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3-METHYL-2,5-DIHYDRO-1-BENZOXEPINS AND 3-METHYL-2,5-DIHYDROOXEPINS

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Abstract – Three preparative procedures of seven-membered *O*-heterocyclic 3-methyl-2,5-dihydro-1-benzoxepin derivatives are summarized. For the *Z*-selective formation of C=C double bond, the first approach used the Grubbs ring-closing methathesis, the second approach used the intramolecular Mitsunobu cyclization of corresponding *Z*-diols prepared using Stille coupling of the benzyl bromide with (*Z*)-vinylstannane, and the third approach used the revised synthesis of the *Z*-diols using *Z*-selective Ando-Horner-Emmons condensation and the following DIBAL-H reduction. Some naturally occurring 3-methyl-2,5-dihydro-1-benzoxepin derivatives were synthesized using these procedures. In these studies, some preparations of 3-methyl-2,5-dihydrooxepin derivatives were also developed.

INTRODUCTION

Few preparative procedures of seven-membered *O*-heterocyclic 3-methyl-2,5-dihydro-1-benzoxepin derivatives (**1**) have been reported. The *Z*-selective formation of C=C double bond was need in the unstable position, none-conjugated with the π electron of benzene or the none-bonding electrons on the ring oxygen. The first approach was the Grubbs ring-closing methathesis for the *Z*-selective cyclization.[1] The second approach was our method which used the intramolecular cyclization of corresponding *Z*-diols prepared by Stille coupling of the benzyl bromide with (*Z*)-vinylstannane.[2] For the third approach, we revised the synthesis of the *Z*-diols using *Z*-selective Ando-Horner-Emmons condensation and the following DIBAL-H reduction.[3] In these studies, some preparations of 3-methyl-2,5-dihydrooxepin derivatives (**2**) were also developed *via* the ring expansions of 2-isopropenyl- cyclopropane-1-carbaldehydes and 2-isopropenyl-2,3-dihydrofurans.

Figure 1. 3-Methyl-2,5-dihydro-1-benzoxepins (**1**) and 3-Methyl-2,5-dihydrooxepins (**2**)

Naturally Occurring 3-Methyl-2,5-dihydro-1-benzoxepins)

Many naturally occurring 3-methyl-2,5-dihydro-1-benzoxepins (**1**), as shown in the structure in Figure 1, were isolated from various kinds of plants, especially from Japanese liverwort, *Radula* sp., as shown in Figure 2.[4a-f]

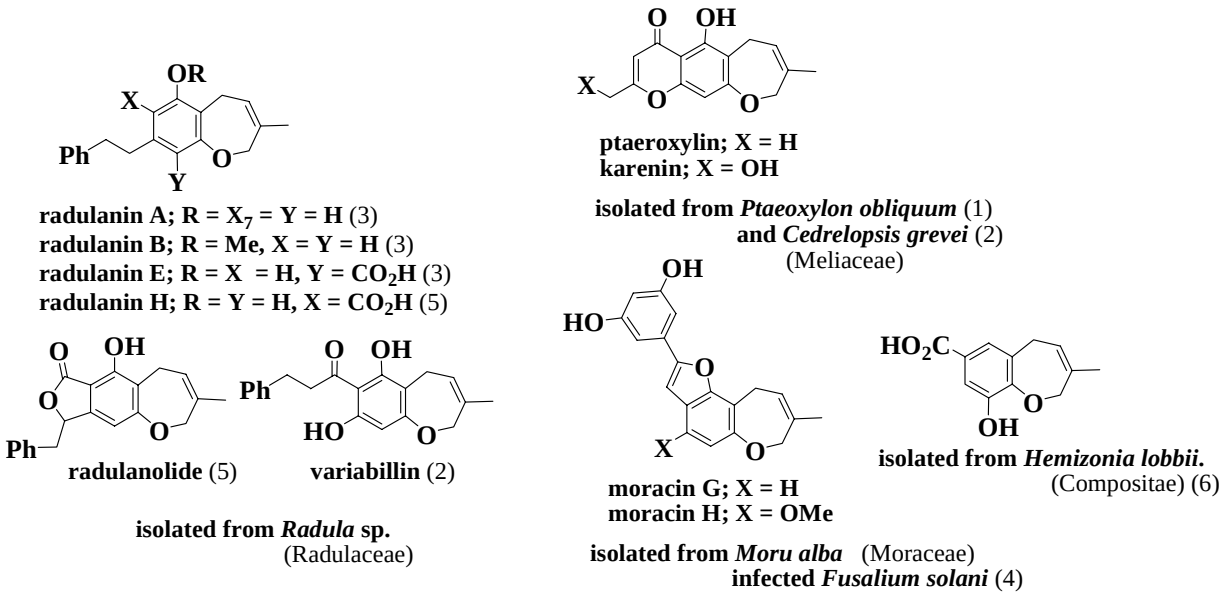
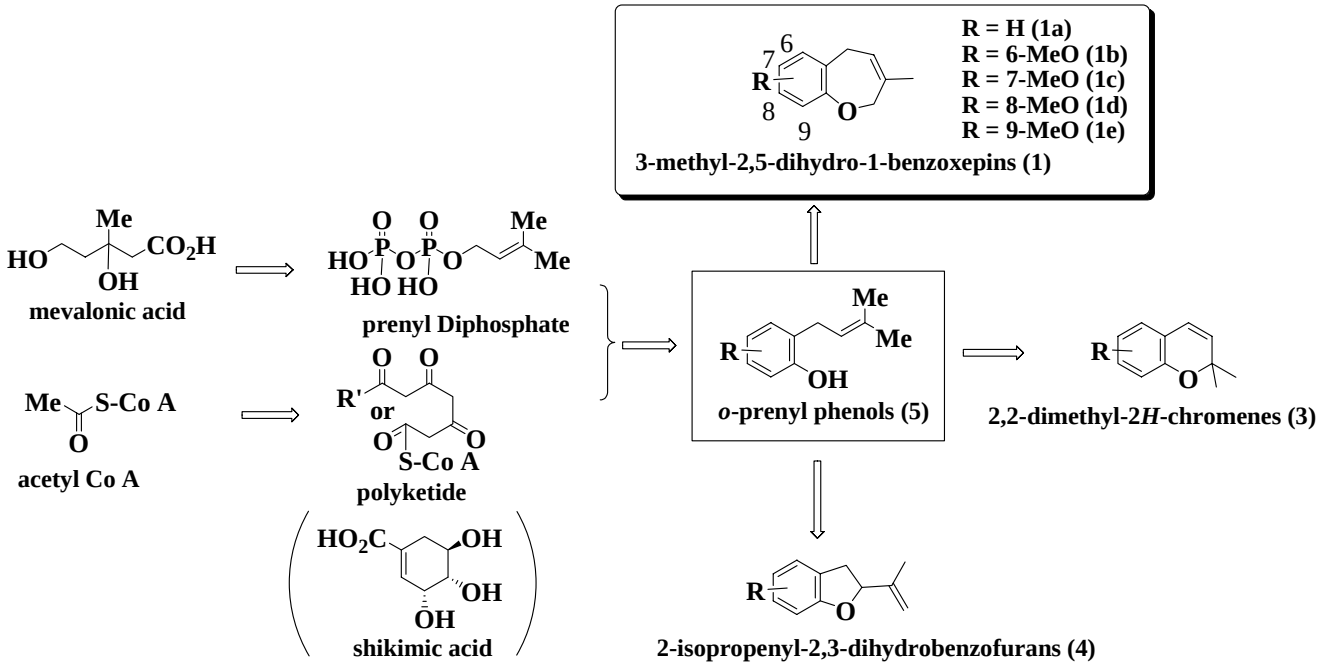


Figure 2. Naturally Occurring 3-Methyl-2,5-dihydro-1-benzoxepin Derivatives

In 1966, D. H. A. Taylor *et al.*[4a] reported the first isolation of a naturally occurring 3-methyl-2,5-dihydro-1-benzoxepin derivative, ptaeroxylin, from *Ptaeroxylon obliquum*, where the angular oxepinochromone structure of 10-hydroxy-3,7-dimethyl-2,5-dihydropyrano[2,3-*g*]benzoxepin- 9-one was proposed, but the structure was soon corrected to the linear oxepinochromone structure of 6-hydroxy-3,9-dimethyl-2,5-dihydropyrano[3,2-*h*]benzoxepin-7-one by P. H. McCabe *et al.*,[4b] where a new linear oxepinochromone karenin, 6-hydroxy-9-hydroxymethyl-3-methyl-2,5-dihydropyrano[3,2-*h*]-benzoxepin-7-one was isolated and the desoxykarenin was shown to be identical with ptaeroxylin. I. T. Eshiett *et al.*[4c] reported the isolation of ptaeroxylin from *Cedrelopsis grevei*, botanically close to *Ptaeroxylon.* Y. Asakawa *et al.*[5a-f] isolated many 3-methyl-2,5-dihydro-1-benzoxepin derivatives, radulanin A, B, E, H, radulanolide, and variabilin, from Japanese moss *Radula* sp. M. Takasugi *et al.*[6]

isolated two oxepinobenzofuran derivatives, moracin G, H, from *Morus alba* L. (Moraceae) infected with *Fusarium solani*. M. Breuer *et al.*[7] isolated an 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid, from *Hemizonia lobbii* (Compositae). S. McCormick *et al.*[8] also isolated three oxepino-flavonoids, 7-(3,4-dihydroxyphenyl)-10-hydroxy-3-methyl-2,5,7,8-tetrahydropyrano[2,3-*g*]-benzoxepin-9-one (7,8-dihydrooxepinoeriodictyol), 8,10-dihydroxy-7-(3,4-dihydroxyphenyl)-3-methyl-2,5,7,8-tetrahydropyrano[2,3-*g*]benzoxepin-9-one (7,8-dihydrooxepinodihydroqurcetin), 1-(6,8-dihydroxy-3-methyl-1-benzoxepin-7-yl)-3-(3,4-dihydroxyphenyl)propa-2-en-1-one (3',4'-dihydro-oxepino- 6'-hydroxybutein), from *Wyethia* sp. (Compositae).



Scheme 1. Naturally Occurring O-heterocyclic Compounds Derived from *o*-Prenylphenols (**4**)

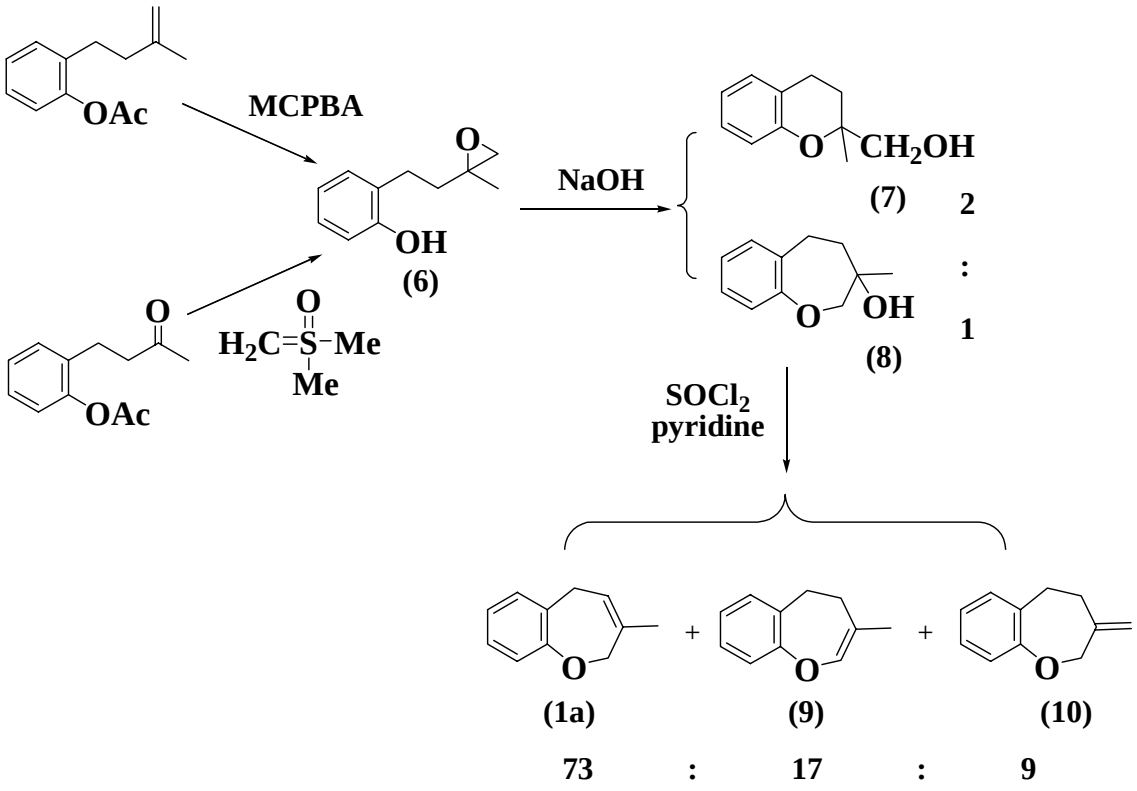
They might be biogenetically derived from *o*-prenylphenols (**5**); an oxidative seven-membered cyclization gives corresponding 3-methyl-2,5-dihydro-1-benzoxepins (**1**); while a similar five- or six-membered cyclization gives corresponding 2-isopropenyl-2,3-dihydrobenzofurans (**4**) or 2,2-dimethyl-2*H*-chromenes (**3**). Because most of the benzene ring of naturally occurring 3-methyl-2,5-dihydro-1-benzoxepins (**1**) might be derived *via* polyketides derived from acetyl coenzyme A, most of naturally occurring 3-methyl-2,5-dihydro-1-benzoxepins (**1**) have some oxygen-functions on the benzene ring, especially on 6 and/or 8 position. For the synthesis of naturally occurring 3-methyl-2,5-dihydro-1-benzoxepins (**1**), the effective preparative methods of 3-methyl-2,5-dihydro-1-benzoxepins (**1**), especillay methoxy-substituted 3-methyl-2,5-dihydro-1-benzoxepins (**1b-e**) were needed.

RESULTS AND DISCUSSION

1 REPORTED APPROACHES FOR 3-METHY-2,5-DIHYDRO-1-BENZOXEPINS

1-1 DEHYDRATION OF 3-METHYL-2,3,4,5-TETRAHYDRO-1-BENZOXEPIN-3-OL

In 1980, K. Baird *et al.*[9] first reported the formation of seven-membered 3-methyl-2,5-dihydro-1-benzoxepin by dehydration of 3-methyl-2,3,4,5-tetrahydro-1-benzoxepin-3-ol (**8**), a minor cyclized product from alkaline cyclization of *o*-(3,4-epoxy-3-methylbutyl)phenol (**6**), which gave an unseparable mixture of 3-methyl-2,5-dihydro-1-benzoxepin (**1a**), 3-methyl-4,5-dihydro-1-benzoxepin (**9**), and 3-methylene-2,3,4,5-tetrahydro-1-benzoxepin (**10**) in dehydration using thionyl chloride in pyridine.

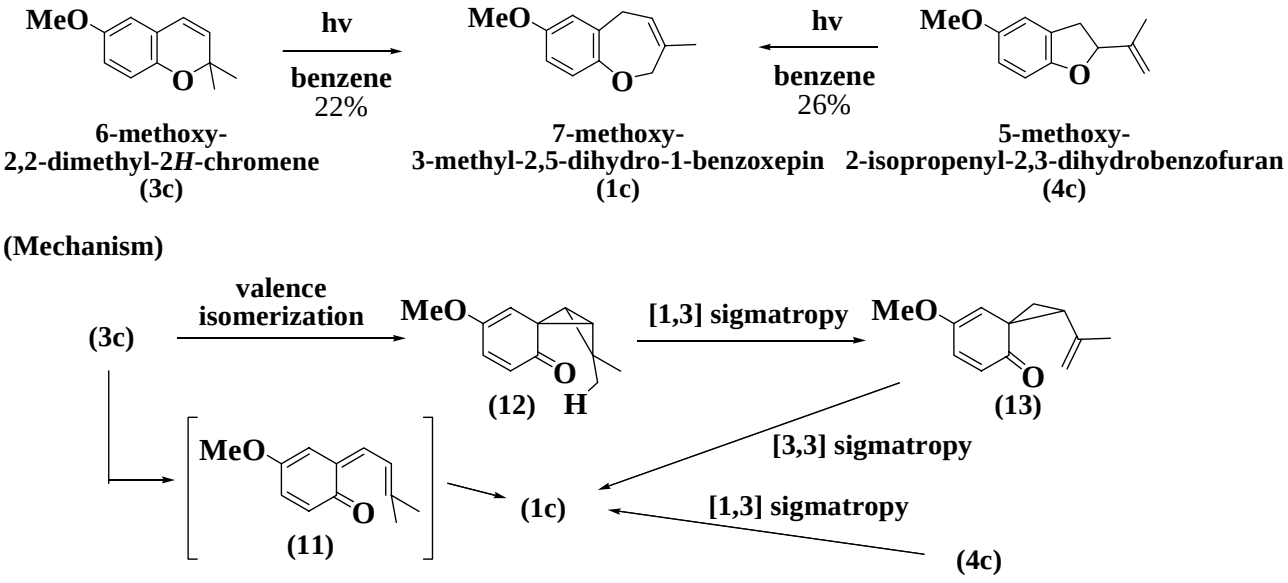


Scheme 2. Dehydration of 3-Methyl-2,3,4,5-tetrahydro-1-benzoxepin-3-ol (**8**)

1-2 PHOTO-RING EXPANSION OF 2,2-DIMETHYL-2*H*-CHROMENES AND 2-ISOPROPENYL-2,3-DIHYDROBENZOFURANS

The second formation was the photochemical ring-expansion of 2,2-dimethyl-2*H*-chromene derivatives, reported by A. Chakrabarti *et al.*,[10] and F. Dallacker *et al.*[11]; the former reported the photochemical ring-expansion of some 3,3,5-trimethylpyrano[2,3-*a*]carbazoles giving corresponding 3,6-dimethyl-1,4-dihydroxepino[2,3-*a*]carbazoles and the latter reported the ring-expansion of 6-methoxy-

2,2,5,7,8-pentamethyl-2*H*-chromene giving 7-methoxy-3,6,8,9-tetramethyl-2,5-dihydro-1-benzoxepin. We also observed the similar photochemical ring-expansion of 6-methoxy- 2,2-dimethyl-2*H*-chromene (**3c**) and also of 5-methoxy-2-isopropenyl-2,3-dihydrobenzofuran (**4c**) giving 7-methoxy-3-methyl-2,5-dihydro-1-benzoxepin (**1c**).[12] However, these photochemical ring-expansions of six-membered 2,2-dimethyl-2*H*-chromene or five-membered 2-isopropenyl-2,3-dihydrobenzofuran derivatives were found to be restricted in compounds having an electron donating group at position 6 in 2*H*-chromenes or at position 5 in dihydrobenzofurans. A. Chakrabarti *et al.*[10] and F. Dallacker *et al.*[11] proposed the mechanism of the ring-expansions mechanism *via* a quinine-dimethylallid (**11**) in their papers, but there were no descriptions about the necessity of the electron donating methoxy substituent. So, we proposed another ring expansion mechanism starting the cleavage of the C-O bond. The electron donating substituent might accelerate the C-O bond cleavage. In 2-isopropenyl-2,3-dihydrobenzofuran **4c**, the 5-methoxy substituent accelerates the furan-ring C-O bond cleavage, and the following [1,3] sigmatropy might lead to to the corresponding benzoxepin **1c**. In 2,2-dimethyl-2*H*-chromene **3c**, the 6-methoxy substituent accelerates the pyran-ring C-O bond cleavage, and might cause valence isomerization to **12** and [1,3] sigmatropy giving an isopropenylcyclopropane intermediate **13**, and the following [3,3] sigmatropy might lead to the benzoxepin **1c**.

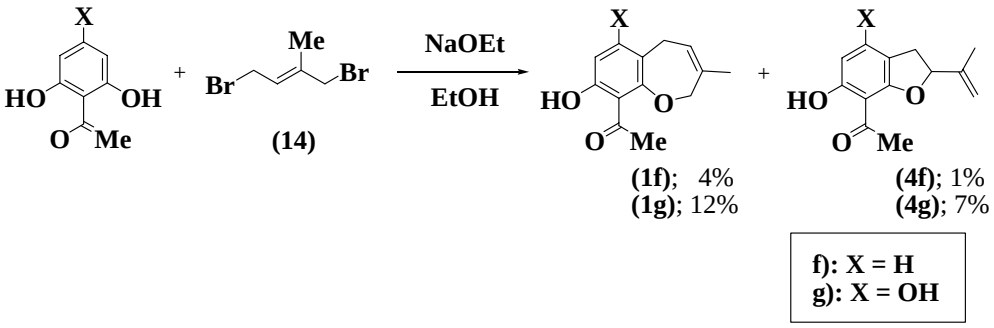


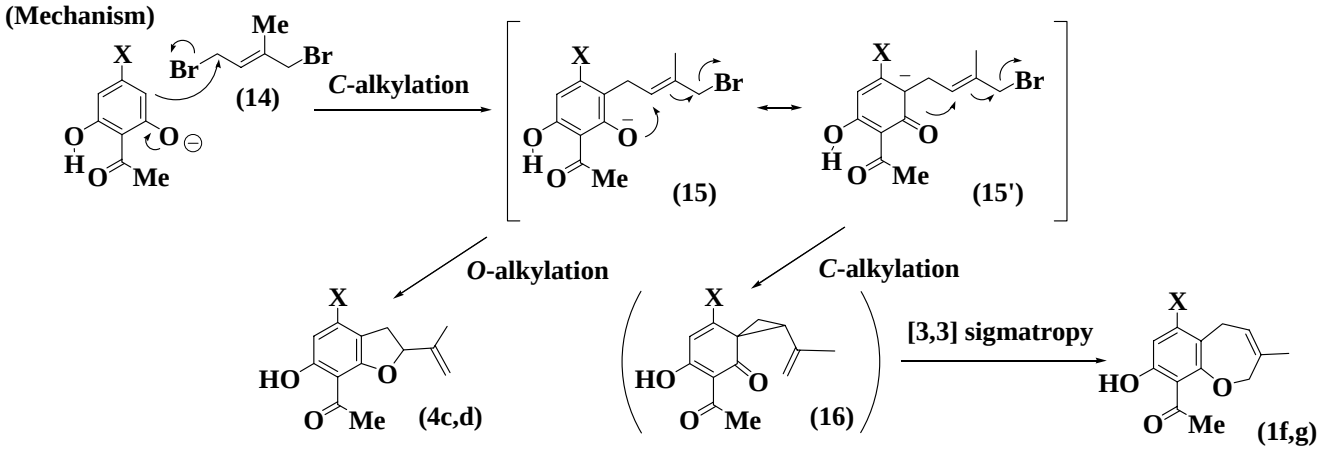
Scheme 3. Photo-ring Expansions of 6-Methoxy-2,2-dimethyl-2*H*-chromene (**3c**) or 2-Isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**4c**)

1-3 ONE-STEP SEVEN-MEMBERED CYCLIZATION

The third formation was the one-step cyclization of 2,6-dihydroxyacetophenone or 2,4,6-trihydroxy-acetophenone with 1,4-dibromo-2-methylbut-2(*E*)-ene giving a separable mixture of corresponding

seven-membered 9-acetyl-3-methyl-2,5-dihydro-1-benzoxepin-8-ols (**1f,g**) and five-membered 7-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-6-ols (**4f,g**).[13a,b] In these cyclizations, very interestingly, considerable amounts of seven-membered cyclization, having a *Z* double bond, were obtained from *E*-1,4-dibromo-2-butene (**14**). So, we proposed the mechanism, *via* [3,3] sigmatropy of isopropenylcyclopropane derivatives (**16c-f**), formed by double *C*-alkylation. However, these one-step cyclizations were also founded to be restricted in compounds having two hydroxyl groups at position 2 and 6 in acetophenones.





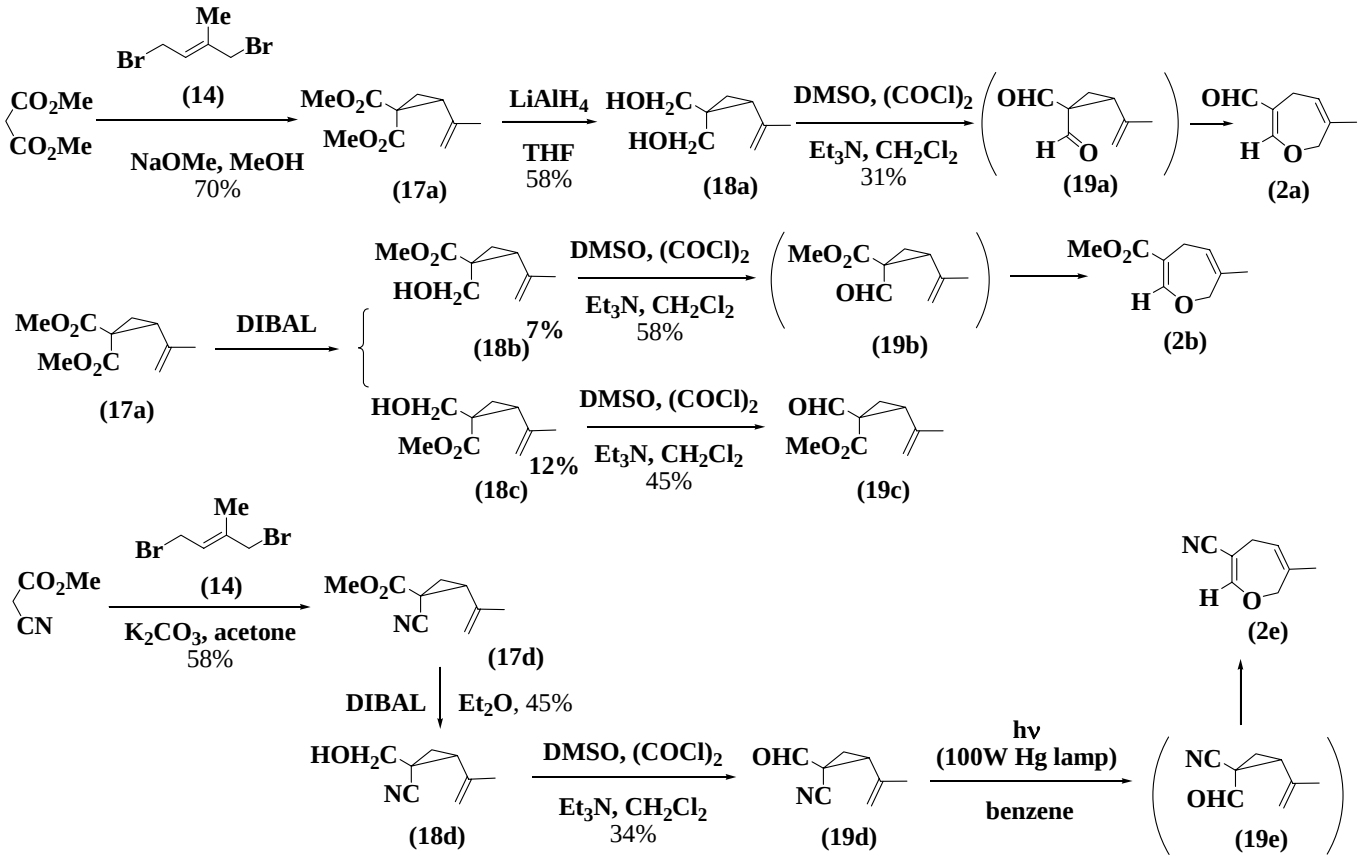
Scheme 4. One Step Cyclizations and Possible Mechanism

Inspite of the early isolation, only few synthetic reports might be due to the synthetic difficulties of the formation of the Z C=C double bond in the unstable seven-membered *O*-heterocyclic ring and the unstable 3,4-position, having no conjugation with lone-paired electrons on the ring oxygen or with π-electrons of the benzene ring.

2 RING EXPANSIONS FOR 3-METHYL-2,5-DIHYDROOXEPINS

2-1 RING EXPANSION OF 2-ISOPROPENYLCYCLOPROPANE-1-CARBALDEHYDE

In our one-step cyclization, described above, we studied a new ring expansion *via* isopropenylcyclopropane intermediate (**16**).[14] To prove the mechanism, an isopropenylcyclopropane intermediate, dimethyl 2-isopropenylcyclopropane-1,1-dicarboxylate (**17a**) was prepared from dimethyl malonate and 1,4-dibromeo-2-methyl-2(*E*)-butene (**14**). The conversion of dicarboxylate **17a** to the corresponding dialdehyde (**19a**) was studied by $LiAlH_4$ reduction giving dimethanol (**18a**) followed by Swern oxidation. Swern oxidation of dimethanol **18a** did not give the corresponding dialdehyde **19a**, but readily caused the ring expansion to give the corresponding seven-membered 6-methyl-4,7-dihydrooxepin-3-carbaldehyde (**2a**).



Scheme 5a. Preparations and Ring-expansions of Isopropenylcyclopropanecarbaldehydes (**19a,b,e**)

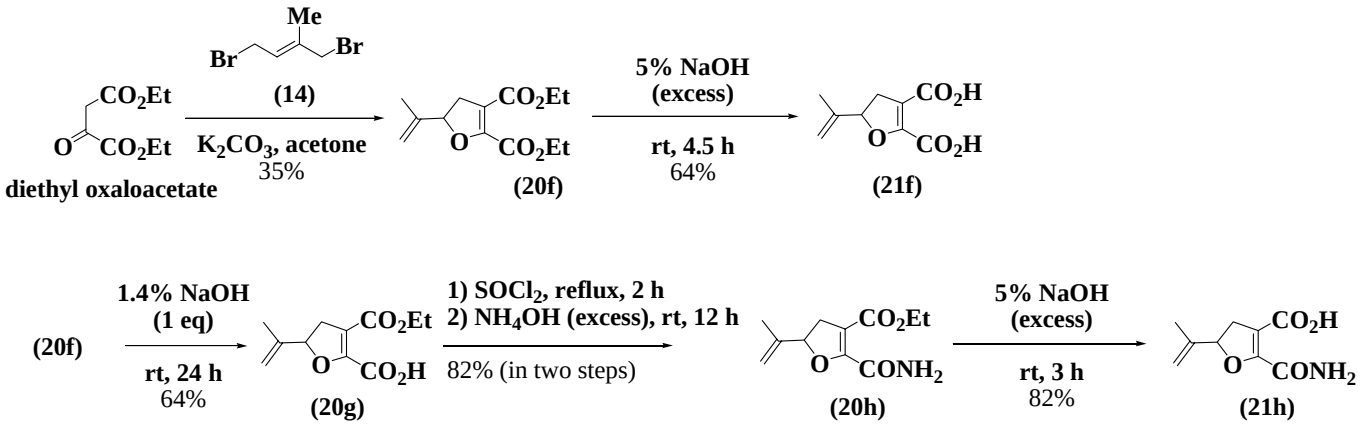
A DIBAL reduction of dicarboxylate **17a** gave a mixture of two stereoisomeric hydroxymethyl-carboxylates (**18b,c**). Swern oxidation of the isomer **18b** caused ring-expansion to give a seven-membered methyl 6-methyl-4,7-dihydrooxepin-3-carboxylate (**2b**), while Swern oxidation of the isomer **18c** gave a three-membered methyl 2-isopropenyl-1-formylcyclopropane-1-carboxylate (**19c**).

These might show the relation between the isopropenyl group and the hydroxymethyl was *cis* in the isomer **18b** and was *trans* in the isomer **18c**.

Similar reaction of methyl cyanoacetate with 1,4-dibromo-2-methyl-2(*E*)-butene (**14**) gave a single isomeric methyl 2-isopropenyl-1-cyanocyclopropane-1-carboxylate (**17d**). DIBAL reduction of **17d** gave a corresponding cyanomethanol (**18d**), and the following Swern oxidation gave a three-membered cyanoaldehyde **19d**. This might show that the aldehyde in the isomer **19d**, the methoxycarbonyl in **17d**, and the hydroxymethyl in **18d**, were all *trans* to the isopropenyl group. Also, the photoisomerization of three-membered cyanoaldehyde **19d** readily caused the *cis-trans* isomerization to give the corresponding seven-membered 6-methyl-4,7-dihydrooxepin-3-carbonitrile (**2d**) *via* **19e**.

2-2 RING EXPANSIONS OF ISOPROPENYLDIHYDROFURANCARBOXYLIC ACIDS

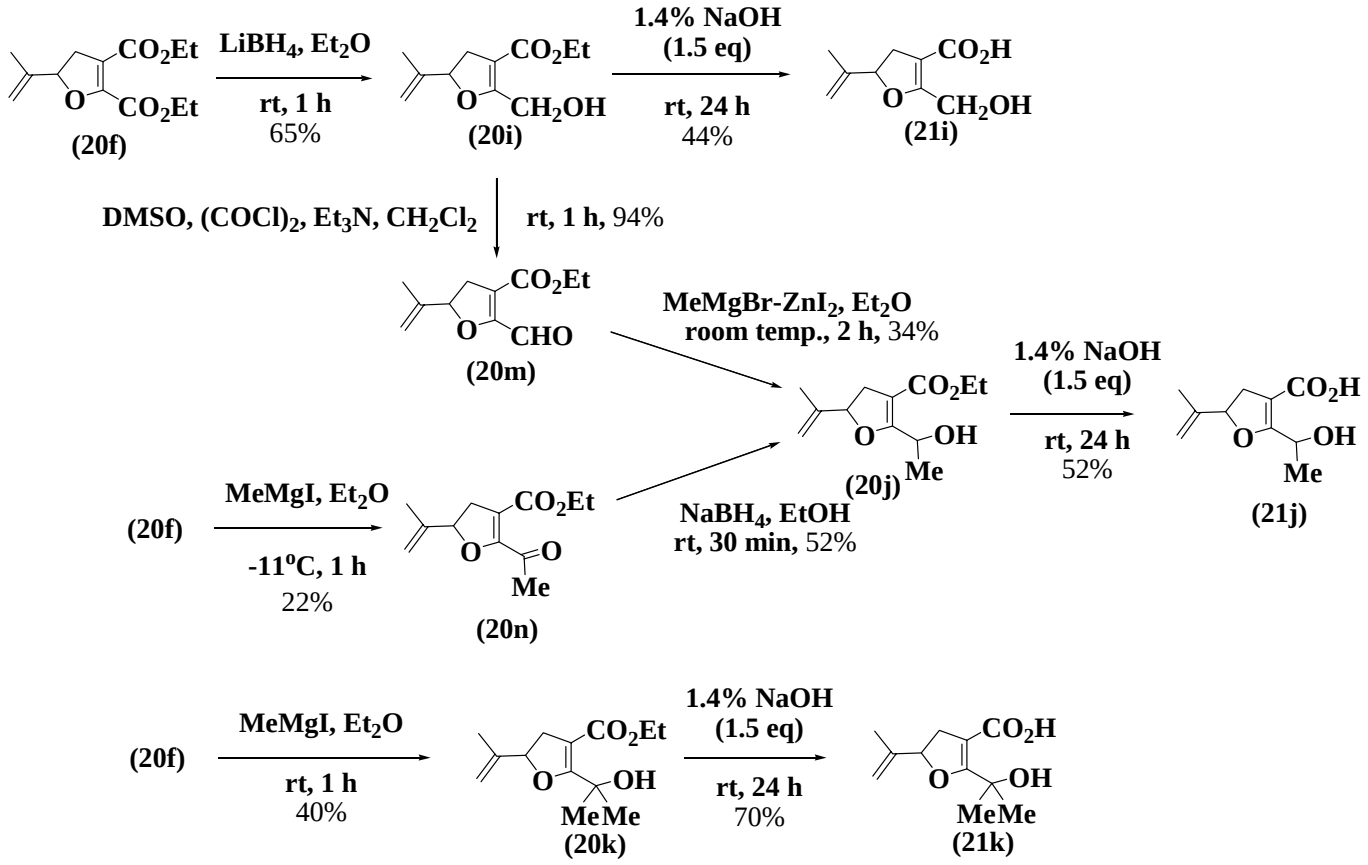
The similar reaction of diethyl oxaloacetate and 1,4-dibromo-2-methyl-2(*E*)-butene (**14**) caused a five-membered cyclization to give diethyl 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylate (**20f**).[15a,b] Thermal alkaline hydrolysis of dicarboxylate **20f** caused the decomposition of the furan–ring. But, mild alkaline hydrolysis of **20f** using excess amount of 5% aqueous sodium hydroxide solution gave a corresponding dicarboxylic acid (**21f**), and another mild alkaline hydrolysis of **20f** using an equivalent amount of 1.4% aqueous sodium hydroxide solution gave a single half-ester, 3-ethoxycarbonyl-5-isopropenyl-4,5-dihydrofuran-2-carboxylic acid (**20g**), which was converted to the corresponding amide carboxylic acid, 2-carbamoyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid (**21h**) *via* a corresponding amide-ester ethyl 2-carbamoyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate (**20h**).



Scheme 6a. Preparation of Isopropenyldihydrofurancarboxylic Acids (**21f,h**)

The regio-selective hydrolysis of 2-ester in diester **20f** was explained as follows. The 3-ester was deactivated by conjugation with the lone-paired electrons on the oxygen in the furan ring, and, in IR spectrum, shows the 3-carbonyl lower (1710 cm^{-1}) and the 2-carbonyl higher (1750 cm^{-1}).

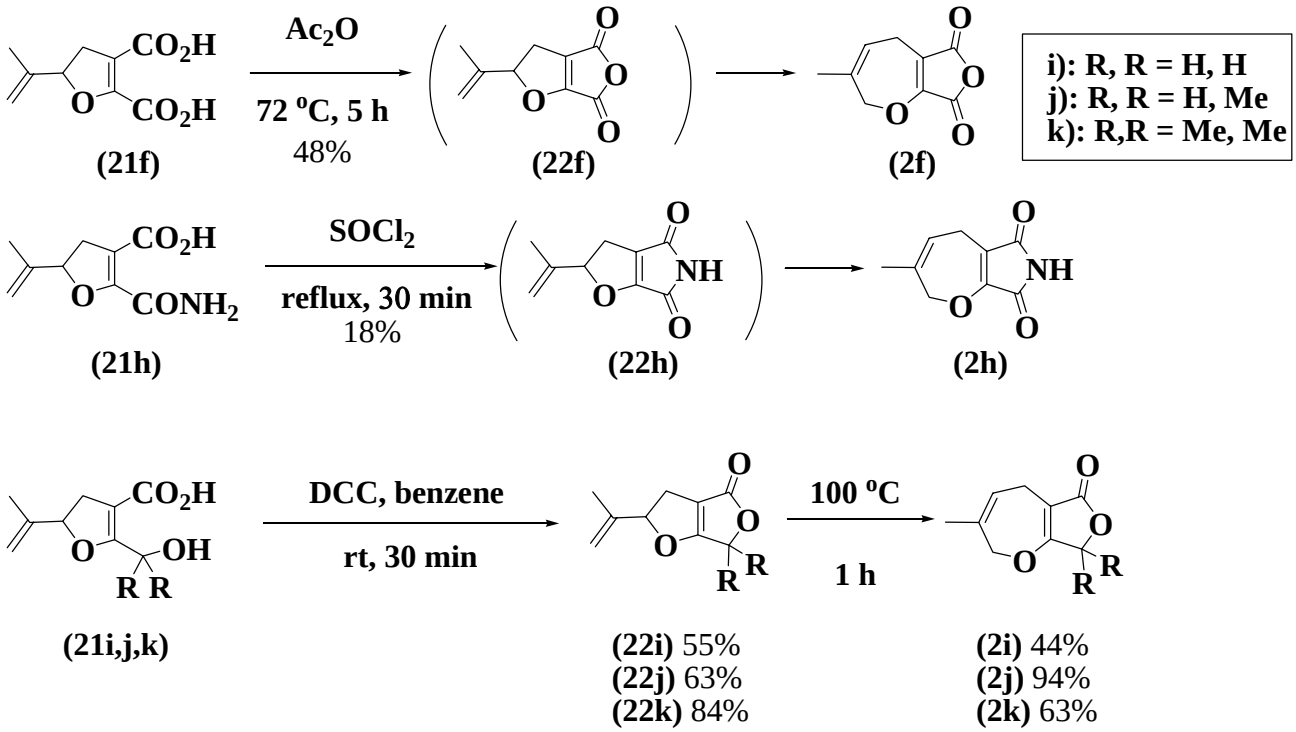
The $LiBH_4$ reduction of diester **20f** also caused a regio-selective reduction to give a single hydroxymethyl-ester, ethyl 2-hydroxymethyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate (**20i**), which was converted to the corresponding hydroxymethyl carboxylic acid, 2-hydroxymethyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid (**21i**). The Grignard alkylation of diester **20f** with methylmagnesium iodide also caused a regio-selective alkylation to give ethyl 2-(1-hydroxy-1-methylethyl)-5-isopropenyl-4,5-dihydrofuran-3-carboxylate (**20k**), which was converted to the corresponding hydroxymethyl carboxylic acid, 2-(1-hydroxy-1-methylethyl)-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid (**21k**). The Grignard alkylation of diester **20f** with methylmagnesium iodide at low temperature caused a regio-selective mono-alkylation to give ethyl 2-acetyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate (**20n**), which was reduced to ethyl 2-(1-hydroxyethyl)-5-isopropenyl-4,5-dihydrofuran-3-carboxylate (**20j**). The 2-(1-hydroxyethyl)-3-carboxylate (**20j**) was also prepared from **20i** by Swern oxidation giving ethyl 2-formyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate (**20m**) and following mild-methylation with methylzinc bromide. The ethyl 2-(1-hydroxyethyl)-3-carboxylate (**20j**), thus obtained, was hydrolyzed to the corresponding hydroxymethyl carboxylic acid, 2-(1-hydroxyethyl)-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid (**21j**).



Scheme 6b. Preparation of Hydroxymethylisopropenyldihydrofurancarboxylic Acids (**21i,j,k**)

The furandicarboxylic acid (**21f**) was subjected to the conversion to the corresponding 5-isopropenyl-4,7-dihydrofuran-2,3-dicarboxic anhydride (**22f**) in usual methods, but treating **21f** with acetic anhydride under mild heating at 72 ^{o}C did not give isopropenyldihydrofuran anhydride **22f**, but caused the ring expansion to give 6-methyl-4,7-dihydrooxepin-2,3-dicarboxylic anhydride (**2f**).[13] The similar ring expansion was observed in 2-carbamoyl-3-carboxylic acid **21h**; treatment of **21h** with refluxing thionyl chloride did not give a corresponding imide, 5-isopropenyl-4,7-dihydrofuran-2,3-dicarboximide (**22h**), but caused the ring expansion to give 6-methyl-4,7-dihydrooxepin-2,3-dicarboxylimide (**2h**). These ring expansions might due to the ring strain of the fused two five-membered rings, and the ring strain caused the heterolytic cleavage of the C5-O bond in the dihydrofuran ring to give a stable enolate cation, where the enolated anion stabilized with the electron withdrawing group in position 3 and the cation also stabilized by conjugation with isopropenyl, and the stable recyclization formed the corresponding seven-membered dihydrooxepins **2f,h**.

The five-membered lactone ring formation of three 2-hydroxymethylfuran-3-carboxylic acids **21i,j,k** were similarly attempted.[15b] The lactone ring formation of **21i,j,k** with dicyclohexylcarbodimide (DCC) at room temperature did not cause the ring expansion to give corresponding five-membered lactones **22i,j,k**, which readily caused ring expansion by heating at 100 ^{o}C to give the corresponding seven-membered dihydrooxepins **2i,j,k**.

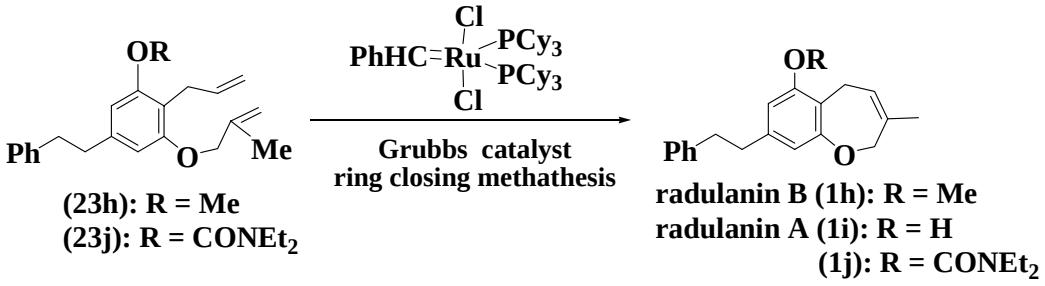


Scheme 6c. Ring-expansion of Isopropenyldihydrofuran Carbonyl Compounds (**21a,c,d,f,h**)

3 EFFECTIVE APPROACH FOR 3-METHYL-2,5-DIHYDRO-1-BENZOXEPINS

3-1 Ring Closing Metathesis

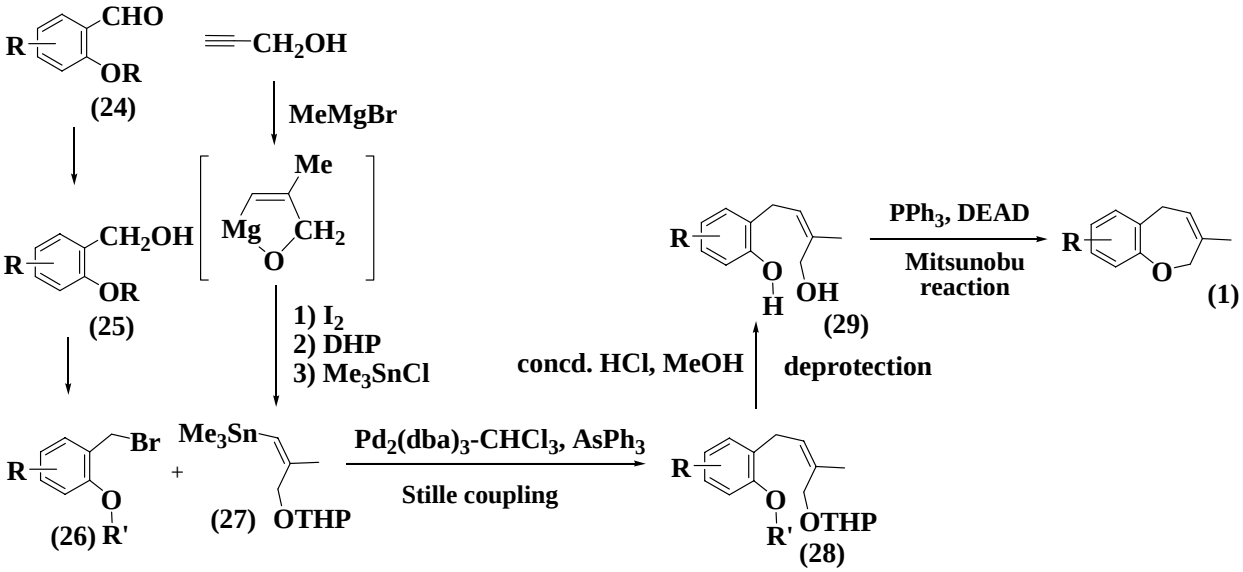
In 1998, M. Stefinovic *et al.*[1] reported the first effective preparation of 3-methyl-2,5-dihydro-1-benzoxepin derivatives; where they used a Grubbs ring closing metathesis for *Z*-selective C=C bond formation. They reported the synthesis of natural radulanin A,B (**1h,i**) *via* this ring closing methathesis of corresponding *o*-allylphenol 2-methylallylethers (**23h,i**).



Scheme 7. Ring-closing Metathesis

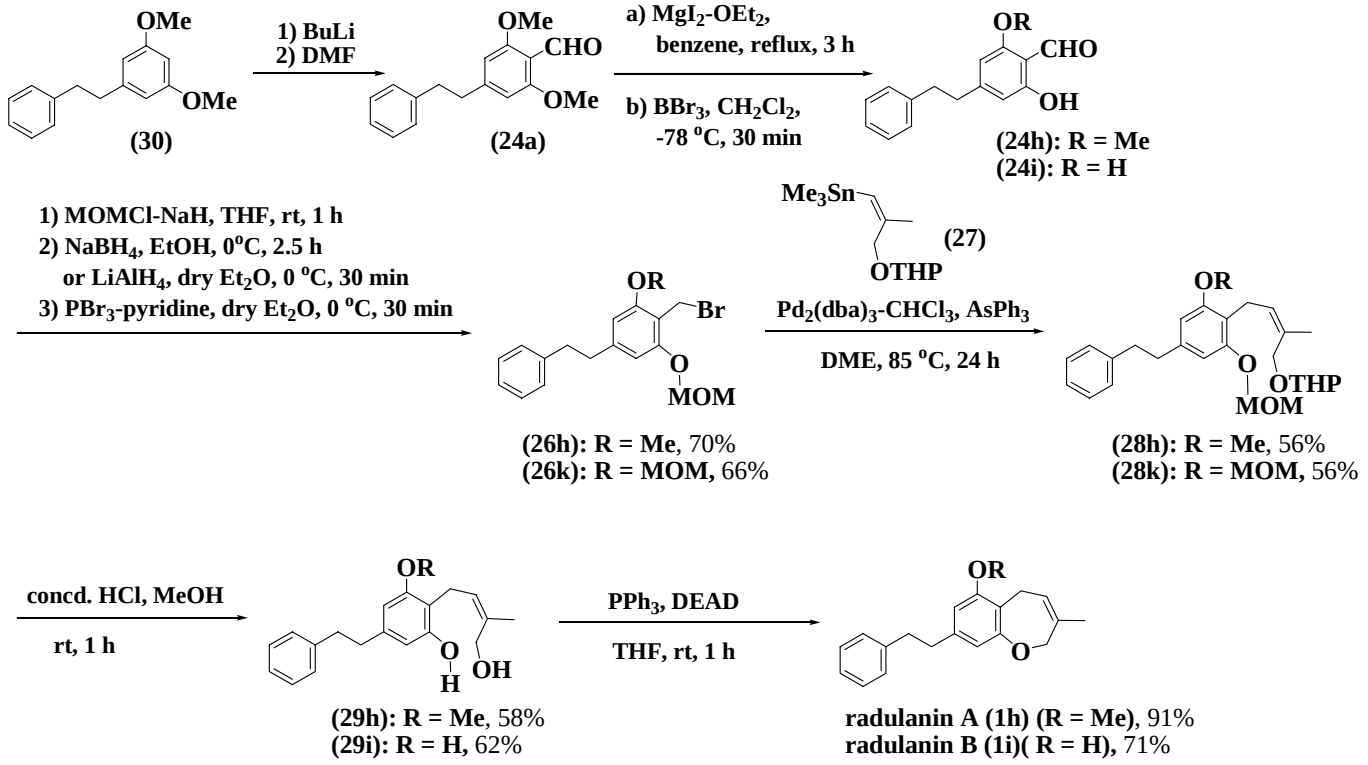
3-2 STILLE COUPLING & MITSUNOBU CYCLIZATION

We reported another preparative procedure;[2a] where we used a Stille coupling of the benzyl bromide (**26**), prepared from the corresponding salicyl aldehydes (**24**), with 2-methylprop-1(*Z*)-enyl trimethylstanane (**27**), prepared by regio- and stereo-selective methylation of propargyl alcohol with methylmagnesium bromide followed by treatment with iodine, dihydropyran, and trimethyltin chloride, and the intramolecular Mitsunobu cyclizations of the *Z*-diols (**29**), prepared by deprotection of the Stille coupling products, effectively gave corresponding 3-methyl-2,5-dihydro-1-benzoxepins (**1**).



Scheme 8a. General Method Using Stille Coupling & Following Mitsunobu Cyclization

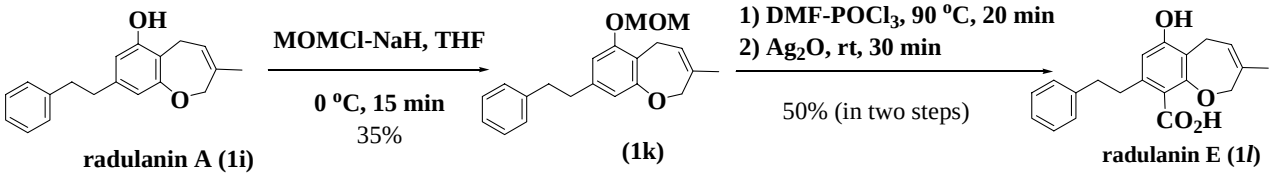
As shown in Scheme 8b, we reported the synthesis of natural radulanin A,B (**1h,i**), using this Stille coupling and following Mitsunobu intramolecular cyclization.[2a,b] The starting material, 3,5-dimethoxy-1-(2-phenylethyl)benzene (**30**), prepared from 3,5-dimethoxybenzaldehyde *via* Wittig condensation with benzyltriphenylphosphonium bromide and following hydrogenation, was converted to 2,6-dimethoxy-4-phenylethylbenzaldehyde (**30**) *via* lithiation with *n*-butyllithium and following formylation with dry DMF. The dimethoxybenzaldehyde **24a** was converted to the salicyl aldehydes (**24h,i**), respectively; the demethylation by refluxing with magnesium iodide diethyl etherate in dry benzene caused mono-demethylation to give **24h**, while the demethylation with boron tribromide at -78 ^{o}C caused di-demethylation to give **24i**. The salicylaldehydes **24h,i**, thus obtained, were converted to the corresponding benzyl bromides (**26h,k**), *via* MOM protection, reduction, and bromination, respectively. Stille coupling of the benzyl bromides **26h,k** with the vinyl stananne **27** using Pd(II) and Ph_3As gave the corresponding coupling products (**28h,k**), which were then deprotected to the corresponding (Z)-diols (**29h,i**). Also, the intramolecular Mitsunobu cyclizations of the (Z)-diols (**29h,i**) effectively gave the corresponding 3-methyl-2,5-dihydro-1-benzoxepins, radulanin A (**1i**) and radulanin B (**1h**).



Scheme 8b. Synthesis of Naturally Occurring Radulanin A,B (**1i,h**)
Using Stille Coupling & Following Mitsunobu Cyclization

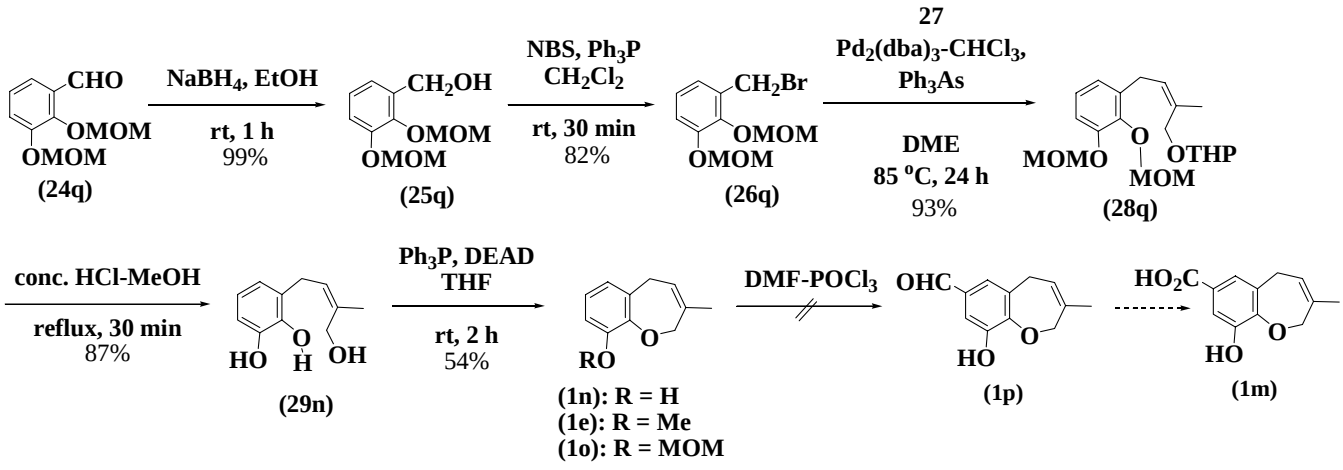
As shown in Scheme 8c, we also reported the synthesis of two naturally occurring benzoxepincarboxylic acids (**1*l*,p**) using this Stille coupling and following Mitsunobu intramolecular cyclization.[2b]

Radulanin E, 6-hydroxy-3-methyl-8-phenylethyl-2,5-dihydro-1-benzoxepin-9-carboxylic acid (**1*l***) was synthesized *via* Vielsmeier formylation of 6-methoxymethyloxy-3-methyl-8-phenylethyl-2,5-dihydro-1-benzoxepin (**1k**). The 6-methoxymethyloxy derivative **1k** was prepared from radulanin A (**1i**) by protection with MOMCl. Vilsmeier formylation of **1k** treating with DMF-$POCl_3$ gave 9-carbaldehyde, which was oxidized to 6-hydroxy-3-methyl-8-phenylethyl-2,5-dihydro-1-benzoxepin-9-carboxylic acid (**1*l***) treating with Ag_2O.



Scheme 8c. Synthesis of Natulally Occurring Radulanin E (**1*l***)
Using Stille Coupling & Following Mitsunobu Cyclization

Synthesis of naturally occurring 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid (**1m**) was first planned *via* similar formylation of 3-methyl-2,5-dihydro-1-benzoxepin-9-ol (**1n**) *via* MOM protection and following Vielsmeier formylation.

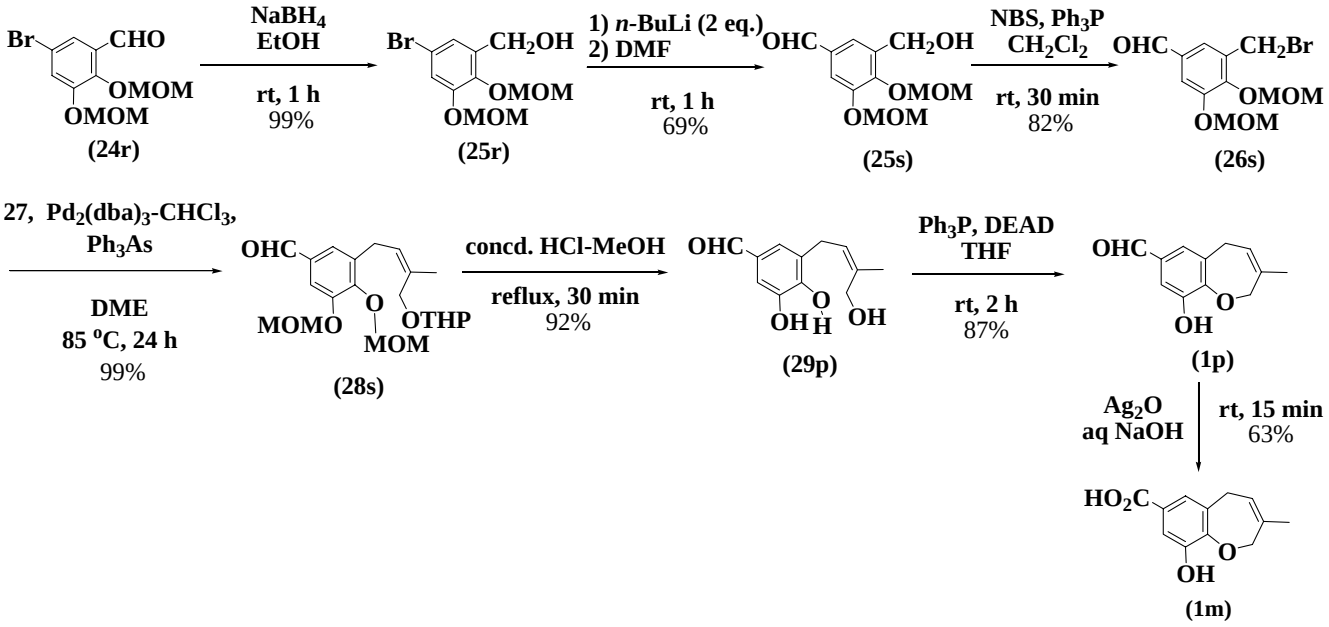


Scheme 8d. Synthetic Studies of Natulally Occurring **1m**
Using Stille Coupling & Following Mitsunobu Cyclization

2,3-Di(MOMoxy)benzaldehyde **24q**, prepared from di-MOM protected catechol by lithiation followed by formylation with DMF, was converted to the corresponding benzyl bromide (**26q**) by reduction with

$NaBH_4$ followed by bromination of the benzyl alcohol (**25q**) with NBS-Ph_3P. Stille coupling of the benzyl bromide (**26q**) with vinyl stananne **27** using Pd(II) and Ph_3As gave the corresponding coupling products (**28q**), which were then converted to the corresponding 3-methyl-2,5-dihydro-1-benzoxepin-9-ol (**1n**) *via* deprotection and following Mitsunobu cyclization, and then converted to **1o** by MOM protection. However, Vilsmeier formylation of **1o** or **1e** did not cause any formylation and recovered the starting material.

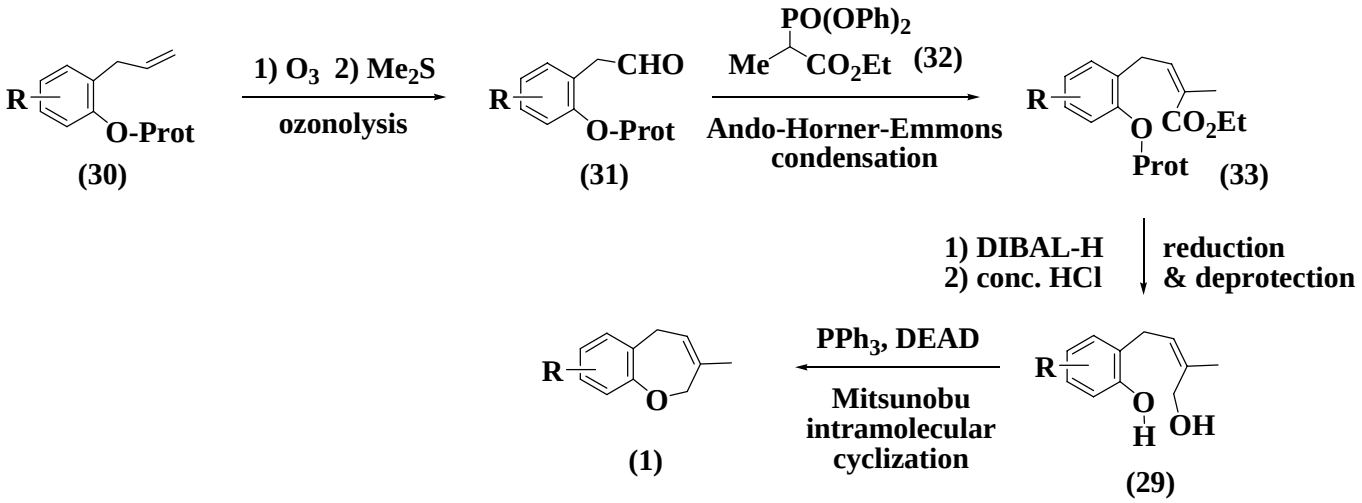
Then, synthesis of **1m** was planned in another procedure. The corresponding 5-formylbenzyl bromide (**26s**), was prepared from 5-bromo-2,3-dihydroxybenzaldehyde *via* 5-bromo-2,3-di(MOMoxy)- benzyl alcohol **27n**. The bromobenzyl alcohol **25r** was prepared by di-MOM protection of 5-bromo-2,3-dihydroxybenzaldehyde with MOMCl giving **24r** followed by reduction with $NaBH_4$. The bromobenzyl alcohol **25r**, thus obtained, was then converted to 5-formylbenzyl bromide **26s** by 1) formylation *via* lithiation with *n*-butyllithium giving the 5-lithio derivative, 2) treatment with dry DMF giving **25s**, bromination with NBS-Ph_3P. Stille coupling of the benzyl bromide (**26s**) with vinyl stananne **27** gave the corresponding coupling products (**28s**), which were then converted to the corresponding *Z*-diol (**29p**) by deprotection. Mitsunobu cyclization of diol **29p** gave 9-hydroxy-7-carbaldehyde (**1p**), which was readily oxidized to 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid (**1m**) with Ag_2O.



Scheme 8e. New Synthesis of Naturally Occurring **1m**
Using Stille Coupling & Following Mitsunobu Cyclization

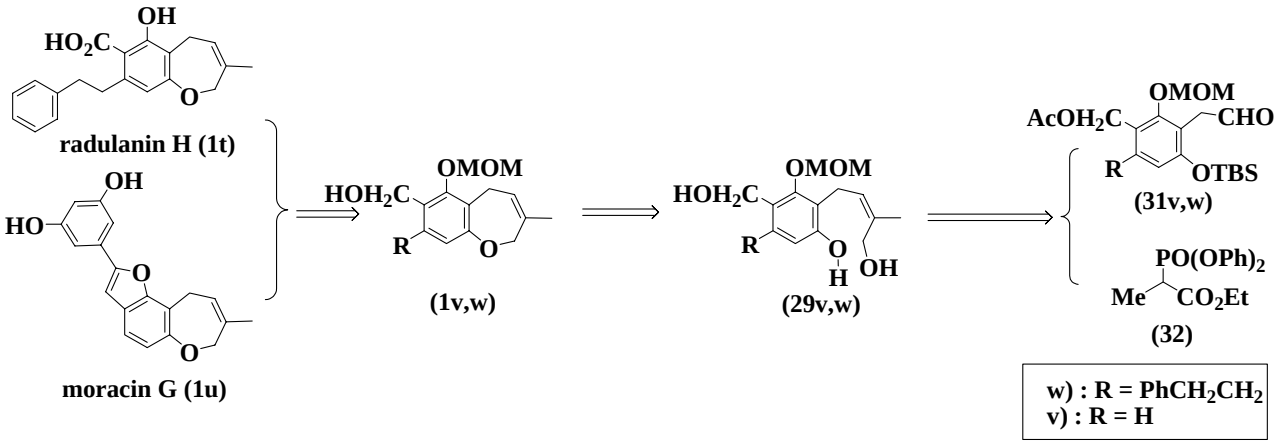
3-3 ANDO-HORNER-EMMONS CONDENSATION & MITSUNOBU CYCLIZATION

Recently, as shown in Scheme 9a, we found another preparative procedure of the Z-diols (**29**) starting from *o*-allylphenols (**30**); where the Ando-Horner-Emmons condensations of phenylacetaldehydes (**31**) with ethyl α-(diphenylphosphono)propionate (**32**) were used for a *Z*-selective C=C bond formation giving Z-conjugated ester (**33**), and the following DIBAL-H reductions effectively gave corresponding Z-diols (**29**).



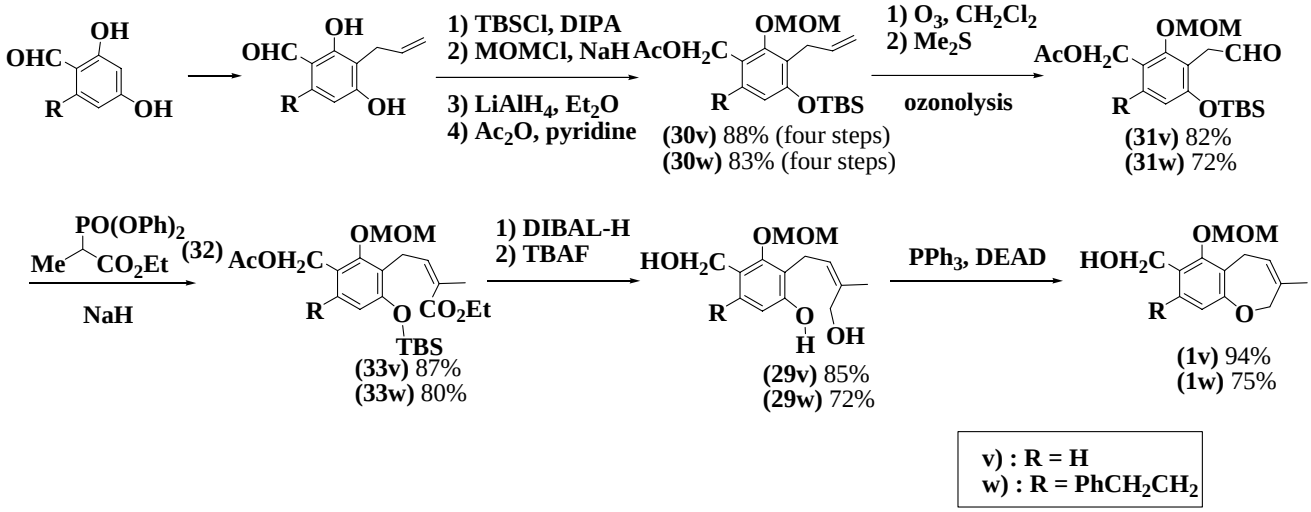
Scheme 9a. Ando Coupling & Following DIBAL Reduction and Mitsunobu Cyclization

So, the synthesis of naturally occurring radulanin H (**1t**) and moracin G (**1u**), were planned using this Ando coupling and following reduction and Mitsunobu intramolecular cyclization, as shown in Scheme 9b.[3] For both naturally occurring benzoxepins **1t** and **1u**, 3-methyl-2,5-dihydro-1-benzoxepin-7-methanols (**1v,w**) might be key intermediates, and they might be prepared by Ando coupling of the corresponding phenylacetaldehydes **31v,w** with **32**, followed by DIBAL reductions and Mitsunobu cyclizations.



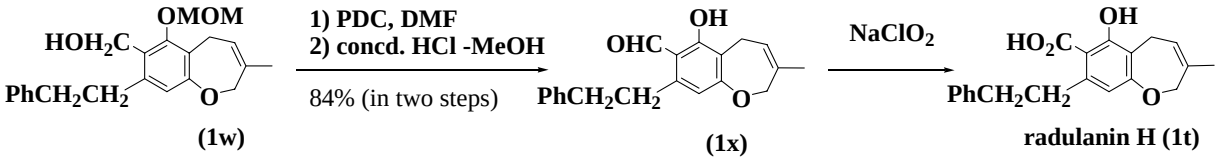
Scheme 9b. Retro-sysnthesis of Radulanin H (**1t**) and Moracin G (**1u**)
via Ando Coupling & Following DIBAL Reduction and Mitsunobu Cyclization

The phenylacetaldehydes **31v,w** for moracin G and radulanin H were prepared from corresponding 2,4-dihydroxybenzaldehydes, as shown in Scheme 9c, *via* allylation giving 3-allyl-2,4-dihydroxy-benzaldehyde, selective protections, $LiAlH_4$ reduction, *O*-acetylation giving **30v,w**, and following ozone cleavage. The Ando condensation of phenylacetaldehydes **31v,w** with reagent **32** gave corresponding 2(Z)-conjugated butenoates **33v,w**, which were then reduced to the corresponding (*Z*)-diols **29v,w** by DIBAL reduction followed by deprotections with TBAF. In addition, the intramolecular Mitsunobu cyclizations of the (Z)-diols **29v,w** effectively gave 6-methoxymethyloxy-3-methyl-2,5-dihydro-1-benzoxepin-7-methanols (**1v,w**).



Scheme 9c. New Synthesis of Benzoxepin-7-methanol (**1v,w**) as Key Intermediates for Radulanin H (**1t**) and Moracin G (**1u**)

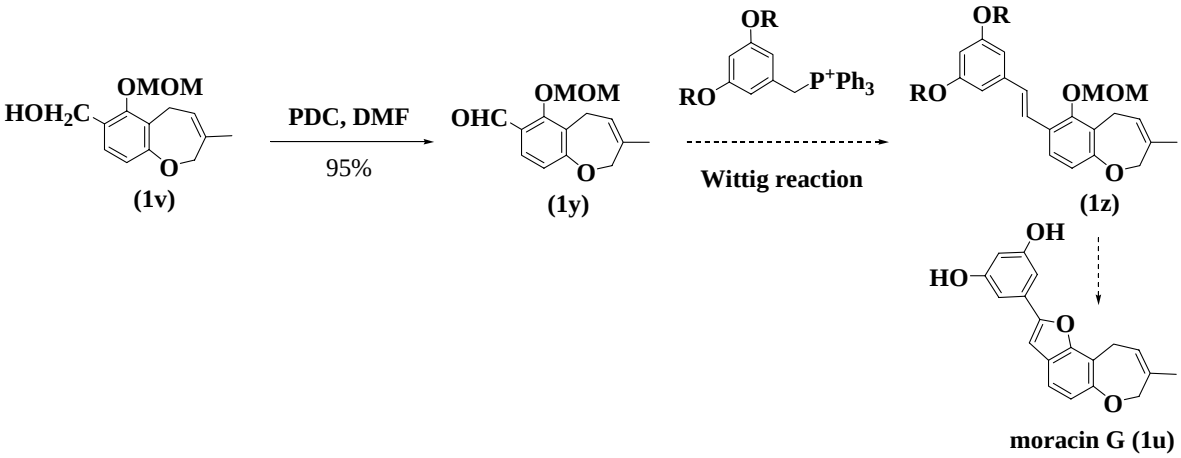
Conversion of **1w** to the corresponding 6-hydoxy-7-carbaldehyde **1x** was effective by oxidation with PDC followed by deprotection with concd. HCl in methanol, and the aldehyde **1x** was converted to naturally occurring radulanin H (**1t**) by the mild oxidation with sodium chlorate.[17]



Scheme 9d. Conversions from Benzoxepin-7-methanol (**1w**) to Radulanin H (**1t**)

Oxidation of **1v** with PDC effectively gave corresponding aldehyde, 6-(MOMoxy)-3-methyl-2,5-dihydro-1-benzoxepin-7-carbaldehyde (**1y**). Also, the oxepin-7-carbaldehyde **1y** might be

convertible to maracin G (**1u**) *via* Wittig condensation and following furan-ring formation and deprotection.[3]



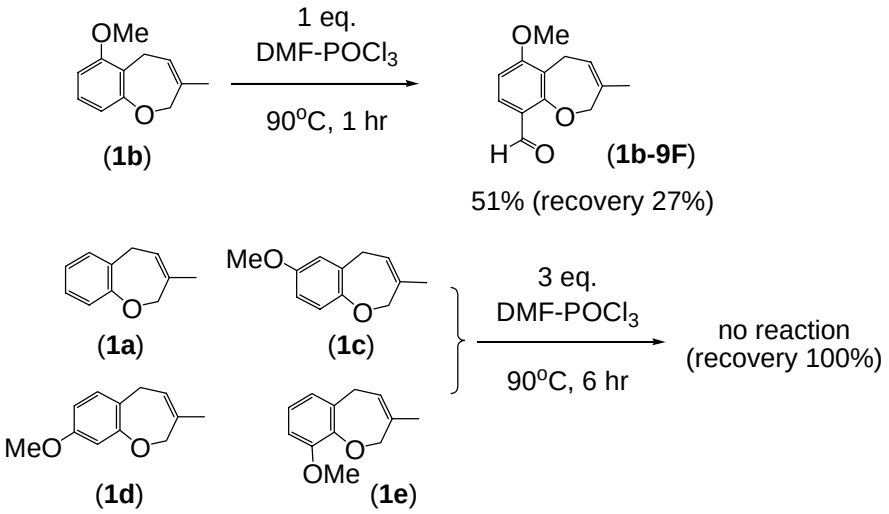
Scheme 9e. Conversions from Benzoxepin-7-methanol (**1v**) to Moracin G (**1u**)

4 ACYLATIONS OF 3-METHYL-2,5-DIHYDRO-1-BENZOXEPINS

We already reported the acylations of 2-isopropenyl-2,3-dihydrobenzofurans,[18] also labile to the acids, and found that Vilsmeier condition were successful for their formylation and an acylation mixture of acetic acid-trifluoroacetic anhydride were also successful for their *C*-acetylation. The seven-membered 3-methyl-2,5-dihydro-1-benzoxepins (**1a-e**) were supposed to be labile to the acidic condition, and the acylations of 3-methyl-2,5-dihydro-1-benzoxepins (**1a-e**) were studied in the similar condition; (formylation) dry *N*,*N*-dimethylformamide-phosphoryl chloride at 90 ^{o}C for 1 h; (*C*-acetylation) acetic acid-trifluoroacetic ahydride at room temperature for 6 hr, and the results of formylation and *C*-acetylation were summarized in Scheme 10a and 10b, respectively.[19]

4-1 VILSMEIER FORMYLATION

In Vilsmeier formylations, 6-methoxy derivative **1b**, only showed the formylation at position 9 to give 6-metyhoxy-3-methyl-2,5-dihydro-1-benzoxepin-9-carbaldehyde (**1b-9F**) in 51% yield, and the structure was confirmed both with the ortho coupling (J = 8.8 Hz) of aromatic protons and with +7% NOE effect of a 7-H signal on irradiation at a 6-MeO signal. Other derivative, none-methoxy **1a**, 7-methoxy **1c**, 8-methoxy **1d**, and 9-methoxy **1e**, showed the recovery of the starting materials. Thus, the 3-methyl-2,5-dihydro-1-benzoxepins showed the poorer reactivities than the corresponding 2-isopropenyl-2,3-dihydrobenzofurans.



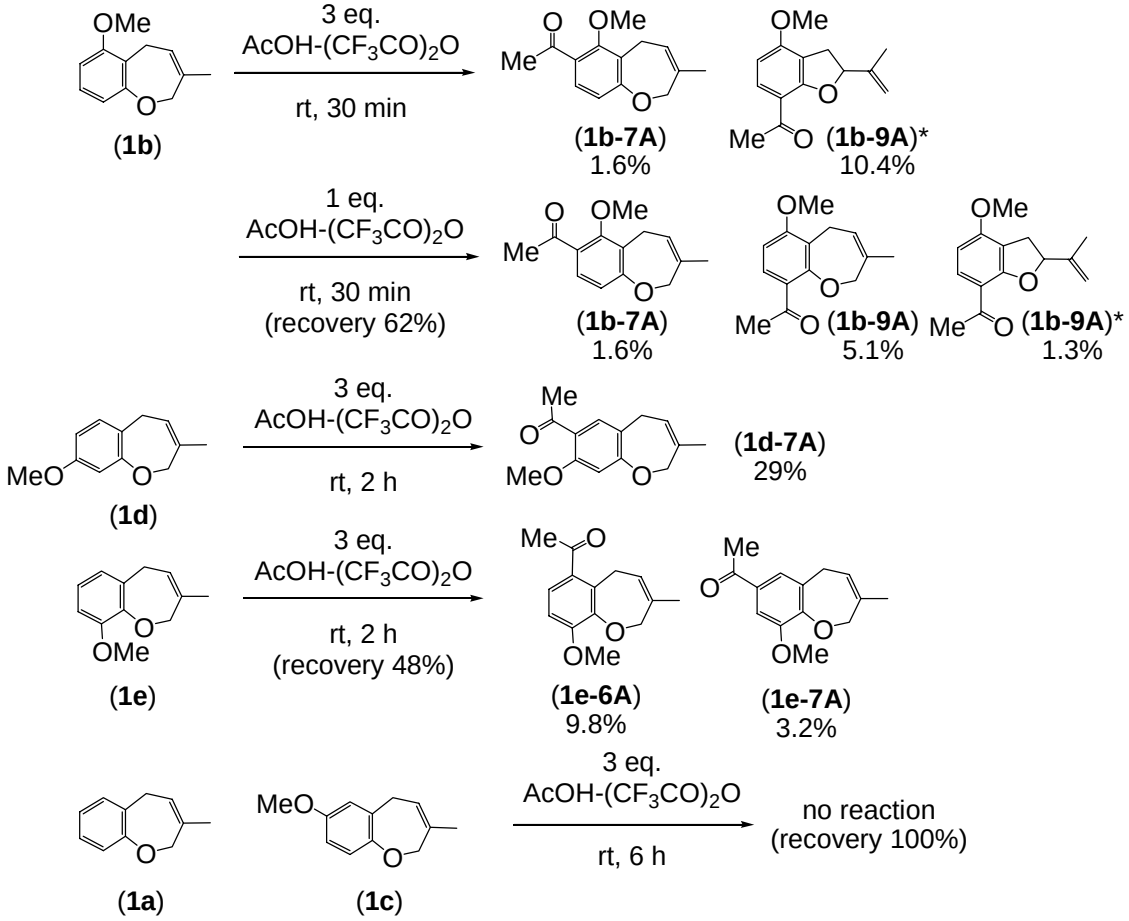
Scheme 10a. Vilsmeier Formylation of 3-Methyl-2,5-dihydro1-benzoxepins **1**

(DMF, $POCl_3$, 90 ^oC, 1 h or 6 h)

4-2 *C*-ACETYLATIONS

In the *C*-acetylations, three methoxy derivatives **1b,d,e** showed the C-acetylation, but in poor yields. The acetylation of 8-methoxy derivative **1d** with 3 eq. AcOH-$(CF_3CO)_2O$ for 2 hr showed the 7-acetylation, ortho to the methoxy-substituent and para to the ring oxygen, to give **1d-7A** in 29%. The acetylation of 9-methoxy derivative **1e** in a similar condition (3 eq. acylating mixture for 2 hr) showed both acetylation, para to the methoxy-substituent or to the ring oxygen, to give a mixture of 6-acetylated **1e-6A** (9.8%) and 7-acetylated **1e-7A** (3.2%), but the yields were very low.

Interestingly, the acetylation of 6-methoxy derivative **1b** with 3 eq. acylating mixture for 30 min gave a mixture of two acetylated products, 7-acetyl-6-methoxy-3-methyl-2,5-dihydro-1-benzoxepin (**1b-7A**), 7-acetyl-2-isopropenyl-2,3-dihydrobenzofuran (**1b-9A***) in 1.6% and 10.4% yields, respectively. In addition, the similar acetylation of **1b** with an equimoler acylating mixture for 30 min, gave a mixture of **1b-7A**, 9-acetyl-6-methoxy-3-methyl-2,5-dihydro-1-benzoxepin (**1b-9A**), and **1b-9A*** in 1.6%, 5.1%, and 1.3% yields, respectively. These showed the both acetylation, ortho/para to the methoxy-substituent and to the ring oxygen, to give a mixture of 7-acetylated **1b-7A** and 9-acetylated **1b-9A**, and only the latter isomer might cause the ring contraction to give 7-acetylbenzofuran **1b-9A***.



Scheme 10b. *C*-Acetylation of 3-Methyl-2,5-dihydro1-benzoxepins **1.**

AcOH, $(CF_3CO)_2O$, rt, 30 min or 2 h (or 6 h)

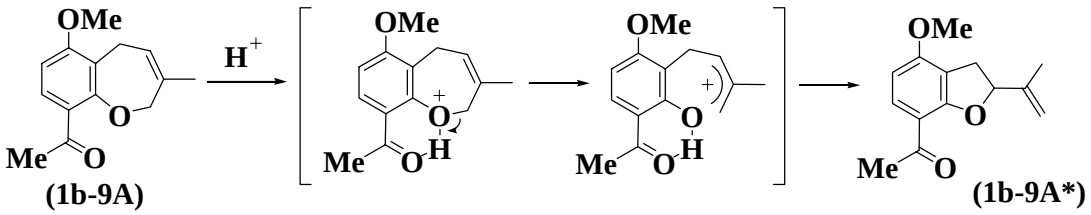


Figure 4. Supposed Mechanism of Ring Contraction from 9-Acetyl-6-methoxy-benzoxepin **1b-9A**

This ring contraction, selective for **1b-9A**, might be explained as following, the protonation on the ring oxygen of **1b-9A** caused the ring cleavage to give the transition state **T**, stabilized the hydrogen bonding with the acetyl, and then caused recyclization to give five-membered **1b-9A***.

Thus, trifluoroacetic acid, derived from trifluoroacetic anhydride in *C*-acetylations, is a stronger acid than phosphoryl chloride, used in formylation. The acetylation of three methoxy- substituted derivatives

(**1b,d,e**) shows better reactivities than the formylation. But, the stronger acidic conditions sometimes caused the decomposition or the isomerization (ring contraction), and the lower reaction temperature (rt) leads to the poorer yields.

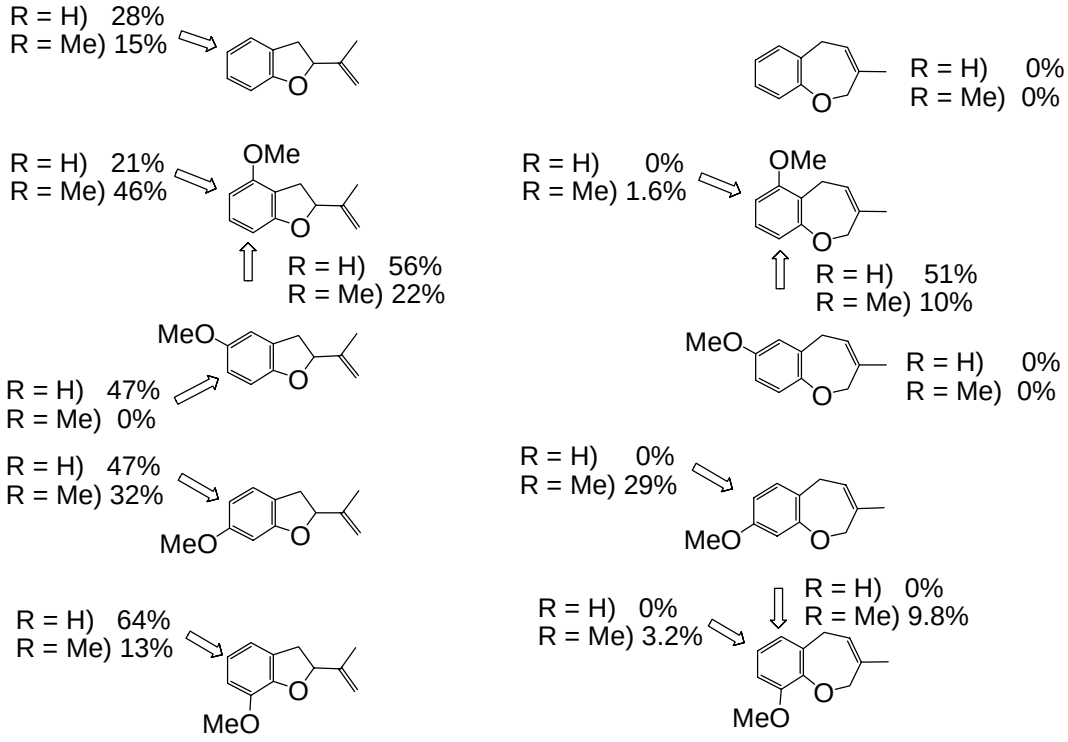


Figure 5. Comparison of the Acetylation of 2-Isopropenyl-2,3-dihydrobenzofurans **3** and 3-Methyl-2,5-dihydro1-benzoxepins **1**

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Seiji Yamaguchi was born in Hiroshima, Japan, in 1943. He received his B.A. (in 1967) and M.S. (in 1969), at Osaka City University, under the supervision of Prof. Takeo Sakan. In 1969, he was appointed Assistant at Toyama University. In 1983, he received his Ph.D. under the supervision of Prof. Yuji Hayashi, and appointed to Associate Professor. Since 2003, he has been a full Professor at University of Toyama. His current research interests include the synthetic studies on naturally occurring *O*-heterocyclic compounds, such as 2-isopropenyl-2,3-dihydrobenzofurans, 2,2-dimethyl-2*H*-chromenes, 3-methyl- 2,5-dihydro-1-benzoxepins, which might be biogenetically derived by the oxidative cyclizations of *o*-prenylphenols in plants.