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A Review on Phoracantholide I Derivatives

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Abstract: *Phoracantholide I is a ten-membered lactone ring found in the highly odoriferous secretion from the metasternal gland of the eucarypt longicorn, Phoracanthasynonyma, as the defence fluid. Moore and Brown reported the elucidation of their structures, with the exception of their stereochemistry at the C-9 position. Although multiple (±)-l and (±)-2 syntheses have been reported, optically active 1 and 2 have yet to be synthesized, thus the stereochemistry at the C-9 site is unknown. The goal of this review is to look into recent breakthroughs in the field of synthesis of Phoracantholide I.es.*

Keywords: Phoracantholide, Lactone, Natural products

I. INTRODUCTION

Various researchers have been working on isolating substituted lactones from various natural sources as natural products for the past few years[1-4]. Phoracantholide **I** 1, Phoracantholide **J** 2, Phoracantholide **K** 3, Phoracantholide **M** 4, and Phoracantholide **O** 5 have been identified from the metasternal gland of the eucalypt longicorn Phoracanthasynonyma beetles as a protective secretion[5-6](**Fig. 1**).

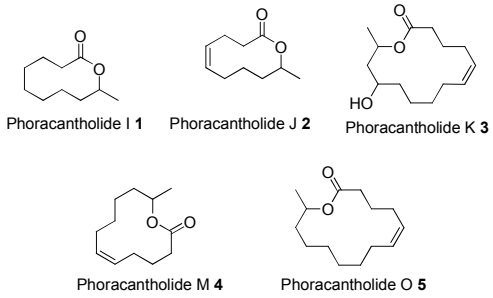

Figure 1: Derivatives of Phoracantholide

Phoracantholide I **1** and Phoracantholide J **2** are ten-member methyl-substituted lactones among the phoracantholide derivatives. Phoracantholide I **1**, on the other hand, has a saturated ring system in its structure, but Phoracantholide J **2** only has one double bond (**Fig. 1**). Because (S)-and (R)- Phoracantholide I are natural products (**Fig. 2**), world-chemists are interested in developing their synthetic methods. As a result, different synthetic procedures for the racemic form of Phoracantholide I (**Fig. 2**) have been published in the literature.

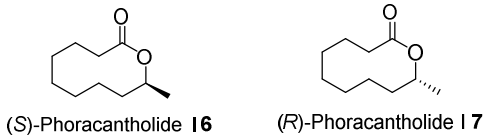

Figure 2: Phoracantholide I

II. REVIEW OF LITERATURE

In the literature, there are few reports available for the asymmetric synthesis of Phoracantholide I **1**[7-12]. However, almost all of the methods reported for the asymmetric synthesis of Phoracantholide I **1** involve either classical resolution of racemates or a chiral pool approach or use of inaccessible costly and toxic metal catalyst which are described below.

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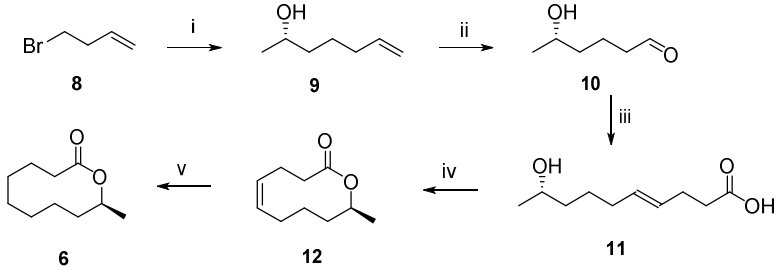
2.1 Schulz's Approach[7]

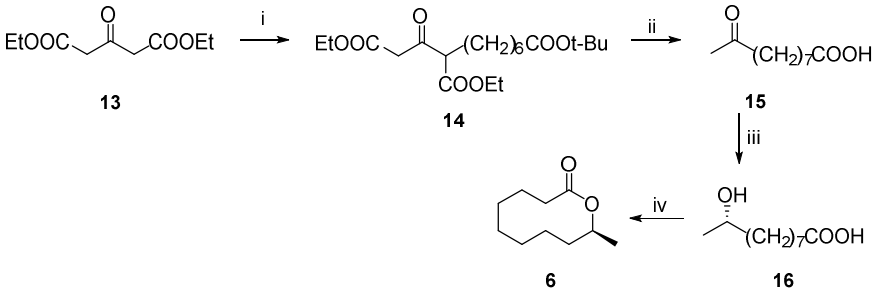
The alcohol **9** was made by reacting homoallyl bromide (4-bromo-1-butene) **8** with (S)-propylene oxide in this method. The aldehyde **10** is produced through the Lemieux-Johnson oxidation of the double bond of **9**. Wittig reaction with (3-carboxypropyl) triphenyl phosphoniumylide transformed aldehyde **10** to hydroxyl acid **11**. The chemical (S)-phoracantholide J **12** is obtained by cyclizing hydroxyl acid **11** using the Corey-Nicolaou technique. Finally, hydrogenation of **12** yields 75 percent of the (S)-phoracantholide I **6** (**Scheme 1**).



Scheme 1: Reagents and reaction conditions: (i) (S)-propylene oxide, Mg, Et_2O CuCN, 0° C, 12 h, 91 %; (ii) K_2OsO_4, $NaIO_4$, dioxane, H_2O, 0° C, 2 h, 71 %; (iii) nBuLi, NaHMDS, $[Ph_3P(CH_2)_3COOH]Br$, THF, -78° C to RT, 2 h, 69 %; (iv) Dipyridiyldisulfide, $AgClO_4$, toluene, reflux, 14 h, 26 %; (v) H_2, 10 % Pd/C, MeOH, 5 h, 75 %.

2.2 Naoshima's Approach[8]

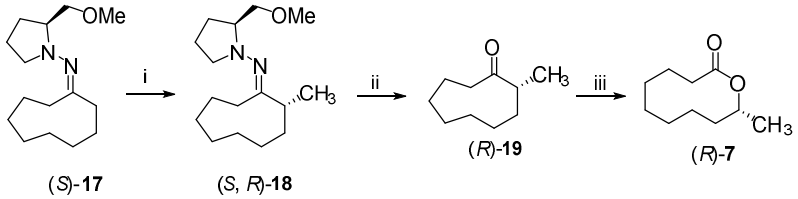
In this method, the diethyl 3-oxoglutarate **13** was regioselectively alkylated with t-butyl 7-bromoheptanoate to get the monoalkylated 3-oxoglutarate **14**, which was then decarboxylated to provide keto acid **15**. In an aqueous solution of KCl, the **15** was treated to a microbial asymmetric reduction using baker's yeast, yielding an optically pure (S)-alcohol **16** in a 46 percent yield. Lactonization of (S)-alcohol **16** yielded (S)-phoracantholide I **6** with a yield of 44 percent (**Scheme 2**).



Scheme 2: Reagents and reaction conditions: (i) t-Butyl 7-Bromoheptanoate, $Mg(OEt)_2$, 88 %; (ii) 15 % NaOH, Reflux, 15 h, 89 %; (iii) baker's yeast, D-glucose, 2 % KCl, 46 %; (iv) triphenylphosphine, dipyridyl disulfide, $AgClO_4$, Benzene, Reflux, 8 h, 44 %.

2.3 Enders's Approach[9]

The chiral (S)-1-amino-2-(methoxymethyl) pyrrolidinehydrazone of cyclononanone**17** was used to create (R)-phoracantholide I **7**. The alkylation of compound **17** with methyl iodide yielded 84 percent of α-substituted hydrazone (S, R)-**18**.The chiral ketone (R)-19 was obtained via ozonolysis of (S, R)-18 in CH2Cl2 at -78 oC. The (R)-phoracantholide I **7** was obtained in 74 percent of the time by oxidising (R)-**19** with m-chloroperbenzoic acid (m-CPBA) at room temperature (**Scheme 3**).



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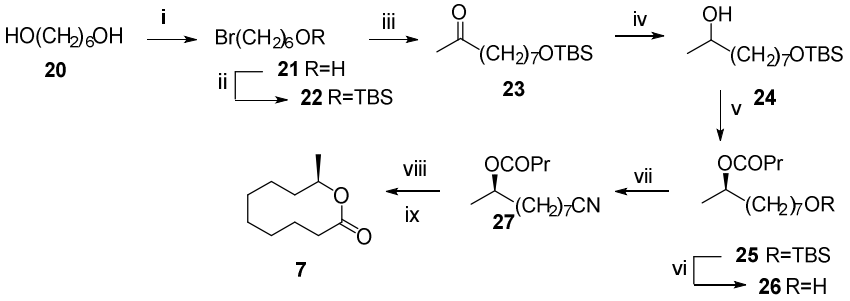
Scheme 3: Reagents and reaction conditions: (i) a) LDA, THF, 0° C, 4 h; b) MeI, -100° C, 16 h 85 %; (ii) O_3, CH_2Cl_2, -78° C, 70 %; (iii) m-CPBA, 4 days, 74 %.

2.4 Chattopadhyay's Approach[10]

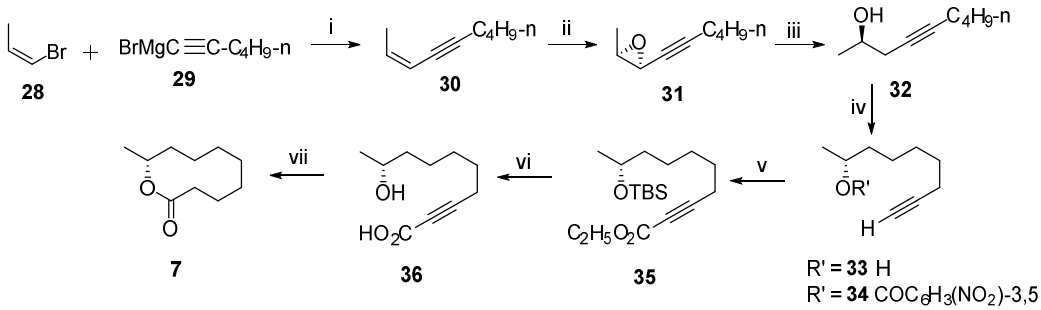
The hexane 1, 6 diol molecule **20** was partly brominated in this method to yield the compound **21**, which was then silylated to yield the silylated compound **22**. The ketone **23** was obtained via α-alkylation of methyl acetoacetate with silylated molecule **22** followed by alkaline hydrolysis. The crucial carbinolsynthon**24** was obtained by reducing ketone **23** with $NaBH_4$. This was then treated to trans-acieration catalysed by porcine pancreatic lipase (PPL), yielding acierated product**25**, which was then distilled to get alcohol compound **26**. The cynohydrin compound **27** was obtained via tosylation of compound **26** followed by treatment with KCN. The (R)-phoracantholide I **7** was obtained via acidic hydrolysis of cynohydrine, de-esterification with alkali, and subsequent acidification (**Scheme 4**).



Scheme 4: Reagents and reaction conditions: (i) 48 % HBr, benzene, reflux, 30 h, 60 %; (ii) TBSCl, triethylamine, DMAP, CH_2Cl_2, RT, 14 h, 88 %; (iii) $CH_3COCH_2CO_2Me$, NaOMe, MeOH, Aqueous NaOH, 2N HCl, 18 h, 48 %; (iv) $NaBH_4$, MeOH, RT, 1 h, 78 %; (v) PPL, TFEB, diisopropyl ether, RT, 18 h, 26 %; (vi) Bu_4NF, THF, RT, 15 h, 84 %; (vii) p-TsCl, pyridine, CH_2Cl_2, KCN, DMSO, 20 h, 68 %; (viii) Conc. HCl, reflux, 16 h; (ix) Alcoholic KOH, 16 h, 61 %.

2.5 Katsuki's Approach[11]

A critical intermediary in this method is chiral epoxide, which was made by epoxidating alkyne molecule **30**. The chiral epoxide **31** is formed by epoxidating chemical **30** using Mn-salen catalyst in the presence of NaClO. Lithium aluminium hydride (LAH) was used to convert the chiral epoxide **31** to homopropargylic alcohol **32**. The terminal acetylene molecule **33** was obtained by treating the homopropargylic alcohol **32** with potassium 3-aminopropylamide (KAPA), which was then transformed to the dinitrobenzoate**34**. The ester compound **35** was created by protecting dinitrobenzoate with t-butyldimethylsilyl (TBS) ether and then ethoxycarbonylating terminal acetylene. The hydroxyl acid **36** was obtained via hydrogenation, desilylation, and hydrolysis of ester molecule **35**.The hydroxyl acid **36** was obtained via hydrogenation, desilylation, and hydrolysis of ester molecule **35**. Finally, employing the Yamaguchi process, the hydroxyl acid **36** was transformed to the (R)-phoracantholide I **7** with a yield of 41% (**Scheme 5**).



Scheme 5: Reagents and reaction conditions: (i) $Pd(PPh_3)_4$, -78° C, 35 % (ii) Mn-salen , NaClO, 80 % (iii) LAH, THF, O° C, 81 % (iv) $KNH(CH_2)_3NH_2$, 79 % (v) (a) TBSCl, imidazole, 94 % (b) BuLi, $ClCOOC_2H_5$, 70 % (vi) (a) H_2, Pd/C, 0° C, 96 % (b) Bu_4NF, THF, 95 % (c) THF, aq. NaOH, 92 % (vii) 3, 4, 5-$Cl_3C_6H_2COCl$, DMP, 41 %.

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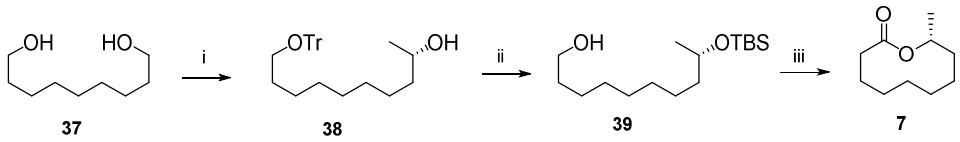
2.6 Jone's Approach[12]

The main step in this method is to induce chirality into a functionalized aldehyde by utilising a chiral arene chromium tricarbonyl-based catalyst to mediate the addition of dimethyl zinc. The chiral secondary alcohol **38** was produced by adding dimethyl zinc to the aldehyde using a chiral arene chromium tricarbonyl based catalyst. The protected chiral secondary alcohol **39** was obtained by protecting the secondary alcohol **38** with t-butyldimethylsilyl (TBS) ether and then deprotecting the trityloxy group with boron trichloride. The (R)-phoracantholide I **7** was obtained in a 75 percent yield by converting the exposed alcohol **39** to carboxylic acid, followed by deprotection of chiral secondary alcohol and macrolactonisation (**Scheme 6**).



Scheme 6: Reagents and reaction conditions: (i) a) TrCl, Et_3N, DMF, 98 % b) Dess-martin periodinane, CH_2Cl_2, 99 % c) Me_2Zn, chromium catalyst, toluene 0^o C, 84 % (ii) a) TBSOTf, 2, 6 lutidine, 97 % b) BCl_3, CH_2Cl_2, 96 % (iii) a) PCC, DMF, RT, 95 % b) HF-Py, 100 % c) Ph_3P, Aldrithiol d) $AgClO_4$, 75 %.

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