy Banerjee and Dr. Elvia V. Cabrera were responsible for study design and revising. Dr. Lisbeth Mendoza reviewed the manuscript and provided valuable comments. Ms. Alexis Maldonado and Prof. Liadis Bedoya revise it.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed consent

Obtained.

Ethics approval

The Publication Ethics Committee of the Canadian Center of Science and Education.

The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

Provenance and peer review

Not commissioned; externally double-blind peer reviewed.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Data sharing statement

No additional data are available.

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