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REVIEW

PHARMACOLOGY AND SYNTHESIS OF DAURICHROMENIC ACID AS A POTENT ANTI-HIV AGENT

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Abstract: Daurichromenic acid (a potent anti-HIV agent) has been surveyed in this review article, not only for its pharmacological assessment comparative to other compounds but also for methodological trends in different synthetic approaches.

Keywords: anti-HIV, 2H-chromen, total synthesis

Acquired Immunity Deficiency Syndrome (AIDS), as is evident by the name, is a disease related to immune system of the human body. It was first reported in the United States in 1981. On acquiring this syndrome the infected human underwent collapse of the immune system, opportunistic infections and cancers. AIDS is caused by a retro virus known as HTLV-III or LAV and it belongs to the family *Lentiviridae*. It is also commonly known as Human Immunodeficiency Virus (HIV). This virus has the tendency to invade the central nervous system (CNS) where it can cause neurological destruction (1).

Reverse transcriptase enzyme in the human body is utilized by HIV to replicate itself. Zidovudine, which is a thymidine analogue, was the first anti-HIV drug, tested in 1984-1985 and was found effective against HIV in rodents and *in vitro* (2-6). There were some side effects too associated with the long term dosage of zidovudine. These include anemia, neutropenia, hepatotoxicity, cardiomyopathy and myopathy. It had been found that these side effects were caused due to high dosage use in the early trials and could be controlled by reducing the drug dose. Some of the origins of these side effects were found to be the depletion of thymidine triphosphate, possible oxidative stress and depletion of intracellular L-carnitine or apoptosis of the muscle cells. The transient depletion of mitochondrial DNA and the sensitivity of an enzyme (γ-DNA polymerase) in the mitochondria of some cells were also found to be the possible reasons of the side effects of zidovudine (7, 8). It has been found that the erythropoietin hormone enhances the production of red blood cells (RBCs) and can in turn control anemia caused by zidovudine (9, 10). The therapeutic strength of zidovudine has been found to be increased by the use of medicines (such as aspirin, nordazepam etc.) which can reduce or inhibit the hepatic glucuronidation. Occasional reports of side effects include mood swings as well as discoloration of skin and nails. Common is the acid reflux, weakness, breathing problems, headache, abdominal fat reduction and increased heartbeat. Above all, this medicine has been designated as possible carcinogenic (11). The dilemma is that the potency of zidovudine is not good enough to stop the replication of HIV altogether. It results in the mutation of

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reverse transcriptase and development of resistant strains of HIV occurs (12).

Another reverse trasnscriptase inhibitor is zalcitabine (13). It is pyrimidine derivative. It was marketed in 1992 as single therapy. This drug was found to be relatively less potent; therefore, it was again marketed in 1996 as a combination drug with zidovudine (14). Unfortunately, this medicine is associated with serious side effects. It has been found that the treatment of patients having advanced HIV infections with combination of zidovudine and zalcitabine is not superior to zidovudine alone (15). These are the reasons the medicine has been discontinued since 2006. This medicine should not be administered with those which can inhibit the phosphorylation process (such as lamivudine) or can cause peripheral neuropathy (such as didanosine). Ulcer (16), nausea and headache are some other side effects of this medicine.

Another medicine used for inhibiting reverse transcriptase of HIV is stavudine. It is also thymidine analogue. Peripheral neuropathy is one of the adverse effects of stavudine. Like zidovudine, decreasing the dose of stavudine can overcome this side effect. The *in vitro* testing shows the tendency of the medicine towards disrupting the genetic information whereas clinical trials do not point out any carcinogenicity. Another side effect of this medicine is that it causes degeneration of adipose tissue (17). For this reason, it is not in use these days in most of the countries for HIV treatment. Although, it has been discontinued in most of the countries since 2009, due to its low price, it is still in use in the developing countries as a treatment of AIDS (18).

It has been observed that all the anti-HIV agents have the tendency to be lipophilic (1). For example, zidovudine has azido group. This group helps the medicine to cross membranes and blood-brain barrier by diffusion. The mode of action of zidovudine is to selectively inhibit the reverse transcriptase enzyme of HIV that is needed to make a DNA copy of its RNA. The double stranded DNA produced as a result gets incorporated into the host cell DNA. The active form of zidovudine is 5´-triphosphate which discontinues the formation of DNA chain of HIV. If administered in high dose, the medicine can also inhibit DNA polymerase which is used by the healthy cells of human body to replicate. Selectivity comes from the fact that the human DNA has the tendency to repair the broken strands whereas HIV's DNA does not have this ability (19). The lipophilicity trend can be also seen in zalcitabine. This drug also gets phosphorylated in the cells and converts itself into the active triphosphate form. This active form selectively discontinues the production of DNA of HIV by providing itself as a substrate for HIV reverse transcriptase thereby halting the replication process due to the unavailability of hydroxyl group. The medicine has half-life of two hours, can be administered orally, renal elimination occurs (20). The activity of stavudine is also dependent upon its activated triphosphate form within the cell by cell kinases. This medicine also presents itself as a natural substrate and stops the replication of HIV DNA by getting incorporated into the DNA strand (21). The property of zidovudine to inhibit the phosphorylation of stavudine within the cell makes it less suitable to administer both together. Stavudine can be administered orally; it gets excreted *via* urinary as well as endogenic pathways (22).

The IC_{50} value (the concentration required to produce 50% decrease in supernatant reverse transcriptase) for zidovudine was 0.013 µg/mL in both HIV-infected H9 cells and peripheral blood lymphocytes (23); IC_{50} for zalcitabine is 0.338 µg/mL (24) and for stavudine is up to 0.8968 µg/mL (25).

The development of resistant strains against these medicines is not a healthy sign. The need of the hour is to find out some more lead compounds, which must be potent enough to deal with the HIV. Many scientists look towards Mother Nature to seek cures for lethal diseases. History shows that there are many examples where scientists found remedy directly or in modified form from natural products. Most commonly observed structural units in natural products are six membered oxygenated heterocycles (pyranes). Daurichromenic acid is an example, where oxygenated ring is present in the form of 2*H*-1-benzopyran (also known as 2*H*-chromen). This moiety is an important structural unit in different members of almost every class of naturally occurring phenolic compounds such as flavonoids, coumarins, rotenoids, stilbenoids and chromene glucosides. A number of pharmacological active compounds possess this 2*H*-chromen ring system in their structure. These compounds are not only important sources for the synthesis of other natural products (26-31) but also act as anti-depressant, anti-hypertensive, anti-ischemic, anti-fungal, anti-tumor, active against snake venom and most importantly anti-HIV agents (27).

Daurichromenic acid has been reported as an effective anti-HIV agent with 0.00567 µg/mL EC_{50} value, when tested against severely infected H9 cells. In the same study, daurichromenic acid has been tested for its inhibitory activity towards uninfected H9 cells, and has showed IC_{50} value of 21.1

µg/mL. An overall therapeutic index (TI) of daurichromenic acid has been rated good with TI value of 3710. Two isomers of daurichromenic acid have also been tested for anti HIV activity, where rhododaurichromanic acid A exhibited comparatively potent anti-HIV activity with EC_{50} value of 0.37 µg/mL and TI value of 91.9, but rhododaurichromanic acid B has not shown any anti HIV activity (27, 28, 32-42).

Comparison of daurichromenic acid with other 2*H*-chromen based compounds

A study has been carried out on eight different compounds having 2*H*-chromen structure. Out of these eight compounds, (+)-calanolide A **1** and (-)-calanolide B **2** (Fig. 1) (43) displayed potency against HIV replication in human T-lymphoblastic (CEM-SS) cells. The EC_{50} and IC_{50} values for **1** were 2.7 µM (1.00019 µg/mL) and 13.0 µM (4.81572 µg/mL), respectively. It was evaluated that **2** also had almost equal potency against HIV when compared with **1**. However, the enantiomers of both **1** and **2** were inactive against HIV (27). On the other hand, the potency of daurichromenic acid, with EC_{50} value of 0.00567 µg/mL, is about 176 times higher than these calanolide molecules. This represents the importance of daurichromenic acid compared to other 2*H*-chromens when it comes to potency against HIV.

A study on the structure-activity relationship were conducted on A **1** and B **2**. In this study 14 different analogues of **1** and **2** were tested on human lymphoblastoid CEM-SS cells in the NCI primary anti-HIV screening assay. The results obtained from these analogues, when compared with the results obtained for both **1** and **2**, showed that a heteroatom is necessary for the anti-HIV activity of these compounds. The relative potency of ketone and azide clearly indicates that a hydrogen bond acceptor is required at position 12. Moreover, the potency of these compounds decreases with increasing bulk of substitution at position 12, for instance (=O > N_3 > OAc). This clearly demonstrates that there is either special limitation or stereoelectronic requirement at

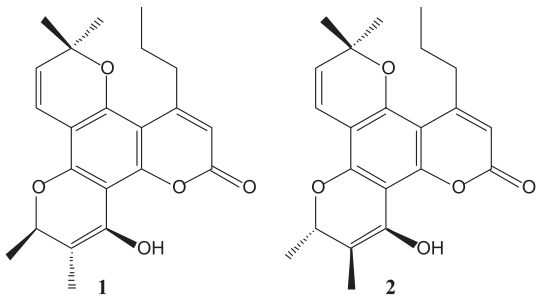

Figure 1. (+)-calanolide A **1** and (-)-calanolide B **2**

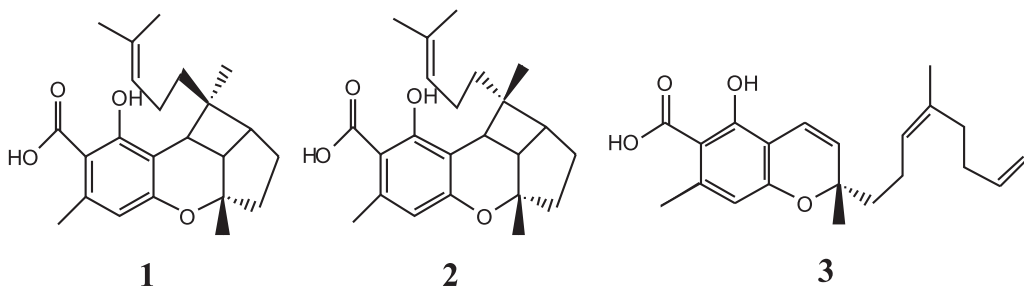

Figure 2. Rhododaurichromanic acid A **1**, rhododaurichromanic acid B **2** and daurichromenic acid **3**

position 12. The oxygen substituent at position 12 must possess "S" configuration. Therefore, 12β-hydroxy group is important for anti-HIV activity (27, 44).

Comparison of (+)-daurichromenic acid with grifolin, grifolic acid and grifolic acid methylester

Synthesis of daurichromenic acid from grifolia has been reported (38). For the estimation of anti-HIV behavior of starting materials, grifolin, grifolic acid and its methylester were tested for anti-HIV effects. These compounds possess anti-HIV activity, which has been categorized as follows:

grifolin > grifolic acid > grifolic acid methylester

EC_{50} values of these compounds were compared with that of (+)-daurichromenic acid. The comparison showed that anti-HIV potential of (+)-daurichromenic acid was about 6700 times better than grifolin, 7000 times better than grifolic acid and 9000 times better than grifolic acid methylester (38).

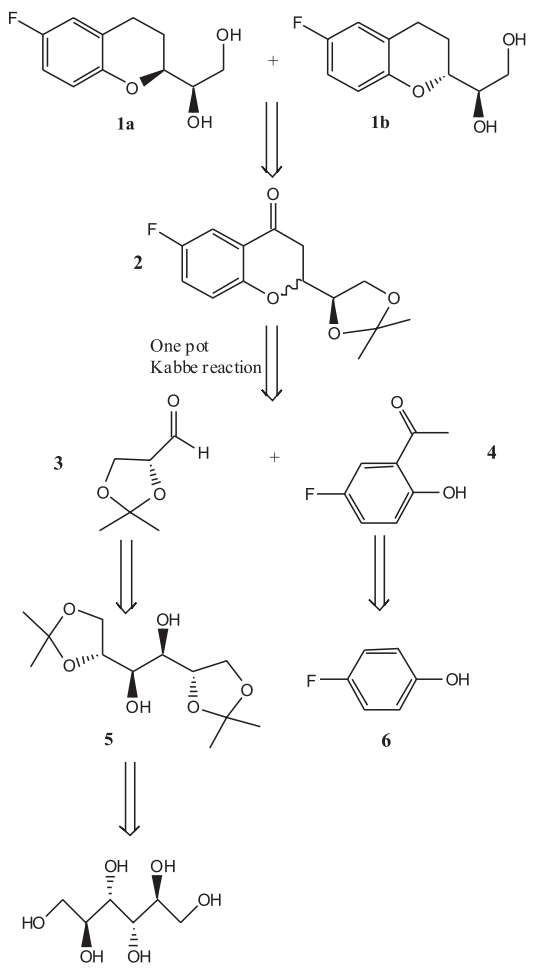

Figure 3. Kabbe reaction in chromen synthesis

Isolation of compound and its derivatives

Rhododendron dauricum (Ericaceae) is a Chinese medicinal plant which is widely distributed in Asia. Daurichromenic acid **3** along with its chromane derivatives rhododaurichromanic acid A **1** and B **2** (Fig. 2) had been isolated from the leaves and twigs of this plant during its screening for novel anti-HIV agents. In the first instance, the methanol extract of the plant showed promising anti-HIV activity (27, 28, 32-37, 39, 42, 45-48). The EC_{50} was less than 20 µg/mL with a TI value less than 5 (27, 39). In the next step, partitioning of methanolic extract was done between ethyl acetate and water. The anti-HIV potential was tracked in the ethyl acetate fraction. This fraction was then further partitioned between *n*-hexane (non-polar) and 90% methanol (polar) fractions. The bioassay guided study revealed that the *n*-hexane fraction was possessing anti-HIV activity. This potent fraction was then subjected to a multifractionation approach; first by silica gel and next by semi preparative HPLC. This bioassay guided fractionation resulted into **1**, **2** and **3**. The absolute configuration of carbon number 2 in **3** is 'S' (28, 34, 35, 39, 47).

In 2009, **3** was isolated from the leaves of another plant known as *Rhododendron adamsii* (41). The benzene extract of the plant was subjected to reverse phase chromatography and eluted with aqueous solution of methanol in an increasing percentage. The last fraction obtained by pure methanol elution was dried and chromatographed using silica gel as stationary phase and ethanol/chloroform as eluent mixture with stepwise increasing percentage of ethanol. Although, a new source of **3** has been discovered, the total percentage of **3** in the extract was only 0.1% (41).

In the year 2010, **3** was isolated from another plant known as *Rhododendron anthopogonoides*. This plant was collected from Sichuan, China in the year 2003. In this study, the plant leaves and twigs were extracted with 60% ethanol. The extract was fractionated into four fractions; *n*-hexane, water, butanol and ethyl acetate. Normal and reverse phase chromatography as well as normal phase HPLC of *n*-hexane fraction resulted in six compounds one of which was **3** (49).

Total synthesis of daurichromenic acid

Daurichromenic acid can be synthesized by uniting benzene ring derivative **4** with pyrone ring

moiety **3**. For this purpose a study has been conducted to design the route for efficient synthesis of chiral chromane intermediates. The retrosynthetic analysis is shown in Figure 3 (50). As per adopted scheme, Kabbe reaction was employed to synthesize pyranone skeleton **2**, which was then converted to chromanone **1a** and **1b**. Then, reduction of **1a** and **1b** resulted in chroman (50), and subsequently in chromen on the route to synthesize daurichromenic acid.

Structural elucidation and stereochemistry of daurichromenic acid cannot be determined through straightforward instrumental analyses, whereas, its chromane derivative, rhododaurichromanic acid A can be analyzed through X-ray crystallography. An indirect structure elucidation and absolute stereochemistry assessment of daurichromenic acid has been reported through its photochemical conversion into rhododaurichromanic acid A and rhododaurichromanic acid B. Isomerization of *trans* double bond at C11-C12 in daurichromenic acid has been reported before photochemical cyclization to produce rhododaurichromanic acid B (32).

Total synthesis of methyl (±)-daurichromenic ester **5** and (±)-rhododaurichromanic acid A and B **'6'** and **'7'** reported by another group (27) has been shown in Figure 4. In this exertion, *trans,trans*-farnesal **1** was reacted with symmetrical 1,3-cyclohexanedione **2** in the presence of piperidine. Reaction conditions favored condensation and electrocyclization of piperidine with **1**, which resulted in the production of 2*H*-pyran ring structure **3** (yield = 70%). Compound **3** was converted to methyl ester **4** in the presence of lithium diisopropyl amide and N≡C-COOMe (yield = 71%). Then, dehydrogenation of **4** was carried out in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) yielding **5** (yield = 44%). A hydrolysis reaction of **5** was

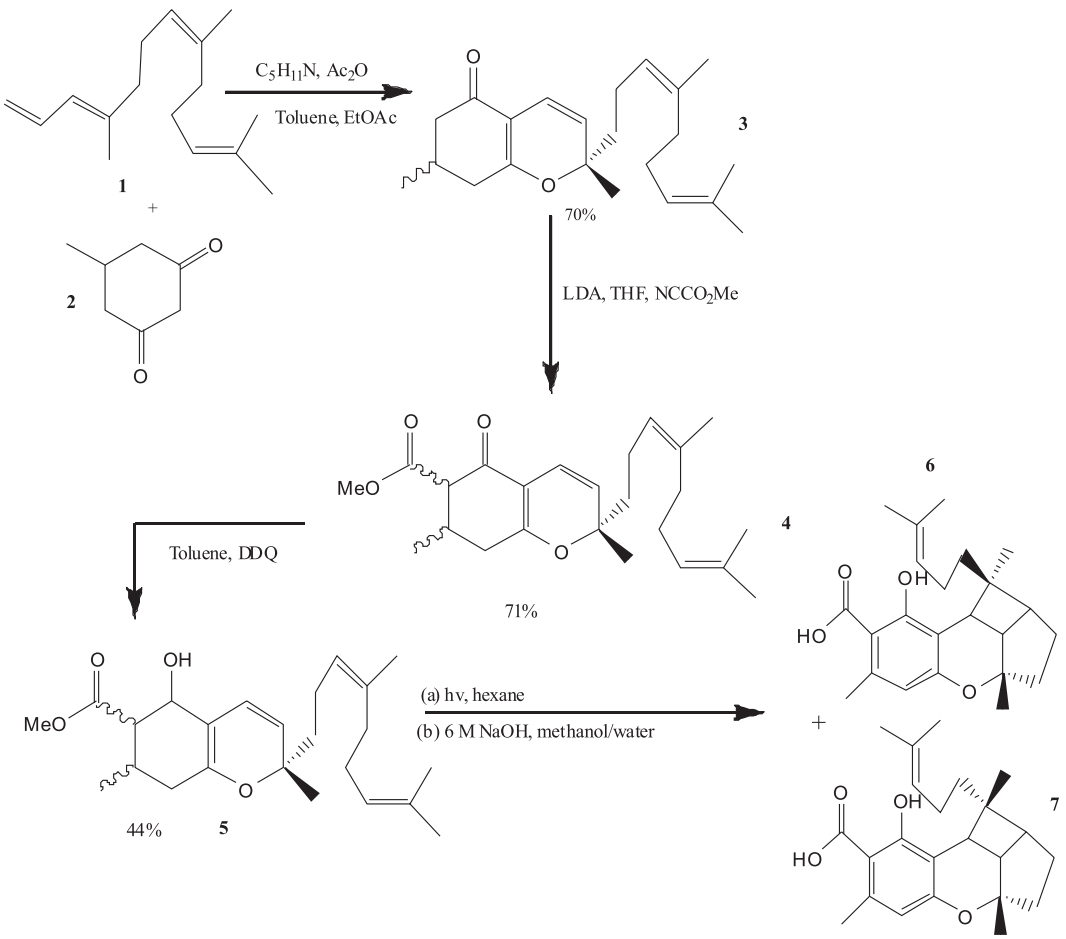

Figure 4. Synthesis of daurichromenic ester **5** and (±)-rhododaurichromanic acid A and B **6** and **7**. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone

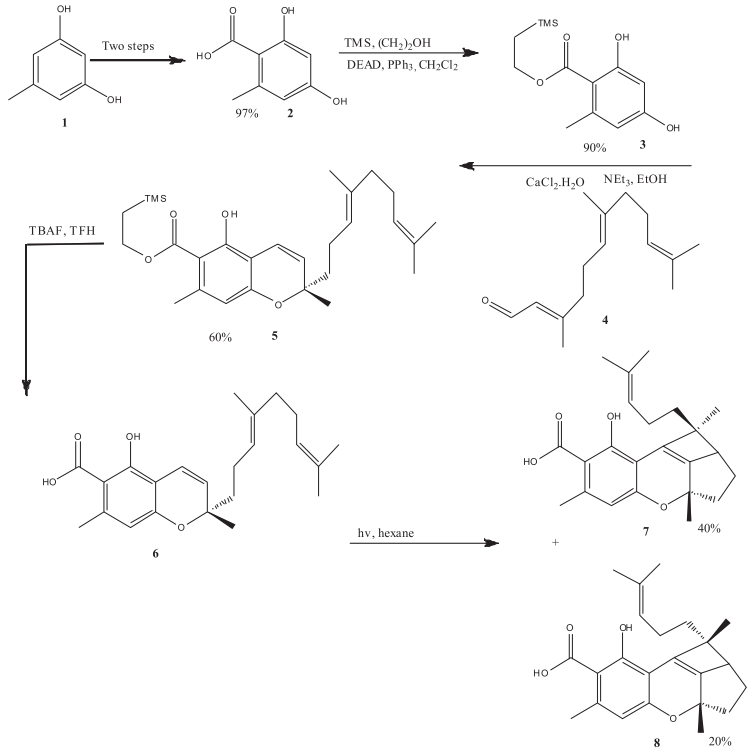

Figure 5. Synthesis of (±)-daurichromenic acid **6**, (±)-rhododaurichromanic acid A **7** and B **8** by using orcinol **1**

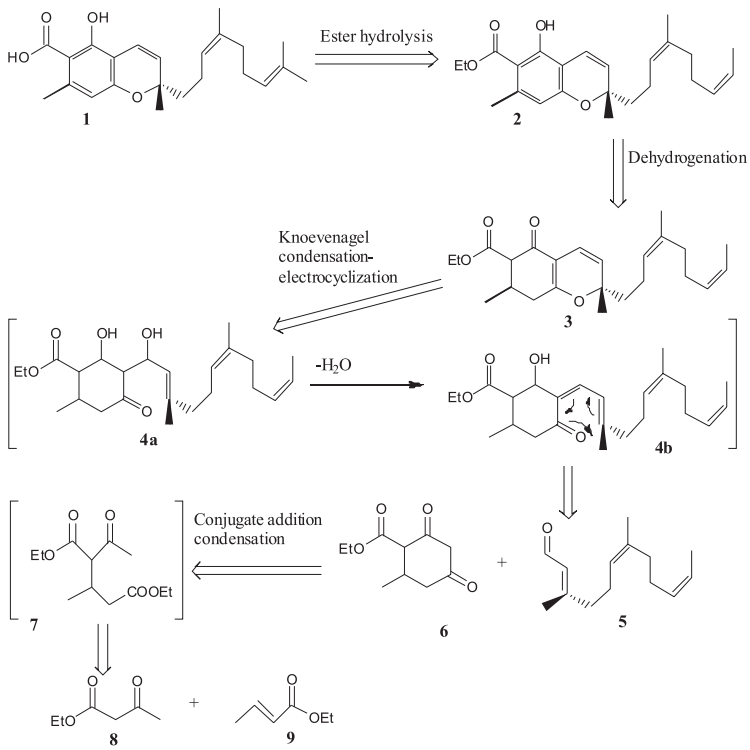

Figure 6. Retrosynthetic analysis of (±)-daurichromenic acid

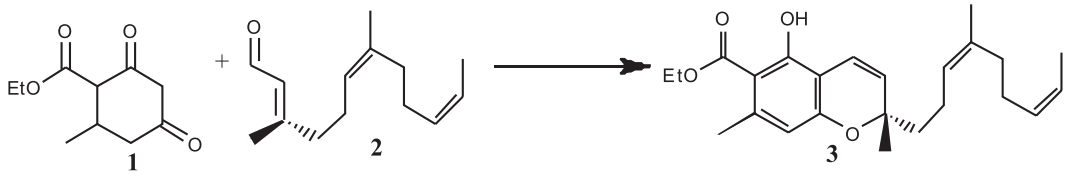

Figure 7. (±) Daurichromenic acid synthesis with Knoevenagel condensation and electrocyclization

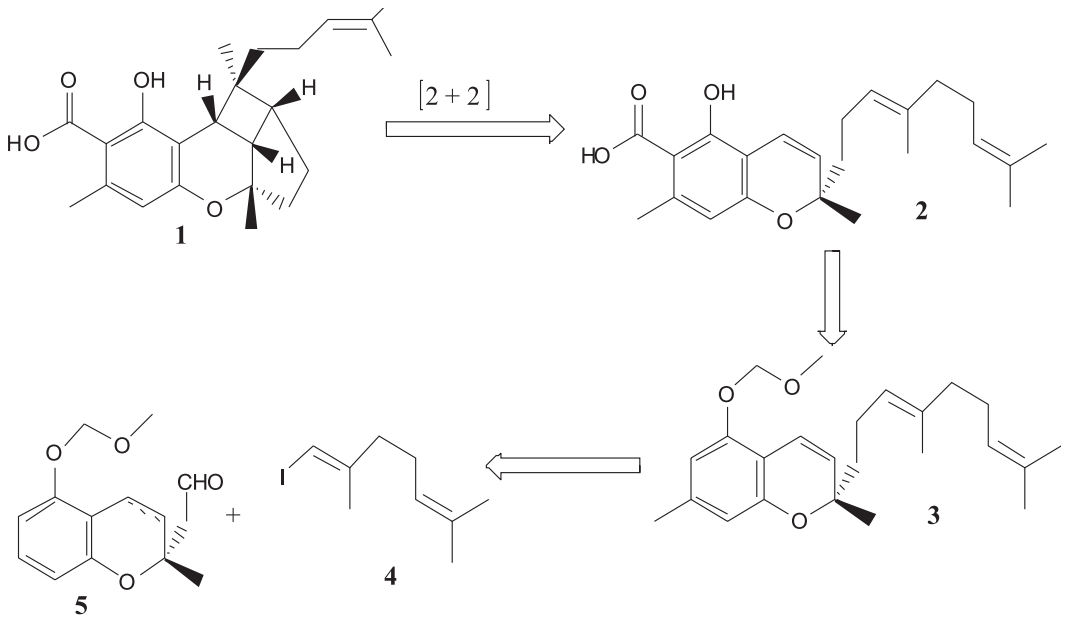

Figure 8. Retrosynthesis of rhododaurichromanic acid A **1** and daurichromenic acid **2**

planned to obtain (±)-daurichromenic acid but Hsung and coworkers could not establish the suitable reaction conditions for this purpose. So, **5** was first photochemically cyclized and then saponified to yield (1 : 1) mixture of **6** and **7** (yield = 74%) (28, 32, 34, 45-47).

In the same time, another group published quite efficient and concise scheme for total synthesis of (±)-daurichromenic acid **6** shown in Figure 5. In this scheme, orcinol **1** was converted into β-trimethylsilyl ethyl ether **3**. Microwave energy has assisted in condensation of **3** with *trans,trans*-farnesal **4** and yielded an ester **5** (yield = 60%). Deprotection of **5** in the presence of THF and tetra-*n*-butyl ammonium fluoride yielded **6** (yield = 94%) (32, 46, 51, 52). A photochemical conversion of **6** (in hexane) produced (±)-rhododaurichromanic acid A **7** (yield 40%) and B **8** (yield = 20%) (28, 32, 34, 45, 47). Meanwhile, another attempt was carried out to synthesize (±)-daurichromenic acid **1** (27). The retrosynthetic approach of this synthesis is presented in Figure 6.

According to this approach, conjugate addition and intramolecular condensation reaction between α,β-unsaturated esters **9** and alkyl acetoacetates **8** may result in 1,3-cyclohexanedione precursors **6**. The Knoevenagel condensation of unsymmetrical **6** with α,β-unsaturated aldehydes **5** would produce β-hydroxycarbonyl intermediates **4b** (the reactions of compounds having carbonyl functionality with active methylenes, for example, malonates and acetoacetates, follows the mechanism of Knoevenagel condensation. The catalytic amount of a base (amine) facilitates the production of alkylidene- or benzylidene-dicarbonyl compounds). Compound **4b** on dehydration converts into **4a** and followed by electrocyclization would yield 2*H*-pyrans **3**. Furthermore, **3** on dehydrogenation (oxidation/aromatization) results into **2** and ester hydrolysis of **2** can yield **1** and its analogues (27, 32, 46).

Based on retrosynthetic scheme, two different analogues of cyclohexanediones have been prepared either having a methyl or a phenyl substitution. Methyl substitutd species (yield = 81%) have been reported from ethyl acetoacetate and ethyl crotonate, whereas phenyl substituted compound (yield = 61%) has been reported from methyl acetoacetate and methyl cinnamate. These methyl and phenyl moieties verified ease of substitution at position 7 in daurichromenic acid. However, according to this study, such substitutions at position 5 and/or 6 were not possible by using methyl acetoacetate and analogous commercially available α,β-unsaturated methyl esters by this direct procedure. Commercially available α,β-unsaturated aldehyde "3,7-dimethyl-2,6-octadienal" (Citral, E/Z ≅ 2 : 1) has been utilized for the synthesis of (±)-daurichromenic acid. Condensation of methyl substituted cyclohexanedione with citral has yielded the precursor of (±)-daurichromenic acid (yield = 87%). The condensation was carried out at room temperature for about 3 h, in the presence of 5 mol % of 1,2-ethylenediammonium diacetate. This thermal treatment of prepared ester with DDQ in benzene for 4-16 h converted the carbonyl group at position 5 to hydroxyl group and yielded the desired precursor of (±)-daurichromenic acid (yield = 11%). The saponification of this precursor with an aqueous solution (5 M) of sodium hydroxide (~10 equiv.) in dimethyl sulfoxide on heating at 80°C for ~16 h yielded (±)-

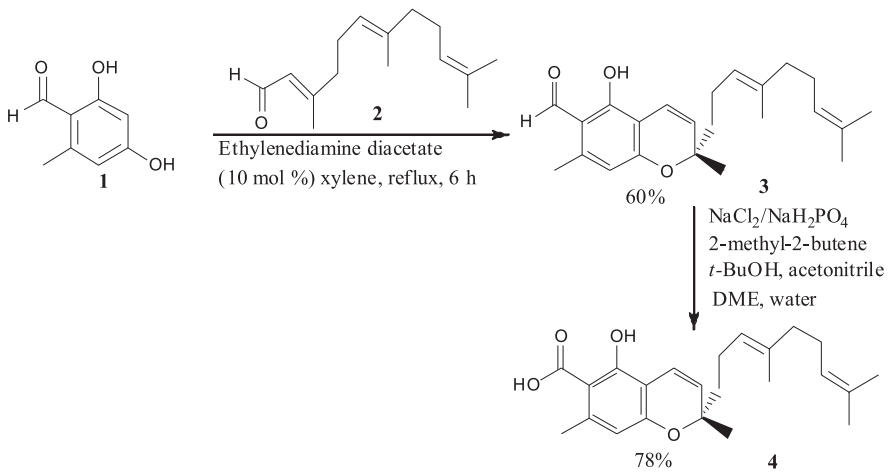

Figure 9. Synthesis of daurichromenic acid **4** from 2,4-dihydroxy-6-methylbenzaldehyde **1**

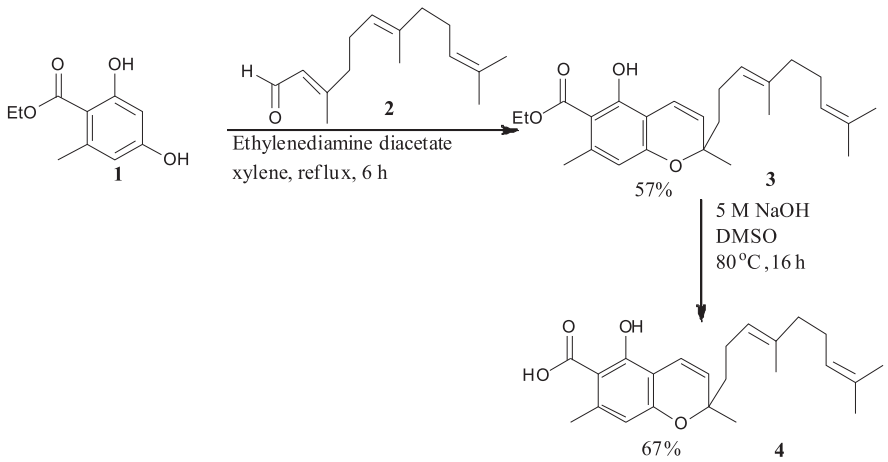

Figure 10. Synthesis of daurichromenic acid **4** from 2,4-dihydroxy-6-methylbenzoate **1**

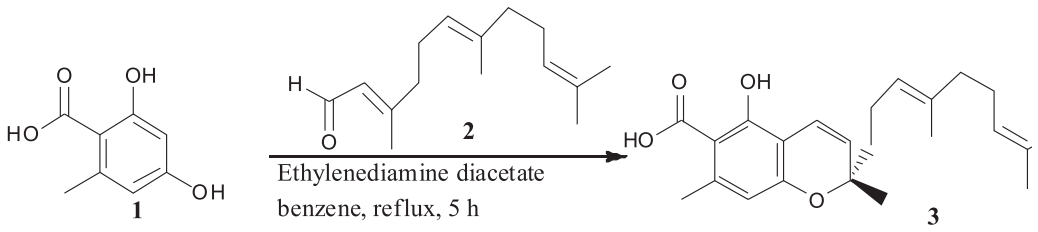

Figure 11. Synthesis of daurichromenic acid **3** from 2,4-dihydroxy-6-methylbenzoic acid **1**

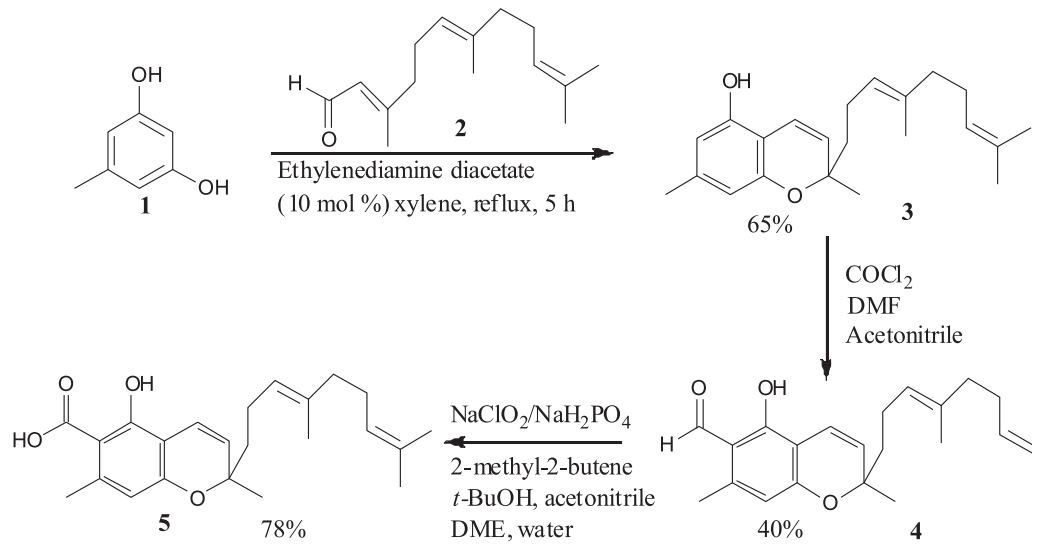

Figure 12. Synthesis of daurichromenic acid **5** from orcinol **1**

daurichromenic acid with a yield of 76%. The spectroscopic data for the synthesized (±)-daurichromenic acid were in full agreement with these reported in the literature for naturally isolated (±)-daurichromenic acid (32). A number of other daurichromenic acid analogues had also been prepared in this study, which signifies that a diverse substituents can be introduced at position 2 and position 7 in the analogues of daurichromenic acid (32). The retrosynthetic approach of another synthesis has been presented in Figure 8 (42).

According to this approach, the daurichromenic acid **2** and rhododaurichromnic acid A **1**, both, can be synthesized by making a carbon-carbon bond between the chiral chromane **5** and vinyl iodide **4** (42). The efforts made to synthesize **1** established that the palladium catalyzed asymmetric allylic alkylation reaction of phenol allyl carbonates facilitate the formation of chiral chromanes and further help in their oxidation to yield chiral chromens. The introduction of the side chain was completed by regioselective allylic deoxygenation using palladium as a catalyst (42).

In the year 2005, another attempt was made to synthesize daurichromenic acid by using either 2,4-dihydroxy-6-methylbenzaldehyde **1** or 2,4-dihydroxy-6-methylbenzoic acid as shown in Figure 9. Both of these starting materials are commercially available thereby making the synthetic route relatively simpler than before. Moreover, the use of **1** as a starting material eliminates the hydrolysis step in the daurichromenic acid **4** synthesis (45). Refluxing of **1** with *trans,trans*-farnesal **2** in xylene for 6 h was carried out in the presence of catalytic amounts of ethylenediamine diacetate (10 mol %). The yield of adduct formed was 60%. The resulting 2*H*-benzopyran **3** in the presence of buffered sodium chlorite at room temperature yielded **4** after 10 h (yield = 78%) (45).

The same group of scientists modified the above mentioned reaction conditions in another

study. They replaced the aldehyde with ethyl 2,4-dihydroxy-6-methylbenzoate **1**, as shown in Figure 10, and refluxed it with **2** in the presence of ethylenediamine diacetate (20 mol %). Although the reaction was successful, the yield of resultant **3** was reduced to 57%. For hydrolysis, 5 M sodium hydroxide was used this time; temperature was raised to 80°C and time was increased to 16 h. Compound **4** produced as a result was significantly lower in yield than before (yield = 67%). The spectroscopic data of **4** synthesized was in agreement with the one published (47, 53).

In a quest to further improve the synthesis of **4** and to bring it to one step synthesis, 2,4-dihydroxy-6-methylbenzoic acid **1** was refluxed with **2** in the presence of ethylenediamine diacetate (10 mol%) in benzene for 5 h. Compound **4** was produced in just one step (yield = 59%) (28).

From the studies of this research group, it can be concluded that shuffling between aldehyde, ester and acid as a starting material or changing the aromatic solvent can affect the yield of the daurichromenic acid produced. Although the best yield of daurichromenic acid obtained was 78% by using 2,4-dihydroxy-6-methylbenzaldehyde as a starting material but the more promising scheme is the one step synthesis of daurichromenic acid with 2,4-dihydroxy-6-methylbenzoic acid as a starting material and benzene as a solvent. It should be noted that the yield of daurichromenic acid in case of one step synthesis is 19% less than the maximum reported yield, this one step synthesis is cost effective, as it requires less chemicals.

When these researchers replaced benzoic acid, aldehyde or ester as a starting material all together with orcinol **1**, as shown in Figure 12, it resulted in the synthesis of daurichromenic acid **5** in three steps (34). Compound **1** has previously been used as a starting material for the synthesis of **5** but it required five steps to accomplish the synthesis (32). First step was similar to the study of these researchers which they did in the year 2005. The **2** was refluxed with **1** in the presence of ethylenediamine diacetate (10

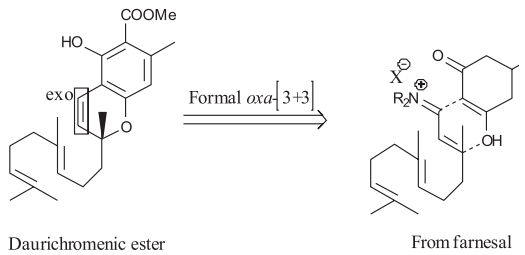

Figure 13. Synthesis of daurichromenic acid by formal *oxa*-[3+3] cycloaddition

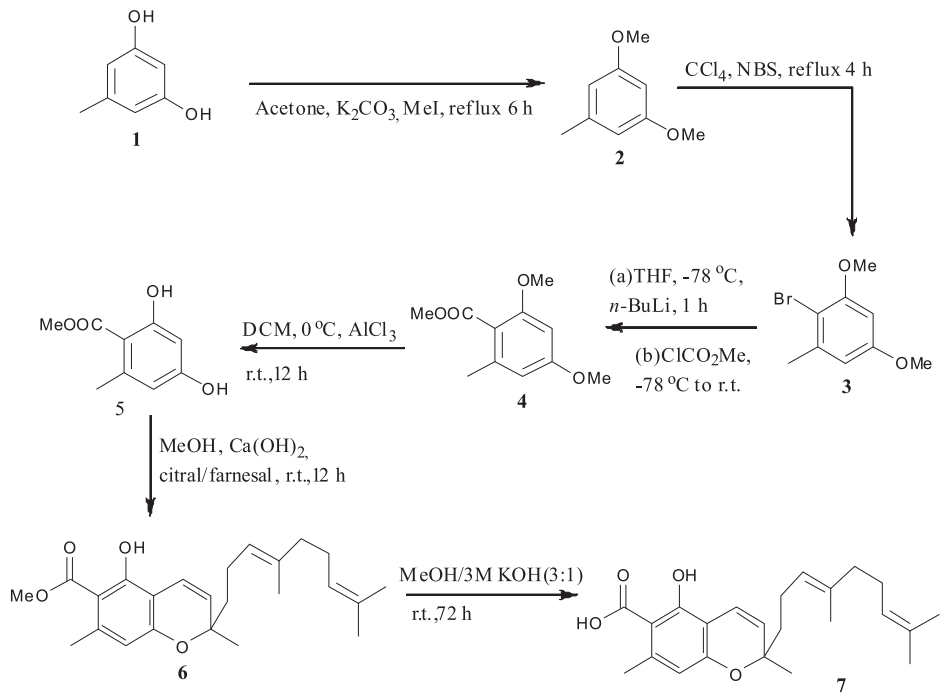

Figure 14. Synthesis of daurichromenic acid **7** from orcinol **1**. NBS = N-bromosuccinimide

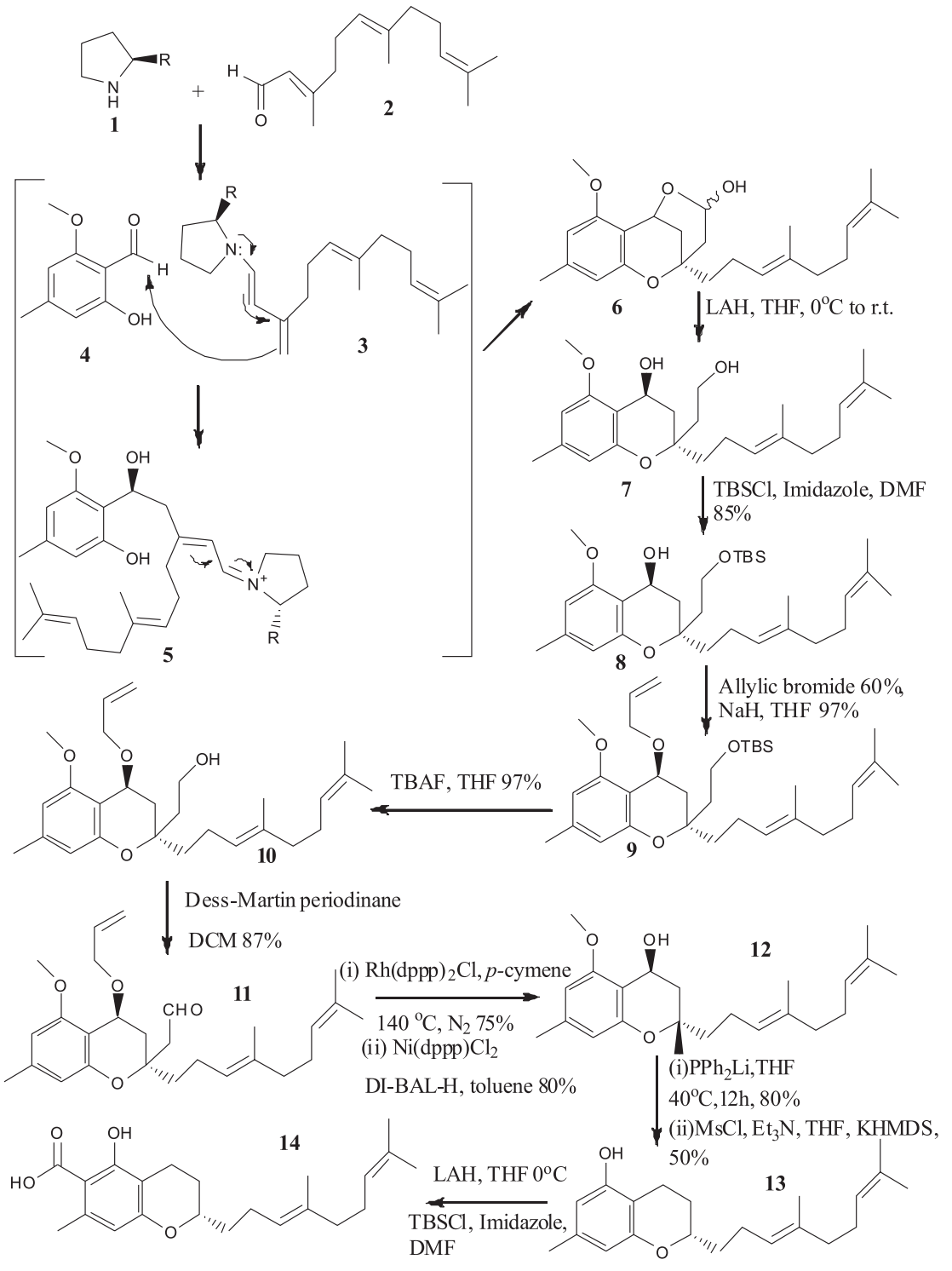

Figure 15. Enantioselective synthesis of daurichromenic acid **14**. Reagents used: LAH = lithium aluminum hydride, THF = tetrahydrofuran, TBSCl = tert-butyldimethylsilyl chloride, DMF = dimethylformamide, NaH = sodium hydride, TBAF = tetra-n-butylammonium fluoride, DCM = dichloromethane, $Rh(dppp)_2Cl$ = [1,3-bis(diphenylphosphino)propane]rhodium(II) chloride, $Ni(dppp)Cl_2$ = [1,3-bis(diphenylphosphino)propane]dichloronickel(II), DI-BAL-H = diisobutylaluminium hydride, PPh_2Li = lithium diphenylphosphide, MsCl = mesyl chloride, Et_3N = triethylamine, KHMDS = potassium bis(trimethylsilyl)amide

mol%) in xylene for 5 h. It yielded (±)-confluentin **3** (yield = 65%). In the next step, formylation of (±)-confluentin **3** was carried out in the presence of oxalyl chloride/DMF in acetonitrile at 0°C. The yield of the resultant compound **4** was 40%. The oxidation of **4** at room temperature for 10 h with buffered sodium chlorite gave **5** (yield = 78%). The spectroscopic data of **5** were in agreement with the literature (34).

Another approach adopted to synthesize the daurichromenic ester was formal *oxa*-[3+3] cycloaddition (36, 54). The retrosynthetic approach is shown in Figure 13. Grifolic acid is a natural product isolated from a fungus *Albatrellus dispansus*. Grifolic acid has been used to synthesize (±)-daurichromenic acid in just one step in the presence of dichlorodicyanobenzoquinone in benzene (yield = 73%). The reaction occurs at 90°C and with stirring time of 30 min. HPLC technique helps to separate (+)-daurichromenic acid and (-)-daurichromenic acid synthesized (38).

In another study, orcinol monohydrate **1** was used as a startng material to synthesize daurichromenic acid **7** (Fig. 14). This **1** was subjected first to methylation to produce **2** and then to N-bromosuccinimide-induced nuclear bromination to yield **3**. Next, lithiation followed by treatment with methyl chloroformate yielded an ester **4** which was demethylated, in the presence of $AlCl_3$, to produce the required phenolic ester **5**. Finally, benzopyran **6** was obtained from **5** by treating it with citral/farnesal in the presence of calcium hydroxide. A possible calcium ion complexation with the phenol groups can be the foundation of the observed regioselectivity. Saponification of **6** resulted in the production of **7** (reported yield 80%) (55). The reaction scheme is in Figure 14. The quest to synthesize daurichromenic acid led to another study in the year 2010. The speciality of this work was the enantioselective synthesis of daurichromenic acid (35). The scheme followed can be seen in Figure 15. In the first step, farnesal **2** and salisaldehyde **4** were reacted in the presence of a derivative of proline **1** to synthesize a lactol **6**. The **1** used was of configuration 'S' as only 'S' configured **1** can yield 'S' configured **6**. Once the 'S' configured **6** was obtained, it was reduced to a diol **7**. This **7** was protected selectively to yield **8** and was reacted with allyl bromide to synthesize **9**. Next, deprotection step (of OTBS) resulted in **10** and it was followed by oxidation to yield an aldehyde **11** which was decarboxylated and then deallylated to yield benzylic alcohol **12**. Demethylation of **12** resulted in an enantioselective chromen. Free phenol bromination at *ortho* position of this chromen followed by carboxylation yielded enantioselective daurichromenic acid **14** (35).

CONCLUSION

Beyond various compounds, explored for anti-HIV activity, daurichromenic acid has been reported with excellent behavior. A high therapeutic index (TI) of daurichromenic acid proves its efficacy. Unlike other commercial anti-HIV products, it has been reported with no adverse side effects. Its pharmacological importance influenced the scientists to work on different synthetic approaches.

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