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An account of organic chemistry research in Botswana

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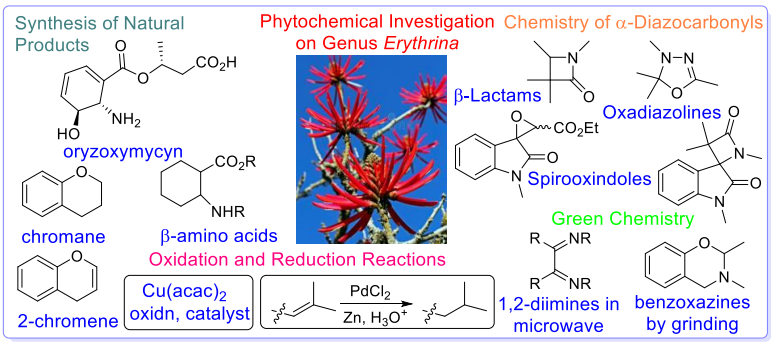
Abstract

The present paper gives an account of research in different areas of organic chemistry carried out at the University of Botswana. It describes the results of phytochemical investigations carried out on eight species of genus *Erythrina*. Several new alkaloids and non-alkaloids have been isolated and screened for different biological activities. Physicochemical properties and fatty acids composition of some oils are described as well. The paper also documents some synthetic approaches to natural products and their derivatives, β-amino acids, β-lactams, 1,3,4-oxadiazolines, spirooxindole-2-azetidinones and spirooxindole-oxiranes. The synthetic approaches include the elaboration of the Diels-Alder product of furan and some dienophiles to give the natural product oryzoxymycin and cyclohexyl-β-amino acids. In addition, studies on synthesis of chromane/chromene ring systems are summarized. The application of α-diazoketones and ethyl diazoacetate in the synthesis of β-lactams, 1,3,4-oxadiazoline, spirooxindole-2-azetidinones, and spirooxindole-oxiranes is described. Some oxidative, reductive, and other reactions of β-lactams are discussed. In the green chemistry domain, results on grinding-induced synthesis of benzoxazines and microwave-assisted synthesis of benzil diimines are presented. Bis(acetylacetonato)copper(II)-catalyzed oxidation reactions of hydrazones and the *sec*-alcoholic group of benzoins to azines and 1,2-diketones, respectively, are described. In addition, the $PdCl_2$-catalyzed transfer hydrogenation of alkenes to alkanes in the presence Zn powder is accounted.



Keywords: *Erythrina*-phytochemistry, oryzoxymycin, chromanes, β-lactams, oxadiazolines, β-amino acids, α-diazocarbonyls, green chemistry

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1. Introduction

Botswana is a sovereign nation in the Southern African region and has been such since September 1966. It has an area of over 600,000 sq. km. with the population of around 2.5 million people. At the time of independence, access to higher learning and middle-level training in Botswana was through the University of Basutoland, Bechuanaland and Swaziland (UBBS) which became the University of Botswana, Lesotho and Swaziland (UBLS) post-independence with its main campus in Lesotho. This university as the name implies, served the three nations of Botswana, Lesotho and Swaziland. Lesotho and Swaziland then opened separate universities, and the University of Botswana (UB) was inaugurated in 1982. To date, a few other public and private tertiary level teaching and research institutions have started operation, but the University of Botswana, with over 15000 students and 2500 staff, remains the largest public university in the country.

The UB started the graduate programs in Chemistry in 1992 by introducing M.Sc. degree programs in analytical and natural products chemistry. These programs appeared attractive to students as many students from Botswana and the neighboring countries joined these programs in the succeeding years. The popularity of these programs led to expansion of the chemistry graduate programs into the M. Phil./Ph. D. programs in analytical and natural products chemistry in 1996. The research activity in the department was thus focused mainly on the extraction, isolation and characterization of natural products, and analytical chemistry. A Review of natural products research at the University of Botswana covering this period has already been published.[1]

With an objective to train students to acquire advanced skills and knowledge in organic chemistry that are required by the public and private sectors in the long run, the department realized the need of broadening the scope of the graduate programs. Accordingly, the Department of Chemistry graduate programs were redesigned in 2000. The department at present offers M.Sc., M.Phil. and Ph.D. programs in all four traditional

streams of chemistry, namely physical, inorganic, organic and analytical chemistry. Despite limited human resources the broadening of the graduate programs gave further impetus to research in organic chemistry. The natural product research is mainly focused on bioassay guided extraction and isolation of secondary metabolites from plants used as herbal medicines by traditional healers. Also, oils from several seeds have been extracted and evaluated for their use in food and biofuels. The synthetic organic chemists are involved in reactions employing carbenoids/ketenes, heterocyclic synthesis, palladium-catalyzed hydrogenation of alkenes, synthesis of flavones, and metal-catalyzed oxidation, etc. These investigations are in important areas of synthetic organic and medicinal chemistry, and have led to the synthesis of azabutadienes, diimines, amides, biologically important heterocyclic compounds such as β-lactams and oxadiazolines, spirooxindoles, and flavonoids. Botswana, through the Chemistry Department of University of Botswana, has made a significant progress in research in different areas of synthetic and mechanistic chemistry. Many of the results have been presented in the IUPAC sponsored conferences and have been published in reputed peer-reviewed journals over the last twenty years. The UB is currently undergoing a major transformation which includes a research strategy focusing on societal and economic needs. It is, therefore, pertinent to account for the diverse types of research work in organic chemistry at the University of Botswana. Accordingly, the present article gives an account of organic chemistry research in University of Botswana.

2. Phytochemical Studies

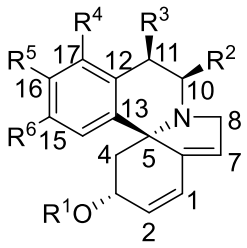
The University of Botswana has had a robust program in natural products research. We have collaborative research programs too with many other universities of Africa. The collaborative program is financially supported mainly by the Network of Analytical and Bioassay Services in Africa (NABSA). The natural product research at the University of Botswana between 1995 and 2001 was reviewed by Majinda *et al*.[1] The present account summarizes what has been done since then with the focus mainly on the genus *Erythrina*, and builds on the previous work.

2.1 Phytochemical studies on genus *Erythrina*

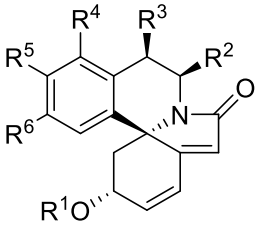
The genus *Erythrina* derives its name from ''erythros", meaning red in Greek referring to the red flowers of the plants. The genus *Erythrina* is known to produce alkaloids (erythrinan-type),[2] flavonoids, isoflavonoids, pterocarpans and triterpene saponins. Extensive work has since been done on the genus *Erythrina* and, to date, eight *Erythrina* species namely *E. latissima*,[3,4] *E. lysistemon*,[5-7] *E. abyssinica*,[8] *E. caffra*,[9-11] *E. livingstoniana*,[12-14] *E. droogmansiana*,[15] *E. brucei*,[16] and *E. sacleuxii*[17-19] have been investigated. The succeeding sub-sections describe the compounds isolated from these species focusing on new/novel compounds. The biological activities of the compounds are described where applicable.

2.1.1 Novel alkaloids from genus Erythrina. Two novel glycodienoid alkaloids were isolated from *Erythrina latissima* seeds (+)-β-D-glucoerysopine **1** and (+)-15β-D-glucoerysopine **2,** along with seven known tetracyclic dienoid alkaloids (Figure 1).[20] The extract from the seed pods, on the other hand yielded a new alkaloid **3**, and a new phenyl benzofuran **8**, while the root bark gave four known pterocarpans and two flavonoids.[3] The seed pod extract was found to be toxic to brine shrimps (*Artemia salina*) with LC_{50} of 6.31 μg/ml and compound **3** showed an LC_{50} value of 12.61 μg/ml.[3] Work on the flowers and pods of *E. lysistemon* yielded four new erythrinan alkaloids, (+)-11β-hydroxyerysotrine **4**, (+)-11β-hydroxyerysotrimidine **5**, (+)-11β-methoxyerysotrimidine **6**, and (+)-11β-hydroxyerysotrine *N*-oxide **7**.[5] Compounds **4**-**6** were weakly radical scavenging while compound **7** showed weak to moderate antioxidant activity with IC_{50} value of 280μg/ml. The

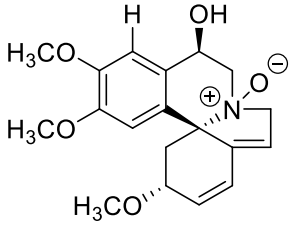
antioxidant activity was studied by radical scavenging assay using 2,2-diphenyl-1-picryl hydrazyl (DPPH) that is a well-known radical and radical-scavenger.



1: R^1 = OMe, R^2 = R^3 = R^4 = H, R^5 = OGlc, R^6 = OH ((+)-16β-D-glucoerysopine)
2: R^1 = OMe, R^2 = R^3 = R^4 = H, R^5 = OH, R^6 = OGlc ((+)-15β-D-glucoerysopine)
3: R^1 = R^5 = R^6 = OMe, R^2 = R^3 = =O, R^4 = H (10,11-dioxoerysotrine)
4: R^1 = R^5 = R^6 = OMe, R^2 = R^4 = H, R^3 = OH ((+)-11β-hydroxyerysotrine)



5: R^1 = R^5 = R^6 = OMe, R^2 = R^4 = H, R^3 = OH ((+)-11β-hydroxyerysotramidine)
6: R^1 = R^3 = R^5 = R^6 = OMe, R^2 = R^4 = H ((+)-11β-methoxyerysotramidine)



7: (+)-11β-hydroxyerysotrine *N*-oxide

Figure 1. New alkaloids from *Erythrina*.

2.1.2 Novel non-alkaloidal components of genus Erythrina. The seed pod of *E. latissima* yielded a 2-phenylbenzofuran derivative **8**,[3] the first one of its kind to be reported in *Erythrina* genus, along with a new erythrinan alkaloid **3**, and nine known compounds (Figure 2). 2-Phenylbenzofuran derivative **8** showed potent antibiotic activity against Gram-positive bacteria (*Staphylococcus aureus* & *Bacillus subtlis*), Gram-negative bacteria (*Escherichia coli* & *Pseudomonas aeruginosa*) and fungi/yeast (*Candida mycoderma* & *Saccharomyces cerevisiae*). Further work on the stem wood of *E. latissima* yielded three compounds, two isoflavones, erylatissin A **9**, erylatissin B **10**, and a flavanone, erylatissin C **11**, in addition to ten known flavonoids.[4] These compounds exhibited weak to moderate activity against Gram-positive & Gram-negative bacteria and fungi. It furthermore showed moderate radical scavenging activity using DPPH.[4]

The flowers and pods of *E. lysistemon* yielded four new alkaloids **4-7** (Figure 1) in addition to ten known alkaloids.[5] The twigs, leaves, stem bark, stem wood and flowers gave three new compounds- an isoflavone **12**, a neolignane **13**, and a hydroxylated unsaturated fatty acid **14** (Figure 3), along with twenty seven known compounds.[6]

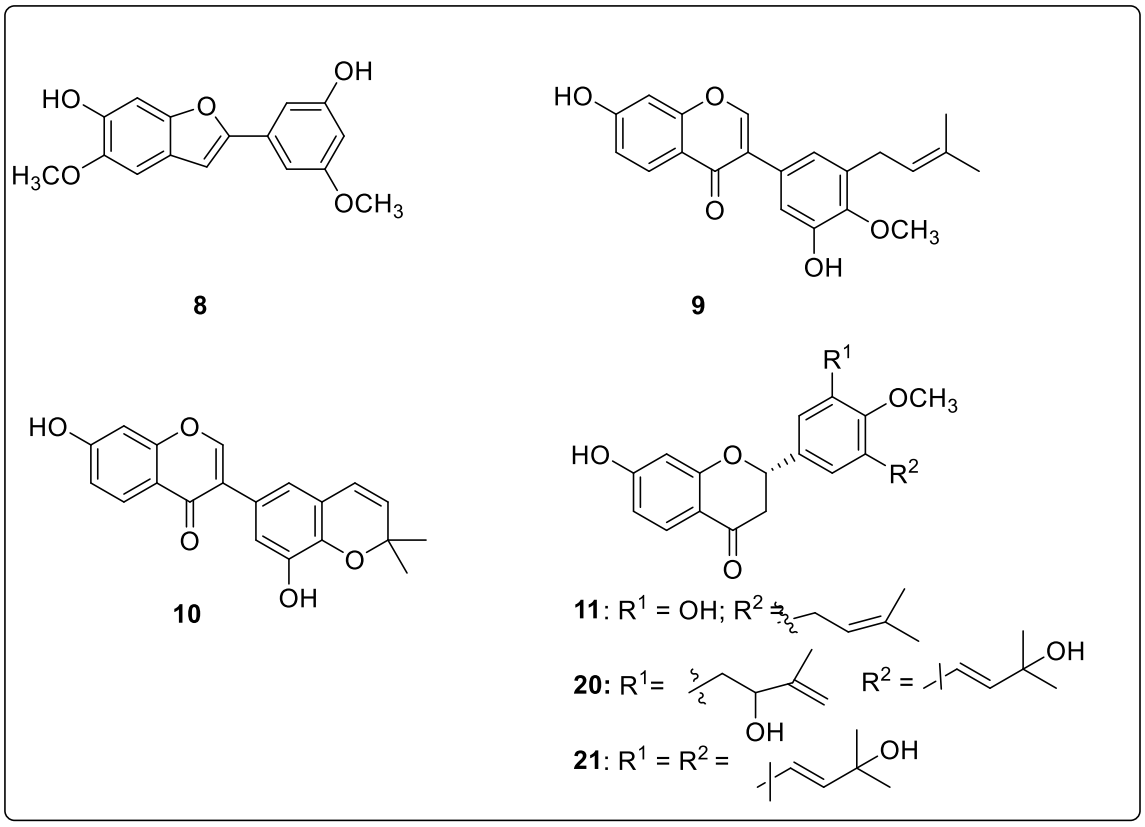


Figure 2. 2-Phenylbenzofuran, flavanone, and isoflavones from *E. latissima*.

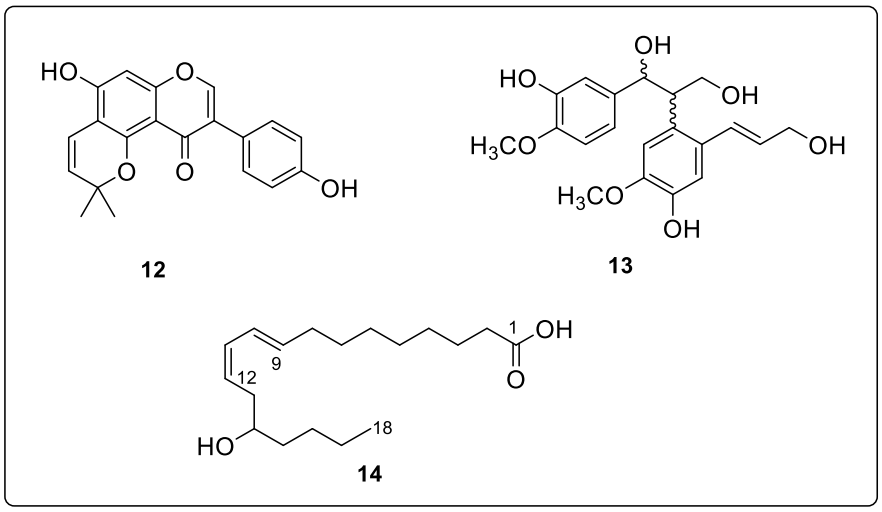


Figure 3. An isoflavone, a neolignane, and a hydroxylated unsaturated fatty acid from *E. lysistemon*.

E. abyssinica: The twigs and roots gave twenty one known compounds as well as a new flavanone abyssinone VII, **15** (Figure 4). Abyssinone VII (**15**) was found to be strongly radical scavenging (DPPH) and weakly antimicrobial (against *B. subtilis, S. aureus*, *E. coli*, and *S. cereviciae*).[8]

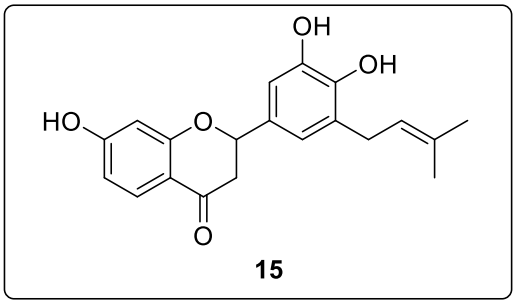


Figure 4. Abyssinone VII from *E. abyssinica*.

E. caffra: Phytochemical investigation of the stem bark gave three new isoflavonoids, erycaffra A **16**, erycaffra B **17**, and erycaffra C **18** (Figure 5), along with eight known compounds.[9] Further work on the stem bark gave four more known compounds and three new flavonoids, erycaffra E. **19** (Figure 5) erycaffra D. **20** and erycaffra F. **21** (Figure 2).[10]

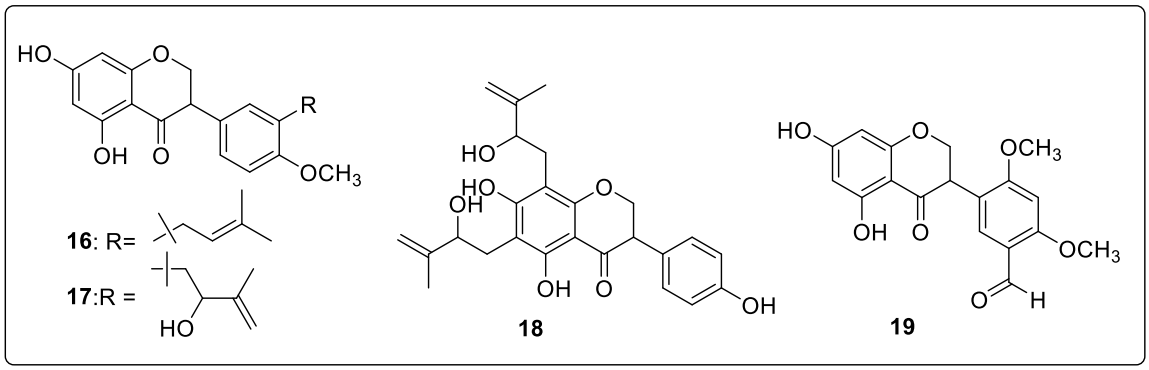


Figure 5. New flavonoids and isoflavonoids from *E. caffra*.

Erycaffra A-E were tested against human cervix carcinoma KB-3-1 cell lines and only erycaffra C **18** showed significant activity.[11] All the compounds showed weak to no antimicrobial activity against *E. coli, B. subtilis, P. agarici, M. luteus, S. ferus*, and *S. minor*.

E. livingstoniana: A total of eleven new compounds **22-32** were isolated and characterized from stem bark, twig, and root bark (Figure 6). The stem bark gave three known compounds and three new compounds erylivingstone A, **22**, erylivingstone B, **23**, and erylivingstone C, **24**. The compounds showed moderate radical scavenging activity with IC_{50} values of 5.7, 4.6 and 4.4 µg/ml respectively.[12] The twigs gave six known compounds and six new compounds erylivingstone D, **25**, erylivingstone E, **26**, erylivingstone F, **27**, erylivingstone G, **28**, and erylivingstone H, **29**, and erylivingstone I, **30**.[13] These compounds displayed very weak antimicrobial activity and weak to moderate radical scavenging (DPPH) activity (IC_{50} 98.3- 4.9 µg/ml) with erylivingstone H (**29**) showing the best radical scavenging activity (4.9 µg/ml), vs 1.2 µg/ml for Trolox (standard reference). These compounds did not show any potential anti-inflammatory activity in prostaglandin E2 (PGE_2) competitive enzyme immunoassay. The root bark gave eight known compounds and two new compounds, erylivingstone J, **31**, and erylivingstone K, **32**.[14]

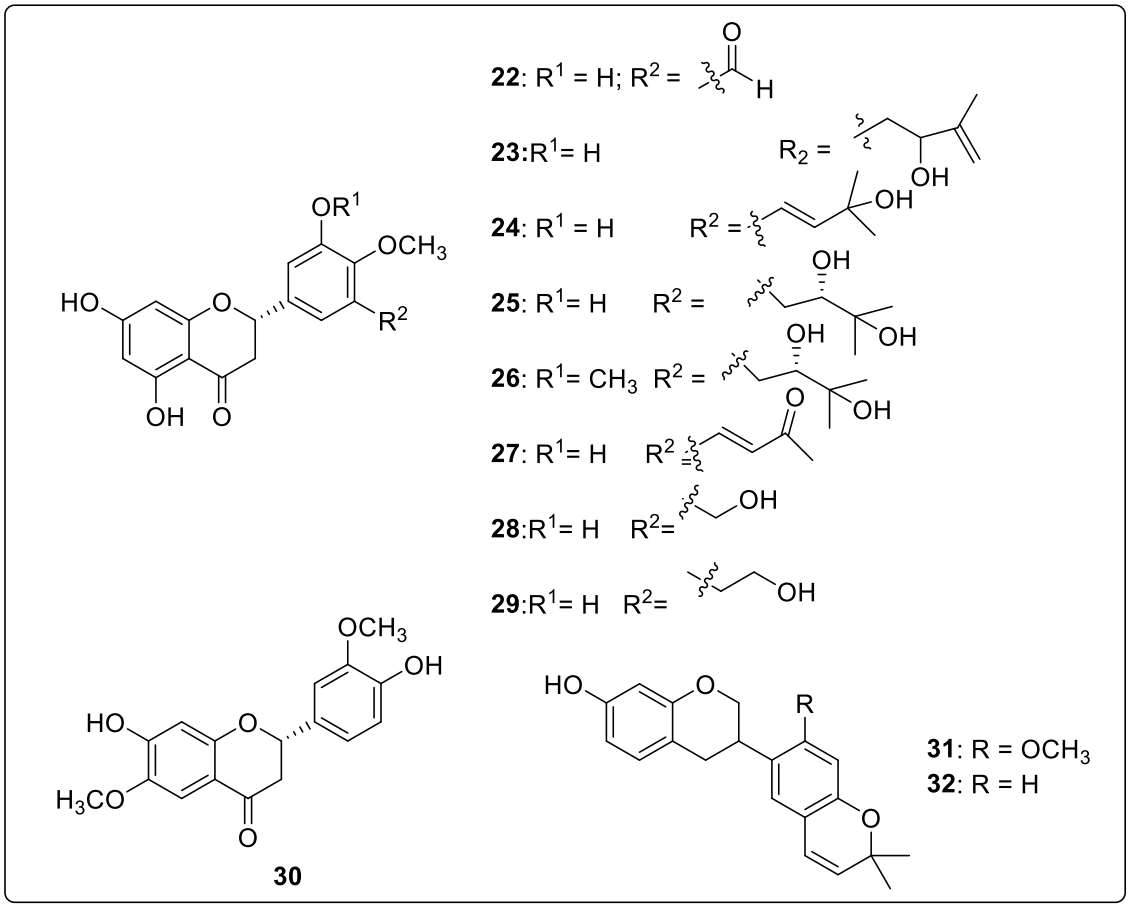


Figure 6. New compounds isolated from *E. livingstoniana.*

E. droogmansiana: This plant was collected from the Mbuazi/Mbaza Ngugu, 150 km west of Kinsasha, Democratic Republic of Congo. Eight known compounds and two new compounds, erydroogmansin A **33** and erydroogmansin B **34** (Figure 7) were isolated from the root bark of this plant.[15] Compounds **33** and **34** showed moderate to strong radical scavenging (DPPH) activity (IC_{50} of 11 and 4.1 µg/ml, respectively, with Trolox giving 1.2 µg/ml).

E. brucei: The plant was collected from western Ethiopia. A total of twenty one compounds including two new compounds, erybrucein A **35**, and erybrucein B **36** (Figure 8) were isolated from the stem and root barks of this plant.[16] These compounds showed weak antibacterial activity (against S. *aureus* (NCTC 6571), *B. cereus* (ATCC 33019), *B. megaterium* (ATCC 14581), and *E. coli* (NCTC 10332)) and moderate radical scavenging (DPPH) activity (IC_{50} of 6.3 & 13.3 µg/ml, respectively).

E. sacleuxii: The plant was collected from Mutsengo, Kilifi County, Kenyan Coast, Kenya. Phytochemical investigation of the stem bark gave eight known and two new compounds, erysacleuxin A **37**, and erysacleuxin B **38** (Figure 9).[17] The compounds were assessed for antifungal activity and showed no activity against *Botrytis cinerea*, *Candida albicans*, *Eremothecium coryli*, *Penicillium notatum*, *Pyricularia oryzae* or *Rhizomucor meihei*. The twigs of the plant yielded seven known compounds and two more new compounds erysacleuxin C **39**, and erysacleuxin D **40** (Figure 9).[18] Erysacleuxins C and D were found to be cytotoxic against human cancer cell line HeLa-S3 with IC_{50} values of 130.4 and 54.9 µM, respectively.[18,19]

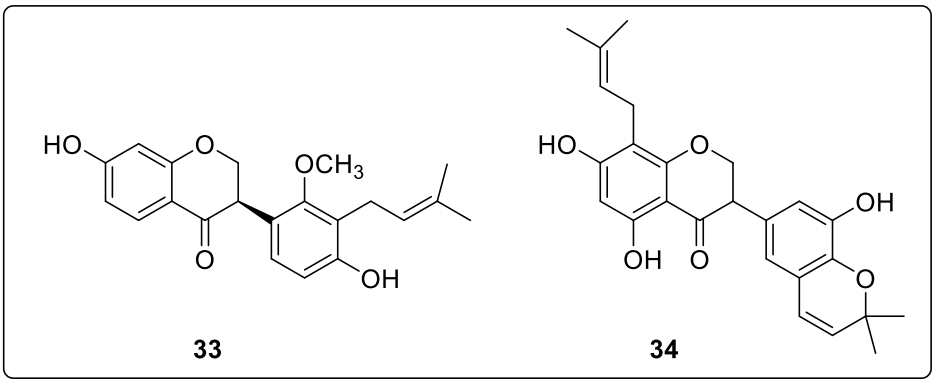


Figure 7. New compounds with radical-scavenging activity from *E. droogmansiana*.

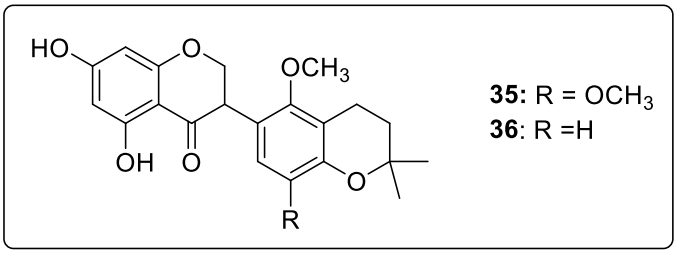


Figure 8. Erybrucein A and B from *E. brucei*.

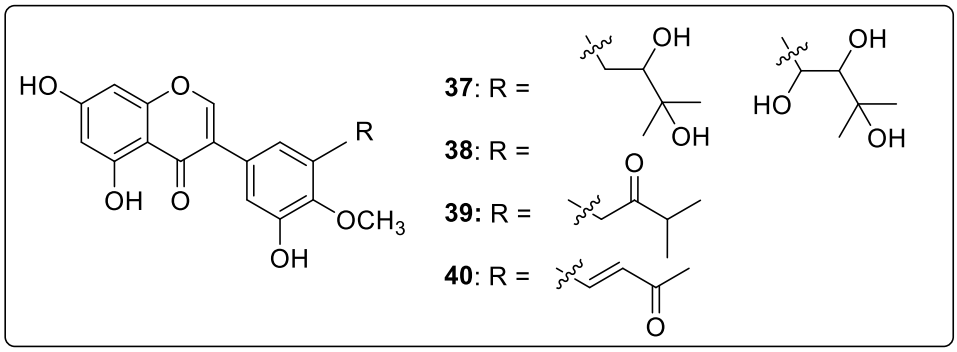


Figure 9. New compounds from *E. sacleuxii.*

2.2 Phytochemical studies on other genera

Bolusanthus speciosus Harms is a monotypic genus (one species) belonging to the family Fabaceae/ Leguminosae. This plant commonly called tree Wisteria due to its striking resemblance to the vine Wisteria. The tree grows up to 7 m tall and due to its beauty has been used as an ornamental plant. The tree is found in South Africa, Botswana, Mozambique, Zimbabwe, and Zambia. The bark of the tree is used to treat abdominal pains, emetism and tuberculosis. Phytochemical work on the stem bark of the plant led to isolation and characterization of four known compounds as well as three new compounds- bolusantol A **41**, bolusanthol B **42**, and bolusanthol C **43** (Figure 10).[21] Further work on the stem bark yielded five known compounds and two new compounds, bolusanthol D **44**, and bolusanthol E **45** (Figure 10). Bolusanthol E was found to be moderately

active against Gram- positive bacteria but weakly active against Gram-negative bacteria while bolusanthol D was weakly active against both Gram-positive and Gram-negative bacteria.[22] The methanolic extract of the root bark yielded three known compounds, a new isoflavanone bolusanthin II **46** (Figure 10), and four new pterocarpans bolucarpan A **47**, bolucarpan B **48**, bolucarpan C **49**, and bolucarpan D **50** (Figure 11). Bolusanthin II was moderately active against Gram-positive and Gram-negative bacteria, and yeast fungi, while bolucarpans A-D were only weakly active against these microorganisms.[23] Work on the root wood of *B. speciosus* yielded eight known compounds and three new compounds, isogancaonin C **51**, bolusanthin III **52**, and bolusanthin IV **53** (Figure 12). These three compounds were weakly active against *Eschirichia coli*. Isogancaonin C was moderately active against *Bacillus subtilis*, *Staphylococcus aureus* and Candida mycoderma, and weakly radical scavenging (IC_{50} 650 µg/ml). Bolusanthin III and IV were weak to moderately active against the three test organisms and strongly radical scavenging (IC_{50} 11 and 29 µg/ml, respectively).[24]

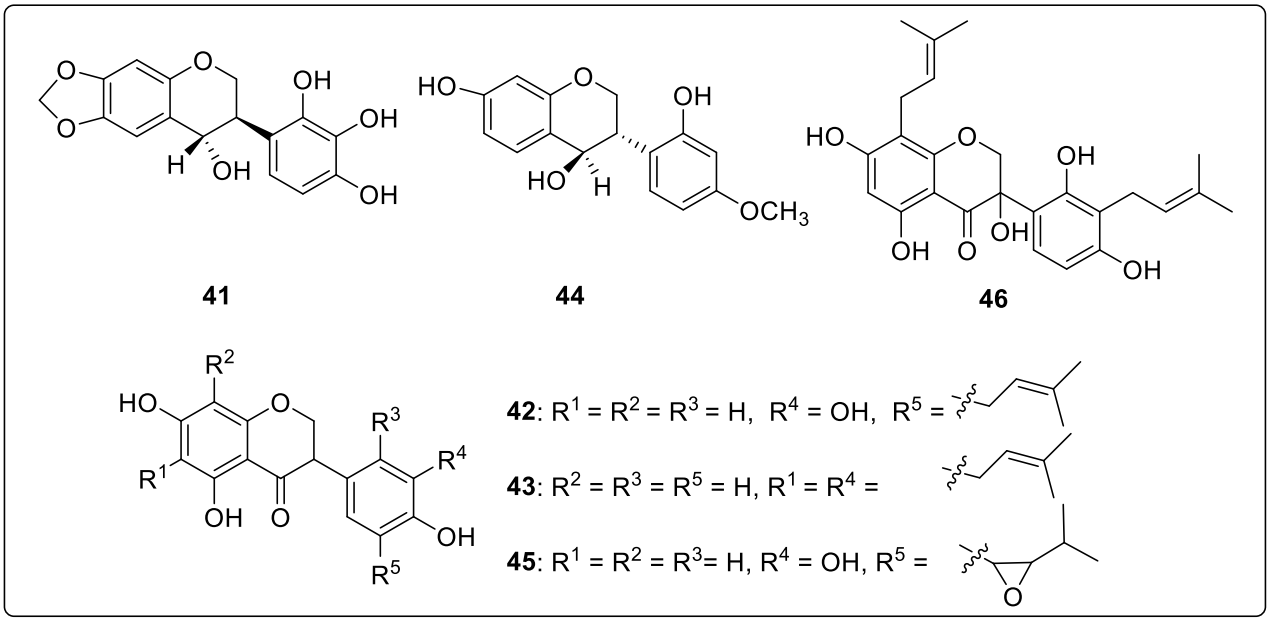


Figure 10. New compounds from stem bark and root bark of *Bolusanthus speciosus*.

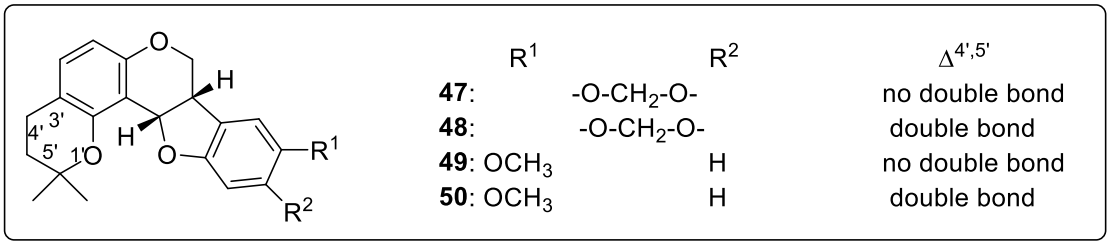


Figure 11. New pterocarpans from root bark of *Bolusanthus speciosus*.

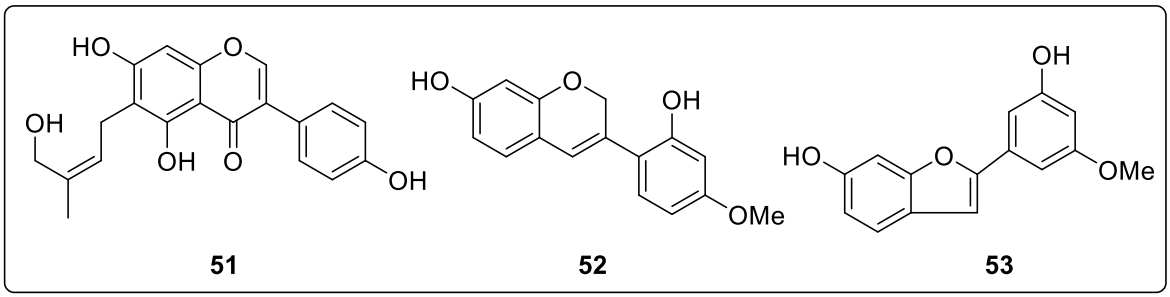


Figure 12. New compounds from root wood of *Bolusanthus speciosus*.

Rhus spp and corn cricket (Heterodes popus L)

Rhus pyroides Burch (Anacardiaceae) is a shrub found in the eastern part of Botswana that can grow to a medium-sized tree. Farmers have noticed that this plant was somehow avoided by corn crickets (*Heterodes popus* L). The corn cricket is known to invade farms and devouring a whole variety of crops and plants leaving fields devastated. This observation led researchers to speculate that the plant could have some components with antifeedant, insecticidal or insect repellant activities. A preliminary project sponsored by the United States Agency for International Development (USAID) was piloted and later a phytochemical investigation of the twigs led to a novel bichalcone named rhuschalcone I **54** (Figure 13), which indeed showed antifeedant activity albeit weak.[1,25] This biflavonoid was accompanied by trace amounts of other bioflavonoids which could not be identified at the time. These minor compounds were later found in substantial amounts in the roots and identified as structures **55**-**59** (Figure 13).[26] Total synthesis of compounds **54**-**56** was achieved using microwave promoted Ulmann synthesis as the key reaction. Compounds **54**-**59** exhibited selective cytotoxicity against HT 29 and HCT 116 colon tumor cell lines.

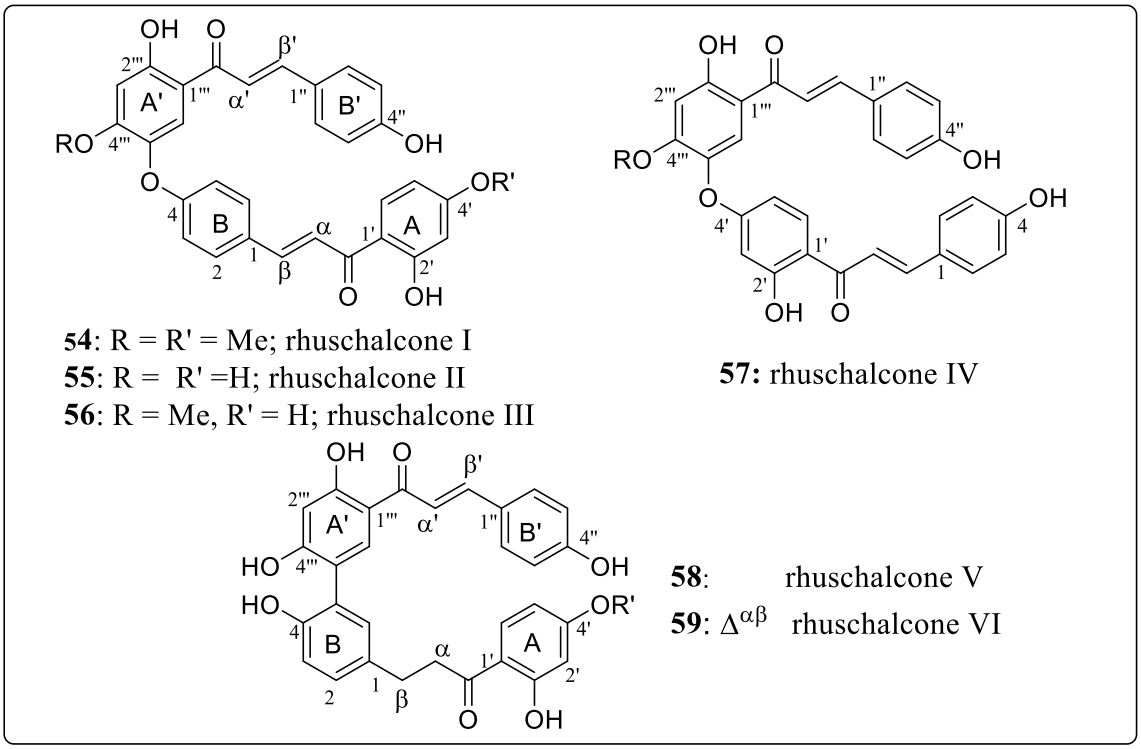


Figure 13. New biflavonoid rhuschalcones from *Rhus spp* and corn cricket.

Detailed work on other genera is covered in a comprehensive review paper published by Abegaz.[27] In this review, the author has described the work on *Bulbine capitata* (Asphodelaceae), *B. abyssinica* and *B. fruteescens* that yielded novel phenyl anthraquinones and isofuranonaphthoquinones which were observed to exhibit antiplasmodial (against asexual erythrocytic stages of two strains of *Plasmodium falciparum in vitro* (K1/chloroquine-resistant and NF 54/chloroquine-sensitive) and antioxidant properties in a human lipoprotein oxidation assay.[28,29] Among the novel phenyl anthraquinones were gaboroquinone A and gaboroquinone B named after Gaborone, the capital city of Botswana where the work was carried out. Work on *Scilla nervosa* (Burch) Jessop *subsp, rigidifolia* and *Ledebouria graminifolia* (Bak) Jessop (Hyacinthaceae) yielded twenty homoisoflavonoids and two xanthones. Some of the homoisoflavonoids were found to be active against MCF7 breast cancer cell lines.[30]

3. Oil-related Studies

Research into vegetable oils started in the late 1990s. Edible oils and fats are plant-derived biological mixtures of esters of glycerol with fatty acids chains.[21] The physical and chemical characteristics of oils and fats are influenced by both the kind and proportion of fatty acids moieties.[32,33] Fatty acids can be classified as saturated (SFA), mono-unsaturated (MUFA), and polyunsaturated (PUFA). The unsaturated fatty acids are also classified into the omega series, the omega carbon being the last carbon of the chain. The ω-9 [e.g., oleic acid, 18:1] (double bond between C-9 and C-10 from the end) fatty acids are non-essential to humans, meaning that the human body can biosynthesize these, while the ω-6 (e.g., linoleic acid, 18:2) and ω-3 (e.g., linolenic acid, 18:3) are essential fatty acids and have to be obtained from the diet. Most of the fatty acids have unsaturated chains and are even-numbered normally comprising of 16 to 18 carbons with a single carboxyl group. However, a small minority of these vegetable fatty acids could also have branched chains, be cyclic or have odd numbered unbranched chains. Vegetable oils and fats typically have a high percentage of unsaturated fatty acid chains in their triacylglycerol structures. Usually, a higher degree of unsaturation in a vegetable oil fatty acid implies a greater susceptibility to oxidative degradation.[33] It is thus essential to know the composition of fatty acids of an oil or fat, be able characterize and determine where there are some adulterations and also to know how stable these products are. The ratio of unsaturated to saturated fatty acids is important for human nutrition. While a high level of saturated fatty acids is desirable to increase stability on the one hand, nutritionally this is undesirable because high levels of saturated fatty acids is associated with an increase in levels of low-density lipoproteins (LDL- bad cholesterol) and increase in incidents of heart diseases and plague formation. Consumption of unsaturated fatty acids is on the other hand associated with an increase in high density lipoprotein (good cholesterol) A useful index to measure in oils is the ratio of polyunsaturated to saturated fatty acids (P/S ratio). An ideal diet should have a P/S index of at least 1 due to the essential nature of the ω-6 fatty acids (linoleic acid).

The chemical properties of oils and fats used to determine the quality are:

(a) acid value (AV) which is a measure of the percentage content of free fatty acids in a given amount of oil. The acid value suitable for edible oils should be ≤ 4 mg KOH/g

(b) peroxide value (PV) is an index of rancidity in oils. A maximum of 10 meq/kg for edible oils and nuts has been set by the Codex Alimentarius Commission. Thus, both AV and PV are used to measure deterioration in the sensory properties of oil.

(c) the iodine value (IV) which is a function of unsaturation and used to measure the relative amounts of unsaturated fatty acids in lipids.

(d) saponification value (SV) which is a measure of the average molecular weight (i.e chain lengths of fatty acids).
(e) *p*-anisidine value used to measure secondary oxidation of oil or fat evidenced by formation of aldehydes particularly those that are unsaturated.
(f) unsaponifiable matter consists of substances present in oils or fats that are not saponifiable by alkali hydroxides.

The physical properties of oils and fats used to determine the quality are:

(a) refractive index (RI)
(b) moisture content
(c) relative density
(d) colour

The results of research work on oils and fats done at the University of Botswana is summarized in Tables 1 and 2. Most of the work, covering the period 1998 to 2017, concentrated on vegetable oils. There is only one animal oil from mophane caterpillar (*Imbrasia belina*), a larval stage, where a comparison was made between the oil from mature caterpillars and oil from young ones. The oil composition of *I. belina* was found to be very similar to vegetable oils. The extraction of oils followed a standard procedure where extraction was done using *n*-hexane or *n*-hexane/2-propanol (3:1) in Soxhlet extraction. The physical and chemical properties of oil samples were determined by standard methods recommended by the IUPAC. For fatty acid composition, oil samples were transesterified by refluxing in dry methanol with ethanoyl chloride to produce fatty acid methyl esters (FAME) and used for chromatographic analysis. Fatty acid composition was determined by capillary GC and confirmed by ^{1}H NMR analysis. The results of the analyses are shown in Tables 1 and 2.

Tylosema esculentum (morama) has great socio-economic importance to communities where it is found. The seeds form a staple diet for inhabitants of Botswana, Namibia and South Africa. The seed oil is used for cooking, making butter and cosmetic products.[34] Work has been done by us on its phytochemical constituents and bioactivity of the extracts and isolates.[35-37] The extracts have been found to exhibit antioxidant, antibacterial, antifungal, antiviral and cytotoxic activities. The oil yield (48.2%),[34] and the high protein content of the seed explains why morama is so popular in areas where it grows.[38] The oil yield compares favorably with commercial vegetable oils such as groundnut (45- 55%), sunflower (22-36%), and rapeseed (22-49%) while the physicochemical properties appear to be within the recommended standards. The other two legumes in this study *Xanthocercis zambesiaca* and *Bauhinia petersiana* in this study (Tables 1 and 2) gave oil yields of 17.6 and 20.8%, respectively with the former showing longer carbon chains ($C_{20:0}$, $_{C22:0}$, $C_{24:0}$ and $C_{26:0}$) and higher unsaturation ($C_{18:3}$). The oil yields of these two legumes compared favorably with soybean oil yields (12-30%).

The larval stage of *Imbrasia belina* (Westwood) (Lepdoptera: Saturniidae), locally called *phane*, is also known as the *mophane* caterpillar. This larval stage goes through five developmental stages, or instars, before pupating. It derives its name from the host plant, *Colophospermum mophane* which the larvae feeds on. It is an important food source and trading commodity not only for people of Botswana but for southern African in general. The boiled and dried larvae has a crude protein content of 47.5% and an oil yield of 29.6% for mature and 22.9% for young larvae.[39] These oil also have a high content of C18:3 fatty acids (29.44% and 16.46 %, respectively). The physical and chemical property profiles are very similar to those of vegetable seed oils such as palm and virgin olive oils.

Melon seed oils from two melon species *Citrullus lanatus* and *C. colocynt*h (Cucurbitaceae) are major food sources in southern, East and West Africa. One West African variety of *C. colocynth* namely *agusi* and one of *C. lanatus,* namely *wrewre* together with three southern African varieties of *C. lanatus* found in Botswana namely *sesoswane*, *tsama* melon and *desert* melon were investigated for their oil producing potential thereof.[40] The

results showed that the physicochemical parameters (Tables 1) of the test Cucurbitacea seeds oils were very closely comparable to those of soybean, sunflower and ground nut seed oils. The fatty acid profiles of these seeds show the principal fatty acid components in these seeds to be linoleic acid (18: 2n-6, oleic acid (18:1n-9), palmitic acid (16:0 and stearic acid (18:0) and again comparable to soybean, sunflower and groundnut (Table 2). What is apparent however is that the Curcubitaceae seed oils totally lack 20: 0 and 22:0 fatty acids which are all present in soybean, sunflower, and groundnut albeit in small quantities. Furthermore, all the Cucurbitaceae oils except *wrewre* lack 18:3n-3 fatty acids which are also presents in small amounts in the three reference oils (Table 2).

The non-traditional seed oils of five Botswana plants *Ricinodenron rautenenii* (Eurphorbiaceae) [*makenti*i], *Hyphaene petersiana* (Arecaceae) [*mokolwane*], *Sterculia africana* (Malvaceae) [*mukukubuyo*], *Ximenia caffra* (Olacaceae) [*moretologo-kgomo*] and *Tylosema esculentum* (Fabaceae) [*morama*] had their physicochemical parameters, fatty acid and triacylglycerol contents investigated and results are shown in Tables 1 and 2 (Results for *Tyloserma esulentum* are not included since it has already been described above).[41] The fatty acid profiles for *S. africana* [*mukukubuyo]* and *R. rautanenii* [*makentii*] seed oils is dominated by oleic (26.1% & 16.7%) and linoleic acids (51.9% &24.4%). Interestingly, *S. africana* also contained significant amount (19.9%) of cyclic fatty acids. *X. caffra* seed oil had a significant amount of 18:1 fatty acids (45.8%) as well as very long chain fatty acids: 26:1 (5.8%), 28:1 (13.9%), 30:1 (3.9%) and acetylenic acids [9a-18:1 (1.5%) and 9a, 11t-18:2 (16.0%)] (Tables 1 and 2).

A study investigating compositional and structural studies of oils from two Ghanaian edible seed oils was conducted.[42] The study seeds were *Cyperus esculentum* (Cyperaceae [tiger nut] and *Pachira insignis* (Malvaceae) [*asiato*] which are important edible seeds not only in Ghana but in the whole West African region, with the view to assess them for their potential use in the region. The results (Tables 1 and 2) show the major fatty acid components for *P. insignis* [*asiato*] to be palmitic acid (56.58%) together with sterculic and dihydrosterculic (20.06%). The major components in *C. esculentum* [tiger nut] are oleic (65.55%), palmitic (16.32%), and linoleic (12.13%) acids. Both oils had 20:0 acids. However, the presence of cyclic propenoid fatty acids in asiato makes it unsuitable for food uses, while tiger nut could replace imported oil in the West African region.

Uamusse and Yeboah did a comparative study of the oils from seeds of four variants of *Trichilia emetica* Vahl (Meliaceae) [*mafura* tree; Cape/Natal Mahogany] grown in Mozambique.[43] The physicochemical properties and fatty acid composition of the edible oils from the four variants (red-bitter, red-sweet, orange-sweet & white-sweet) were determined.[43] The oil yields ranged from 42.2-53.8% and the stability parameters, acid value (AV) and peroxide value (PV), indicated that the four oil samples were stable to hydrolytic and oxidative stress (AV = 0.88-1.02 mg KOH/g and PV= 2.02-2.62 meq/kg). The iodine values (IV= 63.42-78.02 meq/kg) indicated that all four oil samples were moderately unsaturated, while saponification values (SV 183.71-189.03 mg KOH/g) indicated the oil samples to consist mainly of medium length fatty acid chains. The fatty acid profiles (16:0 = 40.29-46.76%, 18:1 = 25.28-30.44%, 18:2 = 24.99-27.64%) confirmed moderate unsaturation and also showed all four oils to consist mainly of C16 and C18 carbon chains. The results further showed the oils from the four seed variants to be similar to each other and their properties compared favourably with some well-known edible oils like palm oil and olive oils. The four variants are thus all equally suitable for further evaluation towards commercial exploitation.

Table 1. Physicochemical parameters of studied oil samples compared with the Codex standards for soybean and sunflower oils

Oil source	Acid value (mg KOH/g)	Iodine value	Peroxide value (meq/kg)	Saponification value (mg KOH/g)	*p*-anisidine value (mmol/kg)	Reference
Tylosema esculentum (morama beans), (***Te***)	2.96	95 ± 3	20.3	174 ± 2	nd	34
Xanthocercis zambesiaca (moshatu seeds) (***Xz***)	2.5	94 ± 3	11.3	183 ± 2	nd	34
Bauhinia petersiana (montantsha beans) (***Bp***)	1.9	98 ± 3	10.6	178 ± 2	nd	34
Imbrasia belina	15.7	94 ± 3	0.27	184 ± 2	nd	39
(phane)	9.0	71 ± 3	0.18	180 ± 2		
(mature) (young) (***Ib***)						
Citrullus colo-cynth (agusi seeds) (***Cc***)	4.0 ± 0.03	104.4 ± 0.2	1.1 ± 0.1	189.5 ± 0.2	0.6 ± 0.1	40
Citrullus ianatus (***Ci***)	1.2 ± 0.1	112.2 ± 0.1	1.1 ± 0.1	190.8 ± 0.1	0.2 ± 0.1	40
wrewre (**wre**)	1.9 ± 0.1	107.8 ± 0.1	3.5 ± 0.1	193.8 ± 0.1	1.3 ± 0.1	
Sesoswane (**ses**)	1.8 ± 0.1	95.8 ± 0.1	9.8 ± 0.1	184.4 ± 0.1	2.2± 0.1	
tsama melon (**tm**) desert melon (**dm**)	2.5 ± 0.1	124.0 ± 0.2	10.9 ± 0.1	182.1 ± 0.1	9.0 ± 0.1	
Ricinodendron rautanenii (manketii) (***Rr***)	0.36 ± 0.01	121.76 ± 1.23	2.51 ± 0.03	185.26 ± 1.23	3.85 ± 0.05	40
Hyphaene petersiana (mokolwane) (***Hp***)	2.02 ± 0.04	65.68 ± 0.42	15.70 ± 0.25	209.00 ± 1.00	2.37 ± 0.03	40

Table 1. Continued

Oil source	Acid value (mg KOH/g)	Iodine value	Peroxide value (meq/kg)	Saponification value (mg KOH/g)	*p*-anisidine value (mmol/kg)	Reference
Sterculia afri-cana (mkuk-ubuyo) (***Sa***)	5.05 ± 0.03	53.07 ± 1.56	5.26 ± 0.03	161.24 ± 0.48	2.18 ± 0.04	40
Ximenia caffra (moretologo-kgomo) (***Xc***)	1.67 ± 0.02	82.00 ± 1.00	6.45 ± 0.04	141.00 ± 0.33	0.98 ± 0.04	41
Cyperus esculentum (tiger nut) (***Ce***)	1.38± 0.15	91.31 ± 0.07	5.54 ± 0.62	180.24 ± 1.99	-2.93 ± 0.16	42
Pachira insignis (asiato seeds) (***Pi***)	4.44 ± 0.14	46.99 ± 3.50	4.04 ± 0.27	189.49 ± 0.55	3.01 ± 0.08	42
Trichilia emetica (***Te***)	1.02 ± 0.229	78.02 ± 1.09	2.53 ± 0.25	183.71 ± 0.86 187.42 ± 0.89	2.12 ± 0.36 2.22 ± 0.99	43
(red-bitter, **r-b**), (red-sweet, **r-s**)	0.89 ± 0.011	69.93 ± 1.60	2.02 ± 0.20	187.02 ± 0.26 189.03 ± 1.44	2.12 ± 0.80 2.90 ± 0.44	
(orange sweet, **o-s**)	0.89 ± 0.005	71.54 ± 1.03	2.51 ± 0.05			
(white-sweet, **w-s**)	0.88 ± 0.036	63.42 ± 0.75	2.62 ± 0.15			
[a]Soybean	4.0	124 - 139	10	189 - 195	10.1	44
[a]Sunflower	4.0	110 - 143	10	188 - 194	9.3	44

nd, not determined; [a]Codex standards

Table 2. Fatty acid composition of studied samples in Table 1

Nature of fatty acid residue ($C_{y:n}$)*												
Hp	***Rr***	***Ci***	***wre***	***ses***	***tm***	***dm***	***Cc***	***Ib*** mature	young	***Bp***	***Xz***	***Te***	**Oil source**
13.13	---		---	---	---	---	---	0.31	0.31	0.03	0.03	0.13	14:0
10.39	11.95	---	20.80	9.91	10.10		14.41	27.24	27.08	16.35	12.76	12.09	16:0
---	---		---	---	---		---	0.39	0.41	---	0.09	0.09	17:0
3.90	11.77	8.90	11.322	7.81	9.22		11.41	12.03	12.51	6.80	7.04	6.75	18:0
---	---		---	---	---		---	0.30	0.35	0.52	1.40	2.76	20:0
---	---		---	---	---		---	---	---	---	1.66	---	22:0
---	---		---	---	---		---	---	---	---	2.65	---	24:0
---	---		---	---	---		---	---	---	---	0.37	---	26:0
---	---		---	---	---		---	0.86	0.90	0.27	0.37	0.38	16:1
---	---		---	---	---		---	0.12	0.12	---	0.06	---	17:1
42.37	24.35		14.22	12.72	15.51		12.24	16.17	16.46	27.58	63.37	49.28	18:1
			---	---	---		---	---	---	0.23	0.79	0.57	20:1
4.29	51.93		61.50	55.21	66.85		62.00	10.55	10.86	44.82	3.11	26.43	18:2
---	---		0.11	---	---		---	29.44	28.54	---	5.32	---	18.3
---	---		---	---	---		---	2.58	2.47	3.40	1.04	1.54	Mn
53.34	23.72		24.33	32.12	17.72		25.82	40.78	40.66	23.73	26.00	21.82	S
42.37	24.35		14.22	12.72	15.51		12.24	17.16	17.48	28.07	64.53	48.56	Mu
4.29	51.93		1.61	55.21	66.85		62.00	39.99	39.40	44.82	8.44	26.43	Pu
0.08	2.19		2.53	1.72	3.77	3.23	2.40	0.99	0.97	1.89	0.32	1.21	Pu/S

Table 2. Continued

[a] Ground nut	[a]Sunflower	[a]Soybean	*Te* (r-b	r-s	o-s	w-s)	*Pi*	*Ce*	*Xc*	*Sa*
---	---	---		---	---	---	0.17	---	---	---
11.0	6.5	10.5	46.76	46.73	43.20	40.29	56.58	16.32	0.94	19.97
---	---	---		---	---	---	0.20	---	---	---
4.6	5.5	4.3	1.41	1.90	1.79	1.36	4.72	5.33	1.15	5.80
2.0	<1.5	<0.6		---	---	---	1.26	0.68	---	1.10
3.0	<1.0	<0.5		---	---	---	---	---	---	---
---	---	---		---	---	---	---	---	2.09	---
---	---	---		---	---	---	---	---	2.11	---
<1.0	<1.0	0.5		---	---	---	0.31	---	---	0.94
---	---	---		---	---	---	---	---	---	---
53.5	24.5	22.0	25.28	26.15	27.27	30.44	10.12	65.55	47.23	20.14
---	---	---		---	---	---	---	---	0.80	1.84
29.0	65.0	53.5	25.48	24.99	27.14	27.64	6.58	12.13	16.24	27.04
< 0.3	< 0.3	7.80		---	---	---	---	---	---	---
---	---	---		---	---	---	---	---	---	---
19.9	13.3	15.3	48.17	48.63	45.21	41.65	62.87	22.33	7.68	26.87
53.5	24.5	22.0	25.28	26.15	27.27	30.44	10.12	65.55	47.51	22.92
29.3	65.3	61.3	25.48	24.99	27.14	27.64	6.58	12.13	16.24	27.04
1.47	4.91	4.00	0.53	0.51	0.60	0.66	0.10	0.54	2.11	1.00

---, not determined; [a]Average values of the range used; $_{Cy:n}$, y = carbon chain length, n = degree of unsaturation; Mn, minor components; S, fully saturated; Mu, monounsaturated; Pu, polyunsaturated (n ≥ 2); * $C_{12:0}$ = lauric acid; $C_{14:0}$ = myristic acid; $C_{16:0}$ = palmitic acid; $C_{17:0}$ = margaric acid; $C_{18:0}$ = stearic acid; $C_{20:0}$ = arachidic acid; $C_{22:0}$ = behenic acid; $C_{24:0}$ = lignoceric acid; $C_{26:0}$ = ceric/cerotic acid; $C_{16:1}$ = palmitoleic acid; $C_{17:1}$ = heptadecenoic acid; $C_{18:1}$ = oleic acid; $C_{18:2}$ = linoleic acid ; $C_{18:3}$ = linolenic acid; $C_{20:1}$ = gadoleic acid' $C_{20:2}$ = eicosadienoic acid; $C_{22:1}$ = erucic acid; $C_{22:2}$ = docosadienoic acid; $C_{24:1}$ = nevonic acid

4. Synthetic Organic Chemistry Research

4.1 Synthesis of the natural product oryzoxymycin

As demonstrated in Section 2, an array of natural products with diverse structural motifs have been isolated from medicinal plants, purified and characterized at the University of Botswana and other parts of the world as templates for new drug lead discovery. It is most unlikely that the natural product itself will become a drug candidate. Further, natural products are in most cases isolated in limited quantities from plants. Initiation of a medicinal chemistry synthesis program at the University of Botswana was considered essential aiming to produce enough amounts of natural product derivatives with the appropriate biological and chemical properties to become a drug candidate. Recognizing the fact outlined above, the Department of Chemistry initiated a synthesis program around 2000 to support its natural product chemistry program.

The first natural product that got our attention was oryzoxymycin **60** mainly due to its structural similarity to **61**, an intermediate in the biosynthesis of anthranilic acid (Figure 14). The glaring difference between the two compounds is the position of attachment of the lactic acid motif. The main aim of the synthesis program was therefore to prove the structure of oryzoxymycin. This compound was isolated from the bacteria *Streptomyces venezuelae* var *oryzoxymyceticus* and was classified as a new antibiotic for inhibiting growth of the globally important rice pathogen *Xanthomonas oryzae*.[45]

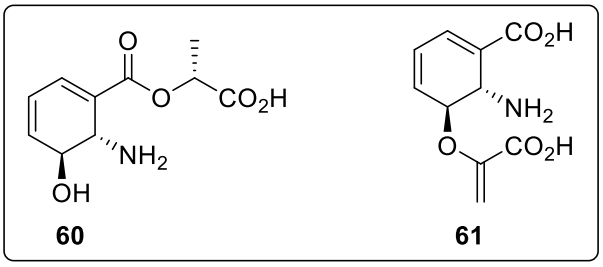
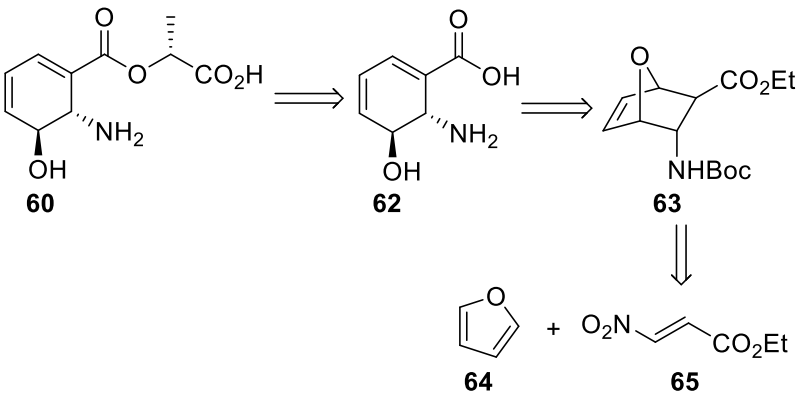


Figure 14

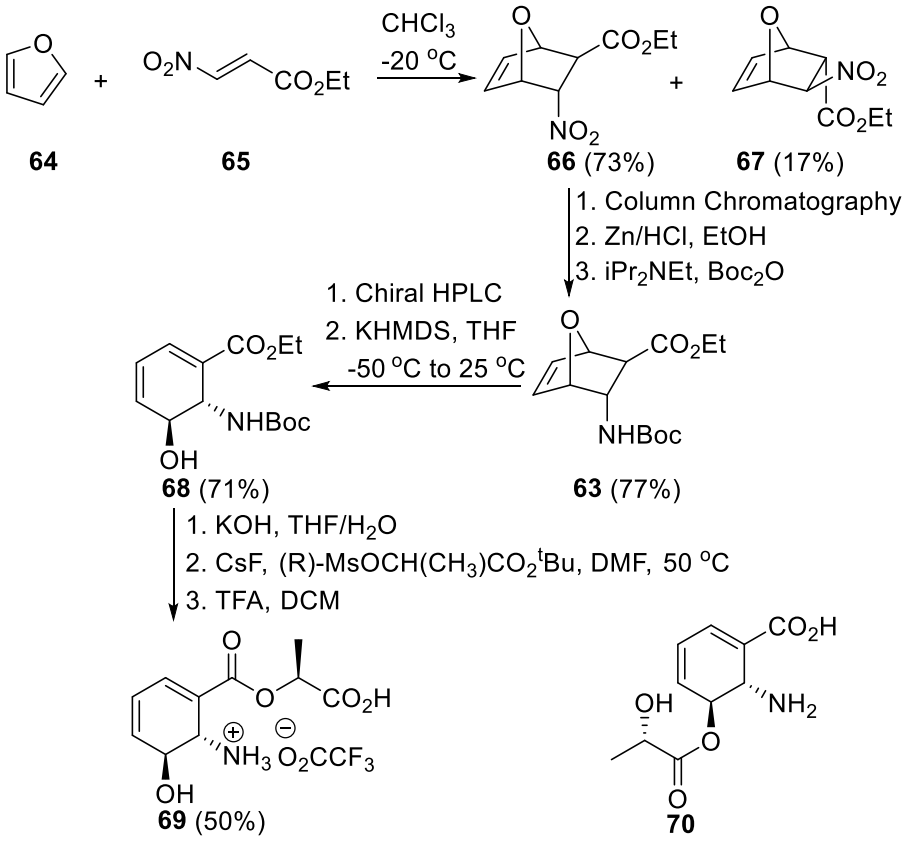
The synthesis of oryzoxymycin was guided by the retrosynthetic blueprint shown below (Scheme 1). Disconnection of oryzoxymycin **60** at the ester bond would furnish intermediate cyclohexadiene **62** and lactic acid. Construction of the cyclohexadiene **62** with the correct relative stereochemistry would hinge on the chemistry described by Campbell and co-workers involving base-promoted elimination of the oxygen bridge of bicyclics of type **63**.[46-49] Bicyclic **63**, in turn, can be prepared by the Diels-Alder reaction of furan **64** and dienophile **65**. On the basis of precedence, it was presumed that dienophile **65** would be prepared from ethyl acrylate.[50]

Using the retrosynthetic analysis discussed above, a plan for the total synthesis of oryzoxymycin **60** was evolved. Dienophile **65** was prepared in grams quantities following a procedure developed by McMurry[51] involving the reaction of ethyl acrylate with N_2O_4 and I_2 followed by the elimination of HI using $^{i}Pr_2NEt$ in ether. Dienophile **65** participated in a Diels-Alder reaction with furan **64** to give adducts **66** and **67** in 73% and 17% yields, respectively (Scheme 2). The two diastereomeric adducts were separated easily by column chromatography. Reduction of the nitro-group of the *endo*-nitro adduct **66** followed by protection of the resultant amino group gave adduct **63** in 77% yield. The transformations discussed thus far were on racemic substrates. Adduct **63** presented an opportunity to carry out a resolution at this stage of the synthesis. To this

end, adduct **63** was subjected to preparative chiral HPLC (chiralpak AD, heptane/ethanol 95:5) to give the two enantiomers of **63** with good recovery.



Scheme 1



Scheme 2

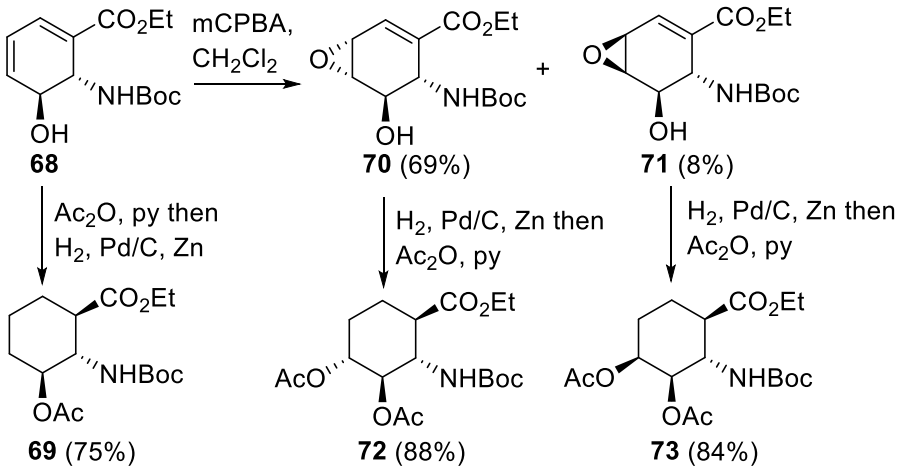
The availability of optically pure adduct **63** set the stage for the crucial base-promoted elimination of the oxygen bridge. The conditions for the LiHMDS-promoted elimination of the oxygen bridge of related adducts were worked out by Campbell and co-workers in connection with their approach to shikimates.[46-49] In the context of adduct **63**, KHMDS was found to work better than LiHMDS. Thus, when a solution of adduct **63** in THF

was treated with KHMDS under controlled temperature, cyclohexadiene **62** was isolated in 71% yield. To complete the synthesis of oryzoxymycin **60**, the ester of cyclohexadiene **68** was hydrolyzed, followed by esterification using (*R*)-MsOCH(CH_3)CO_2tBu in the presence of CsF and diprotection to give the desired product **69** in 50% over the three steps (Scheme 2).[49] The major difference observed between **69** and the original isolated oryzoxymycin **60** was the optical rotation (**69** $[\alpha]^{21}_D$ = -199 (c = 1, H_2O);[46] $[\alpha]^{21}_D$ = +349 (c = 1, H_2O). This observation suggested that the correct structure of oryzoxymycin may be the isomeric ester **70** with the lactate group attached at C-5. Attempts to prepare this isomer were unsuccessful due to elimination reactions to give anthranilic acid derivatives.

4.2 Synthesis of cyclohexyl β-amino acids

During the synthesis of oryzoxymycin, cyclohexadiene **68** was consider as a versatile intermediate from which substituted cyclohexyl β-amino acids could be prepared. Prior to our work that generated cyclohexadiene **68**, Gellman and co-workers had reported the ability of short β-peptides derived *trans*-2-aminocyclohexanecarboxylic acid (ACHC) to form secondary structures analogous to those formed by natural peptides.[52-56] It is instructive to note that cyclohexadiene **68** has much in common with ACHC. β-Peptides are resistant to proteolytic degradation,[57] and can therefore be used as mimics of peptides-based antibiotics that are susceptible to enzymatic degradation.[58] The development of synthetic procedures for the preparation of the building blocks for β-peptides has therefore attracted interest of chemists. Within this context, cyclohexadiene **68** presented an attractive intermediate for the synthesis of ACHC derivatives.

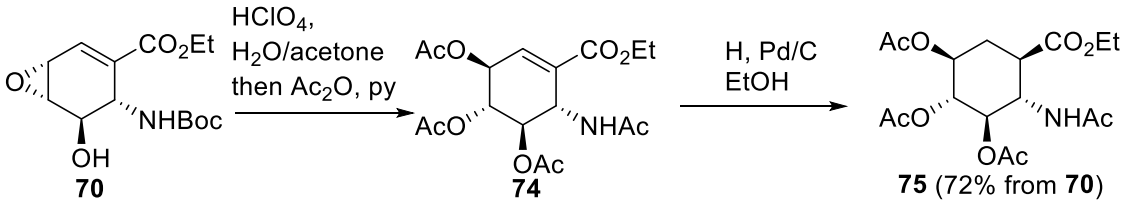
Simple reduction of cyclohexadiene **68** with H_2 over Pd/C proved to be highly *facio*-selective and gave only ACHC **69** in 75% yield.[59] Further, elaboration of cyclohexadiene **68** through mCPBA-mediated epoxidation reactions gave epoxides **70** and **71** in 69% and 8% yields, respectively with the major isomer arising from the reaction occurring on the same face as the Boc carbamate. The two epoxides were easily separated by column chromatography. It is instructive to note that preliminary acetylation of the hydroxyl group of cyclohexadiene **68** resulted in the epoxidation reaction being stereospecific giving only the acetyl derivative of epoxide isomer **70**. Treatment of each of the epoxides **70** and **71** with H_2 on catalytic amount of Pd/C in the presence of excess Zn powder gave ACHC **72** (88%) and **73** (84%) respectively (Scheme 3).[59]



Scheme 3

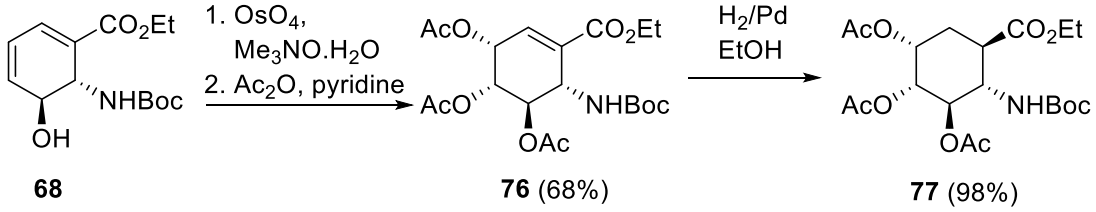
With the availability of epoxides **70-71**, a study toward trihydroxy ACHC derivatives now became possible. The conditions for the acid-catalyzed ring opening of epoxide by H_2O was originally worked out by Diggle and co-workers.[60] Indeed, exposure of epoxide **70** to H_2O in acetone in the presence of catalytic amount

of $HClO_4$ led to the opening of the epoxide and subsequent acylation of the product gave cyclohexene derivative **74**. The attack by H_2O occurred at the allylic position and proved to be *facio*-selective. The stereochemical outcome suggest that the reaction proceed through an S_N2 type reaction. Finally, reduction of cyclohexene derivative **74** gave AHCH derivative **75** in 72% from epoxide **70** (Scheme 4).[61]



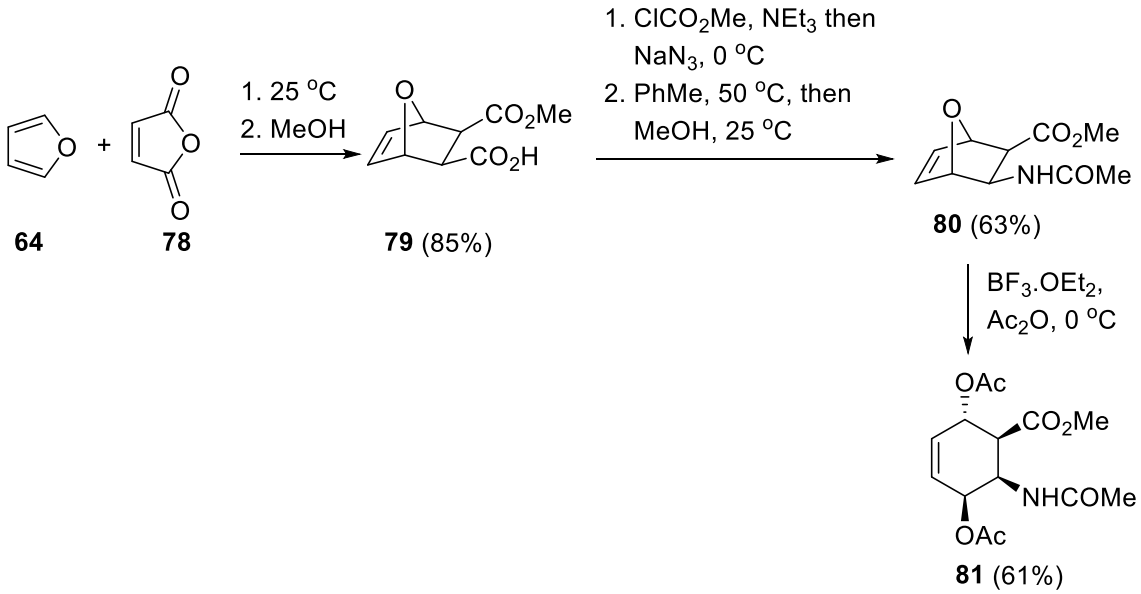
Scheme 4

Having achieved the expedient synthesis of AHCH **75** which involved a *trans*-dihydroxylation of cylohexadiene **68**, it was logical to explore the synthesis of the *cis*-4,5-diol isomer of AHCH **75**. OsO_4 is a common and efficient oxidant used in the *syn*-dihydroxylation of alkenes. OsO_4 is an expensive and toxic reagent, though, and is used exclusively in a catalytic amount in the presence of a co-oxidant. Co-oxidants that have been used extensively include H_2O_2, tertiary amine *N*-Oxides and $K_3[Fe(CN)_6]$.[62] Indeed, exposure of cyclohexadiene **68** to a catalytic amount of OsO_4 in the presence of stoichiometric $Me_3NO.H_2O$ followed by acetylation give intermediate **76** in 68% yield. Subsequent reduction of **76** gave trihydroxy AHCH derivative **77** in 98% yield (Scheme 5).[58] It is evident from the stereochemical outcome that the OsO_4-mediated dihydroxylation is directed strongly by the homoallylic carbamate group of cyclohexadiene **68**. This observation is consistent with work reported by Donohoe and co-workers.[63]



Scheme 5

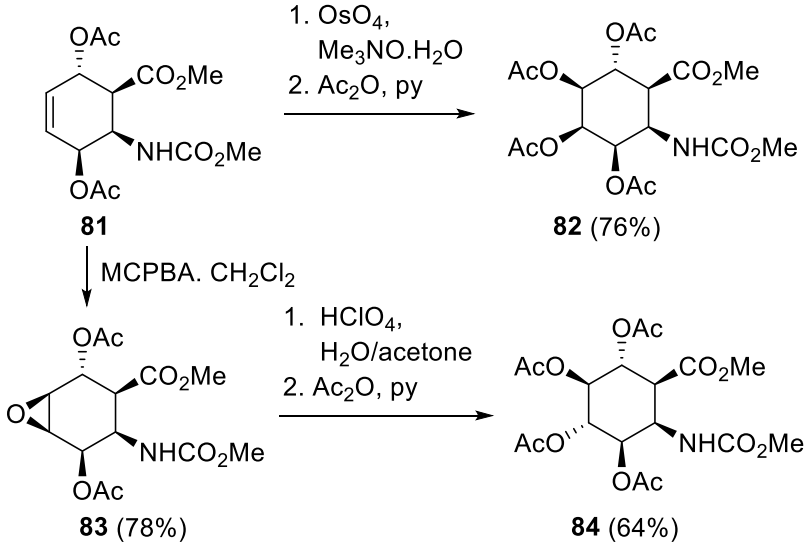
It was conceivable that an alternative synthesis of ACHC derivatives would involve the Diels-Alder reaction of furan and maleic anhydride followed by a Curtis rearrangement and elimination of the oxygen bridge of the bicyclic adduct. Gratifyingly, when a suspension of maleic anhydride **78** in furan **64** was stirred at room temperature followed by treatment with MeOH, half ester **79** was isolated as the only detected product in 85% yield (Scheme 6).[64] The ability of the Diels-Alder reaction of furan and maleic anhydride to give the thermodynamic *exo*-adduct as the main product instead of the kinetic *endo*-product is well document.[65-67] The results above were therefore not surprising. Subsequent activation of the acid group of **79** with $ClCO_2Me$, followed by a substitution reaction with NaN_3 and treatment with toluene followed by elevation of the temperature to 50 °C led to the Curtius rearrangement reaction. Treatment of the Curtius rearrangement product with MeOH gave adduct **80** in 63% yield. The elimination of the oxygen bridge of adduct **80** was achieved by reacting it with $BF_3.OEt_2$ in Ac_2O to give cyclohexene **81** in 61% yield.[64]



64 **78** **79** (85%) **80** (63%) **81** (61%)

Scheme 6

Cyclohexene **81** was further elaborated to tetrahydroxy ACHC derivatives through both *cis*- and *trans*-dihydroxylation reactions. Subjection of cyclohexene **81** to OsO_4-promoted *cis*-dihydroxylation conditions described earlier followed by acetylation gave tetrahydroxy ACHC derivative **82** in 76% yield. *Trans*-hydroxylation involved epoxidation of cyclohexene **81** to give epoxide **83** in 78% yield. Subsequent acid-catalyzed hydrolysis of epoxide **83** and acylation gave tetrahydroxy ACHC derivative **84** in 64% yield (**Scheme 7**).[64]



81 **82** (76%) **83** (78%) **84** (64%)

Scheme 7

4.3 Synthesis of chromane/chromene ring systems

Having achieved the synthesis of oryzomycin, our attention shifted to developing reliable methods for the synthesis of flavonoids. A large array of flavonoids have been isolated from medicinal plants and characterized at the University of Botswana since the 1980s.[68] The majority of the isolated flavonoids have the chromane (benzopyran) **85** or chromene **86** and **87** ring systems as their basic structure (Figure 15). The flavonoids were isolated in minute quantities and this reality impeded the testing of the isolated compounds for biological

activities. We therefore decided to develop reliable synthetic methods for the synthesis of the chromane or chromene ring systems as a platform for the synthesis of the natural flavonoids and their derivatives.

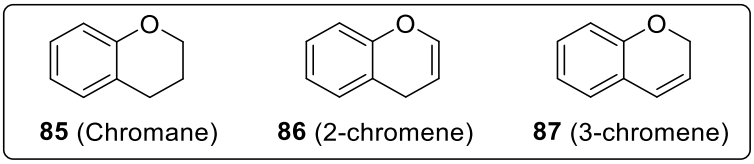
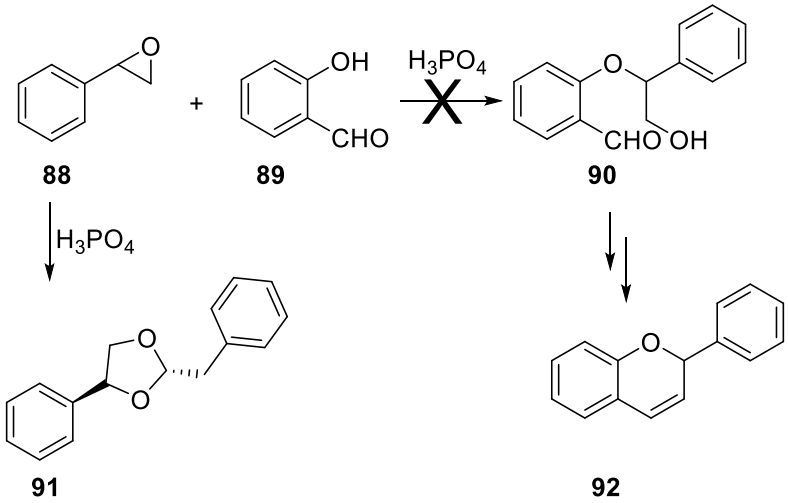


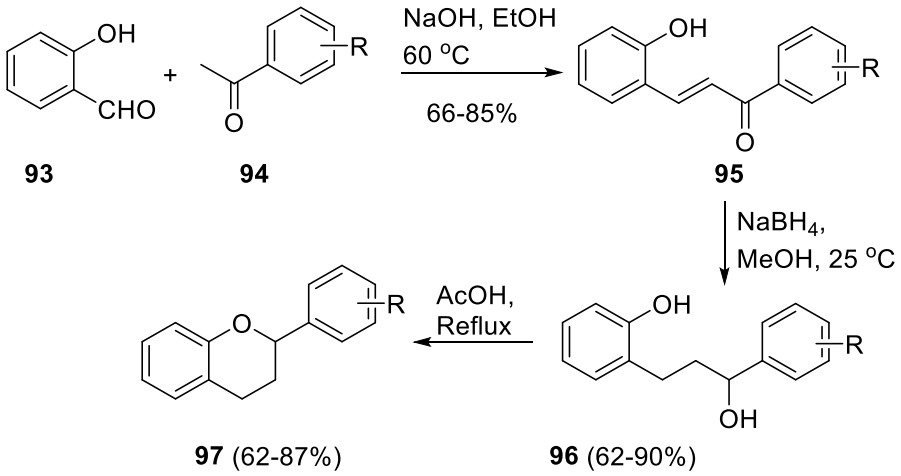
Figure 15. Structures of chromane, 2-chromene, and 3-chromene.

Our first attempt in the synthesis of flavenes involved the reaction of styrene oxide **88** and salicylaldehyde **89** to give intermediate **90**. It was anticipated that intermediate **90** would then be elaborated to flavene **92** through a Grignard reaction (Scheme 8). The first reaction in the plan described above instead of giving the desired intermediate **90** gave the styrene oxide cyclodimer **91** as the major isomer.[24] It is instructive to note that a 1,2-hydride shift was involved in the formation of cyclodimer **91**. The reaction was also successful for styrene oxides with *o*-, *m*- and *p*-chloro substitutions. However, electron-donating methoxy groups stop the 1,2-hydride shift and substituted 1,4-dioxanes were formed instead.[69]



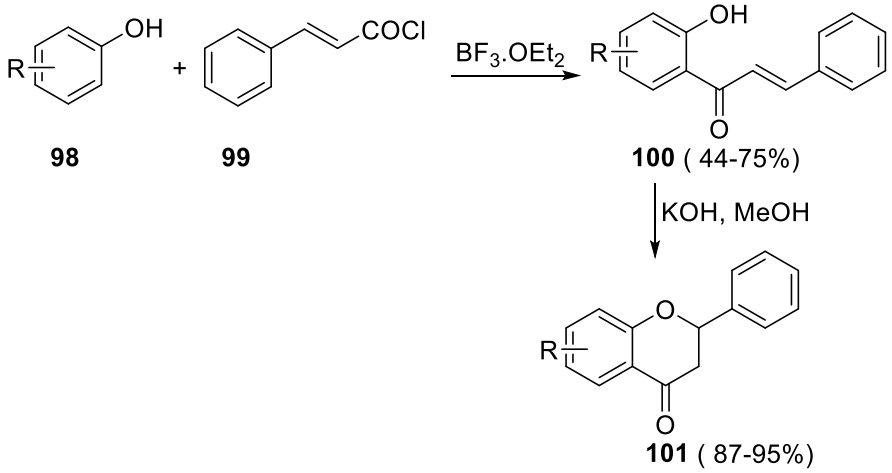
Scheme 8

The disappointing failure to prepare intermediate **90** forced us to modify our synthetic strategy. While the conventional way of preparing the chromene ring systems involves the reaction of 2-hydroxyacetophenone with benzaldehyde and its derivatives, we decided to use salicylaldehyde **93** and acetophenone derivatives of type **94** as starting reagents. The convergent union of salicylaldehyde **93** and acetophenone **94** (R = H) was brought about by adding NaOH to a stirring solution of the two reagents to give chalcone **95** in 85% yield.[70] To set the stage for the crucial cyclization reaction, the α,β-unsaturated system of chalcone **95** must be reduced. To this end, treatment of a solution of chalcone **95** in MeOH with $NaBH_4$ gave the corresponding reduced products **96** in excellent yields. Subsequent refluxing of a solution of compound **96** in AcOH gave flavans **97** (Scheme 9).[70] While *o*-methoxyacetophenone gave comparable yields to *p*-methoxyacetophenone for the three reactions, *m*-methoxyacetophenone gave relatively lower yields. This observation suggest that the three reactions involved in the synthesis of flavans are affected by the position of extra groups relative to acetyl group on the acetophenone.



Scheme 9

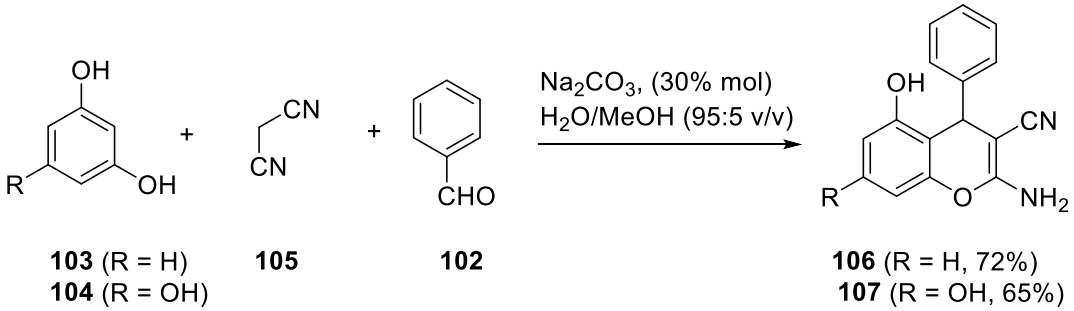
Next, we decided to develop a facile synthetic method for flavanones. In our approach to flavanones, phenols of type **98** were reacted with cinnamoyl chloride **99** to give the corresponding chalcones of type **100** in 44-75% yields. The reaction proceeds through an esterification reaction followed by a Fries rearrangement. It was observed that electron-donating groups on the phenol led to higher yields of the chalcones while electron-withdrawing groups and their position relative to the hydroxyl group led to low yields of the chalcones. Attempts to use 4-nitrophenol in the reaction for example failed to give the corresponding chalcone. A base-mediated internal Michael reaction of the chalcones of type **100** gave the corresponding flavanones of type **101** in 87-93% yields (Scheme 10).[71] This last step of the synthesis is not significantly affected by the substituents on the phenol.



Scheme 10

In addition to the synthesis of the natural products inspired chromane compounds described above, we have also reported the synthesis of unnatural 2-amino-4*H*-chromenes through a three-component reaction of benzaldehyde, malononitrile and resorcinol or phloroglucinol. In this approach, a mixture of benzaldehyde **102** malononittrile **105** and resorcinol **103** in H_2O/MeOH was stirred at room temperature in the presence of catalytic amount of Na_2CO_3 to give chromene **106** in 72% yield (Scheme 11). When **103** was replaced by phloroglucinol **104**, the three-component reaction proceeded to give the corresponding chromene **107** in 65%

yield.[72] The reaction was found to be tolerant to both electron donating and electron withdrawing groups on the benzaldehyde.



103 (R = H) **105** **102** **106** (R = H, 72%)
104 (R = OH) **107** (R = OH, 65%)

Scheme 11

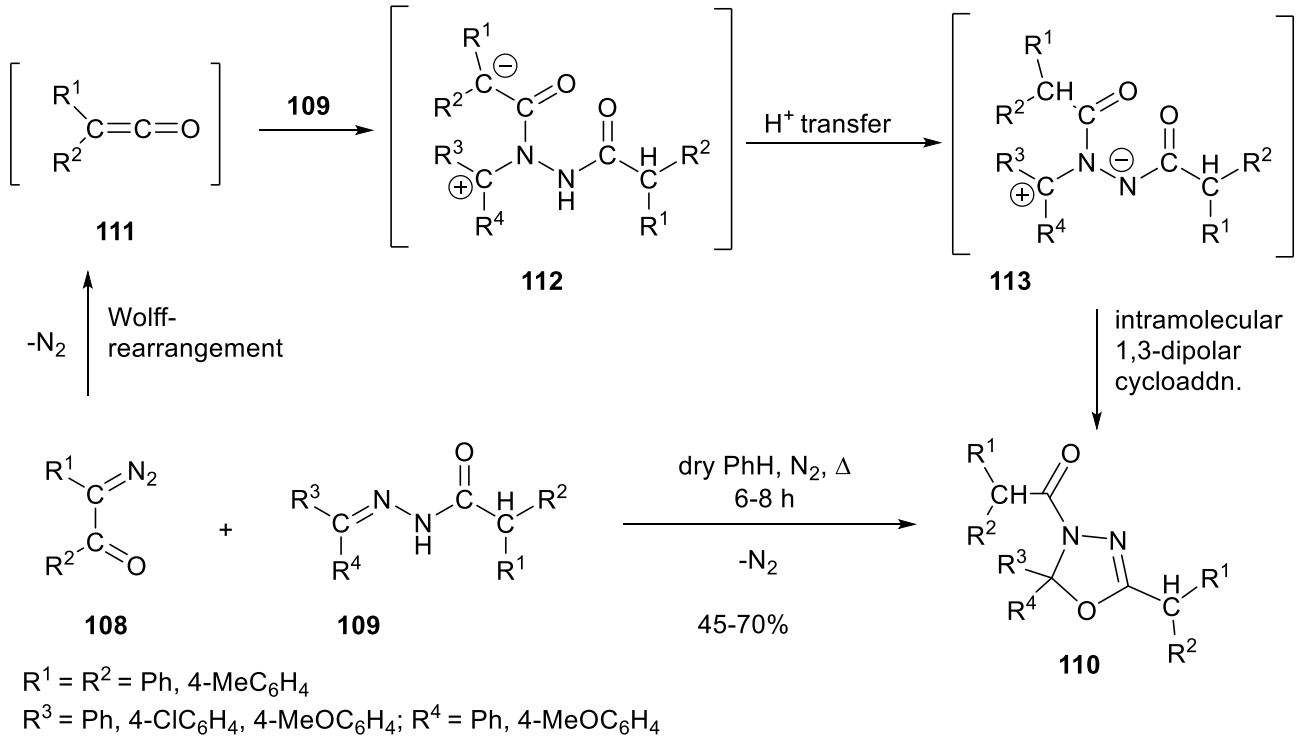
4.4 Reactions of α-diazocarbonyls: synthesis of 3- to 5-membered heterocycles

α-Diazocarbonyl compounds constitute a valuable class of compounds in the realm of synthetic organic chemistry.[73] Their reactions have been employed as key reaction in the synthesis of several natural molecules with complex architecture.[74] The reactions of α-diazocarbonyls through ketenes and metal-carbenoids offer entry to a wide range of biologically important heterocyclic motifs.[75-78] α-Diazocarbonyl compounds are easily prepared in laboratory by different methods such as i) Regitz diazo-transfer reaction, ii) Earnst-Eistert method, and iii) by oxidation of hydrazones.[79-81]

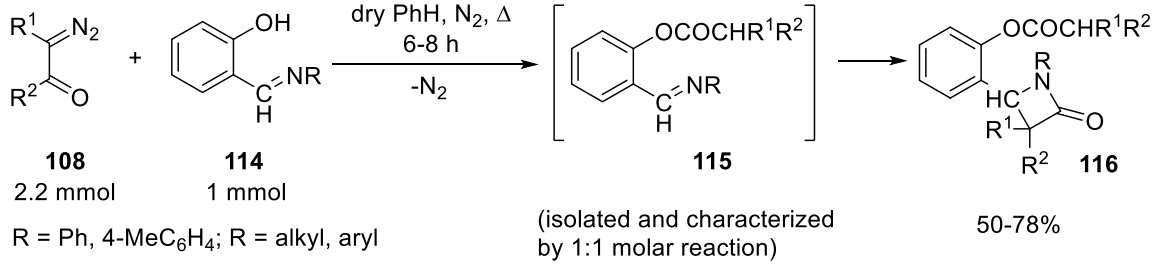
Singh and coworkers at the University of Botswana have been investigating the reaction of 2-diazoketones and ethyl diazoacetate through ketenes and carbenoids with the objective to discover new and convenient routes for the synthesis of heterocyclic compounds. The first report was published on the synthesis of 1,3,4-oxadiazolines **110** from the reaction of 2-diazo-1,2-diphenylethanone **108** and benzophenone-*N*-(diaryl)acyl hydrazones **109**.[82] The scope of this reaction was further extended by taking other 2-diazoketones as precursors for diarylketenes and synthesizing new 1,3,4-oxadiazolines.[83] The reaction of diarylketenes **111**, generated *in situ* from the thermal decomposition of 2-diazoketones followed by the Wolff-rearrangement of the resulting α-ketocarbenes, with azomethine nitrogen led to the formation of the final product via intermediates **112** and **113** (Scheme 12).

After achieving the synthesis of a five-membered heterocycle, we focused our research on the synthesis of new β-lactams, the well-known four-membered heterocyclic amides of biological importance, from the reaction of 2-diazoketones with diverse types of imines. We published first report in 2005 on the synthesis and antimicrobial activity of new β-lactams by the Staudinger ketene-imine cycloaddition of diarylketenes, generated *in situ* from 2-diazo-1,2-diarylketones, and *N*-substituted imines of thiophene-2-carbaldehyde (Figure 16).[84] We extended our study to imines **114** derived from the reaction of salicylaldehyde with diverse amines. The 1:1 molar reaction of these imines with 2-diazoketones **108** led to the formation of products **115** due to the reaction of diarylketenes **111** with phenolic hydroxyl group present in the imines.[85] A further 1:1 molar reaction of the products obtained with 2-diazoketones, however, led to the formation of β-lactams **116**. A 2:1 molar reaction of 2-diazoketones **108** with salicylaldehyde *N*-substituted imines **114** also afforded β-lactams **116** in good yields (Scheme 13).[86] These products exhibited moderate to good antibacterial (against *E. coli, P. aeruginosa, B. subtilis*, and S. *aureus*) and antifungal (against *C. mycoderma* and *S. cerevisiae*) activities. Later on, β-lactams with moderate to significant antileishmanial activity were synthesized from the reaction of imines,

obtained from 1-methylindole-3-carbaldehyde and amines, with diarylketenes (Figure 16).[87] The compounds were tested *in vitro* for their antileishmanial activity against *Leishmania major*.



Scheme 12



Scheme 13

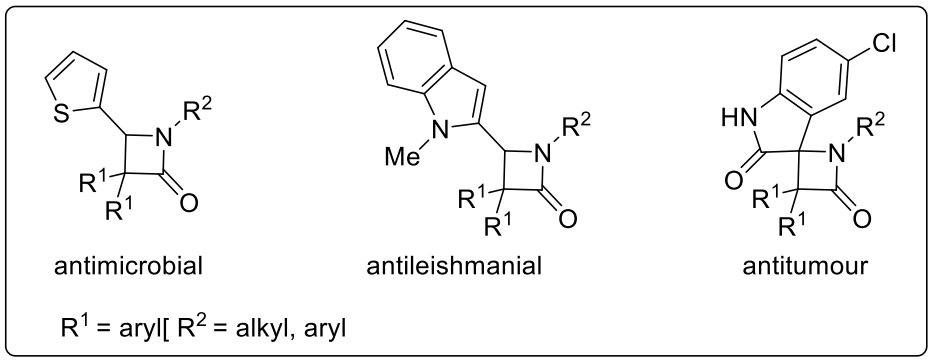
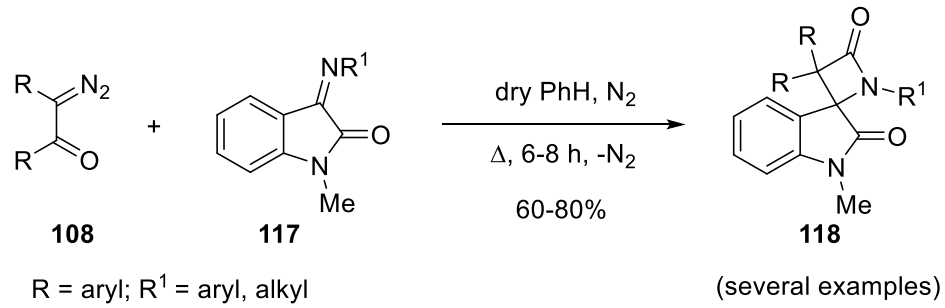


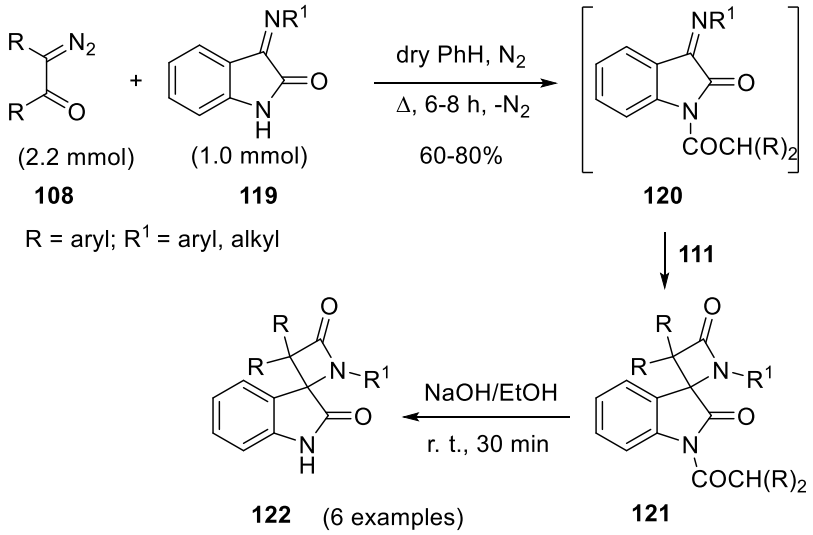
Figure 16. β-Lactams with antimicrobial, antileishmanial, and antitumor activities.

Studies on the synthesis and chemistry of the spirooxindole motif got impetus around the beginning of this century from the point of view of both synthetic chemistry and medicinal chemistry.[88] The chemistry of 2-diazo-1,2-diarylketones was employed for the synthesis spirooxindole-2-azetidinones. The reaction of 2-diazoketones **108** with *N*-substituted 3-imino-2-oxindoles **117** (commonly known as isatin imines) via diarylketenes led to the synthesis of several new spirooxindole-2-azetidinone derivatives **118** (Scheme 14).[89,90] The new products were investigated for antimicrobial activity but unfortunately, they didn't show any significant activity. Some spirooxindole-2-azetidinones (Figure 16) synthesized recently using imines of 5-chloroisatin showed moderate anticancer activity against MDA-MB-231 and MCF-7 cells.[91]



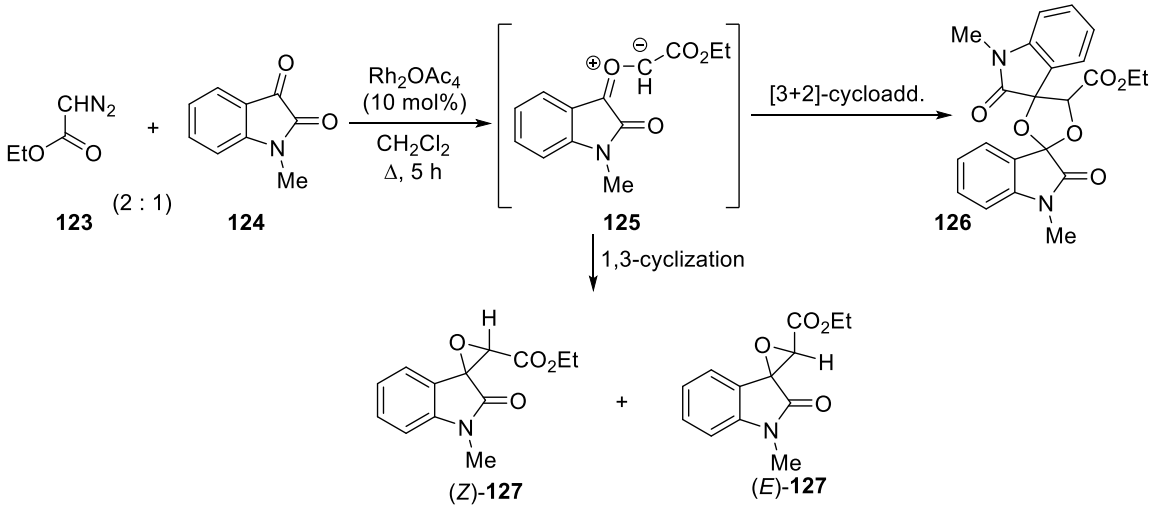
Scheme 14

The study was extended to the synthesis of NH-spirooxindole-azetidinones. It was observed that in an equimolar reaction of 2-diazoketones **108** with NH-isatin 3-imines **119**, the ketenes reacted at the NH of isatin forming *N*-(diary)acylisatin imines **120**.[91] The 1:2 molar reaction of such imines with 2-diazoketones afforded the corresponding spirooxindole-azetidinones **121** in good yields (Scheme 15). Using these methods and treating the spirooxindole-azetidinones with sodium hydroxide led to the chemoselective cleavage of the *N*-(diphenyl)acyl linkage on the 2-oxindole ring and afforded NH-spirooxindole-azetidinones **122** in quantitative yields (Scheme 15).[93]



Scheme 15

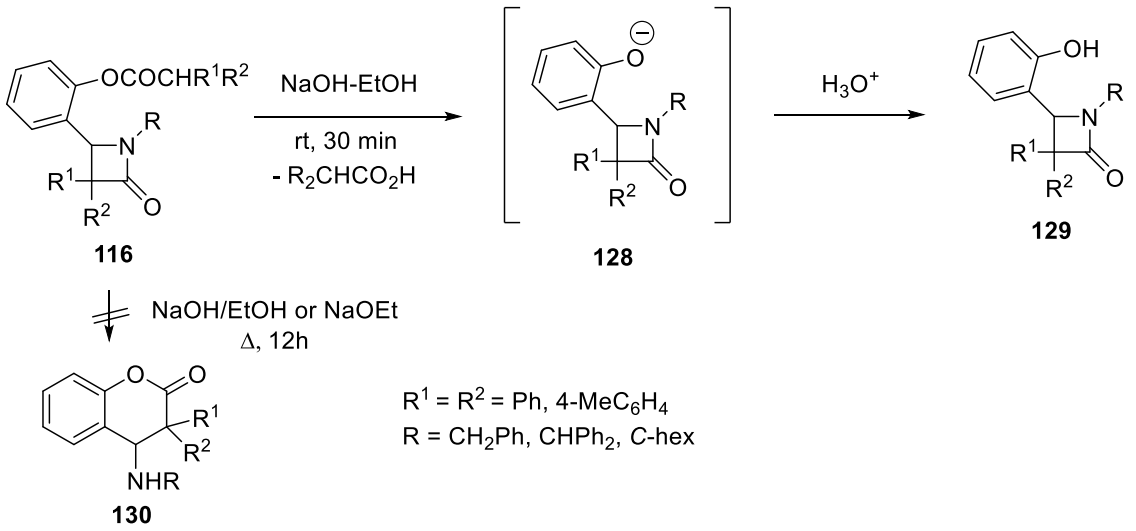
The reactions of α-diazocarbonyls in the presence of metal salts and complexes are known to proceed through metal-carbenoids.[94-96] Dirhodium tetraacetate [$Rh_2(OAc_4)$]-catalyzed reaction of ethyl diazoacetate **123** with *N*-methylisatin **124** were investigated for the synthesis of spirooxindole-oxiranes.[97] This reaction led to the formation of diastereomeric oxiranes **127** spiro-fused to *N*-methyl-2-oxindole together with 1,3-dioxolane bis-spiro-fused to *N*-methyl-2-oxindole **126** (Scheme 16). The formation of the products was explained through the ylide **125**, generated from the reaction of rhodium-carbenoid with the C-3 carbonyl group of the *N* methyl-isatin **124**. The ylide underwent a 1,3-cyclization to give the products **127**, and a (3 + 2)-cycloaddition with another molecule of *N*-methylisatin **124** to give the 1,3-dioxolane **126**. The *E*–*Z*-configurations of the spiro-oxirane-oxindoles was determined by nuclear overhauser effect (NOE) spectroscopy. A similar reaction of ethyl diazoacetate with isatin also furnished spirooxindole-oxirane but the 2-diazo-1,2-diarylketones failed to react with isatin or *N*-methylisatin.[98]



Scheme 16

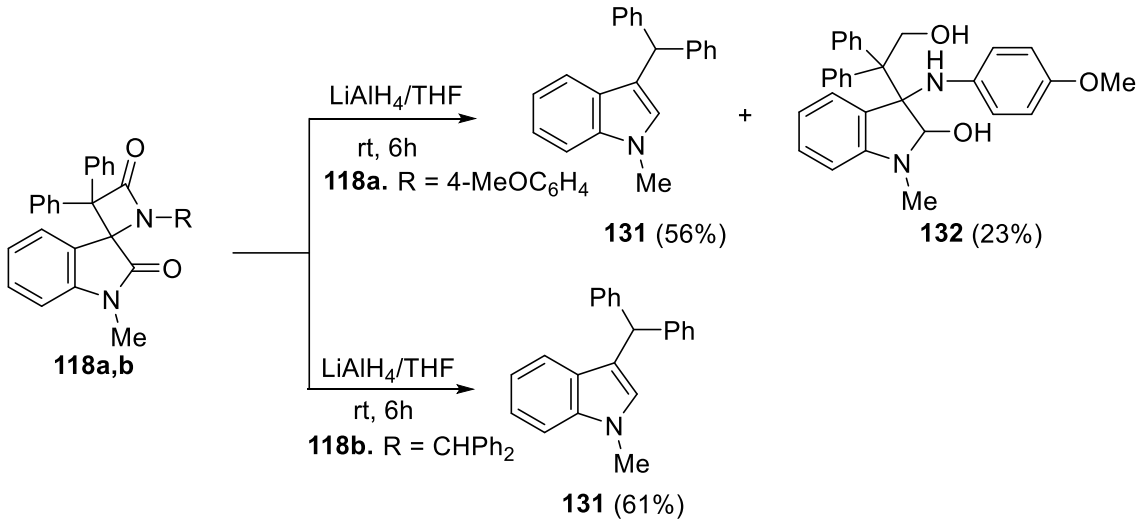
4.5 Reactivity of β-lactams

Besides being compounds of biological interest, β-lactams are powerful synthons in organic chemistry. The β-lactam ring-cleavage and transformation of groups on the ring have been employed in the synthesis of diverse types of biologically important heterocyclic compounds.[99] β-Lactams with two aryl groups on the C-3 position of the ring are fairly stable unless there is a trigger at C-4 position. β-Lactam ring with two phenyl groups on the C-3 position and a pyrrol-2-yl group on C-4 was reported to cleave under the influence of strong base.[100] The chemoselective cleavage of amide linkage in *N*-(diaryl)acyl-substituted spiro-oxindole-azetidinones furnishing NH-spiro-oxindole-azetidinones has been described in preceding section.[94] In another investigation to synthesize β-lactams containing a phenolic ring at C-4, esters of 1,3,3-trisubstituted 4-(2-hydroxyphenyl)-2-azetidinones **116** were treated with sodium hydroxide in ethanol at room temperature.[101] This resulted into chemoselective cleavage of phenolic ester linkage to afford the 1,3,3-trisubstituted 4-(2-hydroxyphenyl)-2-azetidinones **129** via intermediate **128** in quantitative yields (Scheme 17). Another possible structure **130** for the reaction product was ruled out by advanced NMR spectroscopic studies.[102]

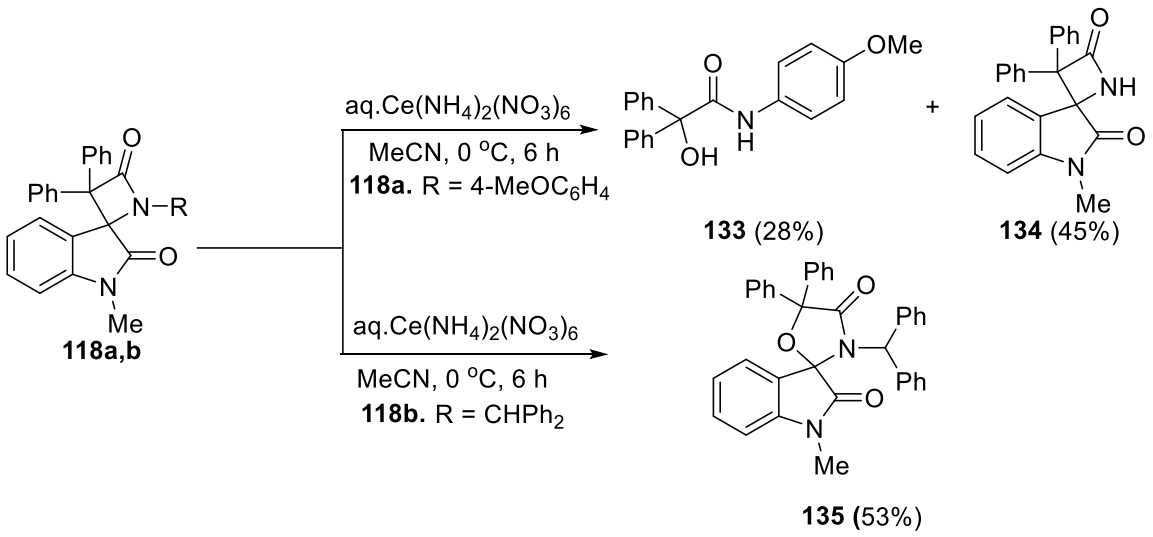


Scheme 17

Reductive and oxidative cleavages of spiro-fused 2-azetidinones, 1-substituted 3,3-diphenyl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-diones were investigated using lithium aluminum hydride (LAH) and ceric ammonium nitrate (CAN).[103] Spiroazetidinones **118a,b** underwent reductive cleavage on treatment with excess LAH furnishing 3-benzhydryl-1-methylindole **131** as the main product together with a γ-amino alcohol **132** in the case of 2-azetidinone ring having a 4-methoxyphenyl group on the β-lactam nitrogen (Scheme 18). Treatment of **118a** with CAN yielded 2-hydroxy-*N*-(4-methoxyphenyl)-2,2-diphenylacetamide **133** besides the anticipated *N*-unsubstituted 2-azetidinone **134** whereas a similar treatment of 1-benzhydryl-3,3-diphenyl-2-azetidinone **118b** afforded the ring-expansion product 1,3-oxazolidin-4-one **135** (Scheme 19). Clearly, the cleavages were governed by substituents present on the nitrogen atom of the 2-azetidinone ring.



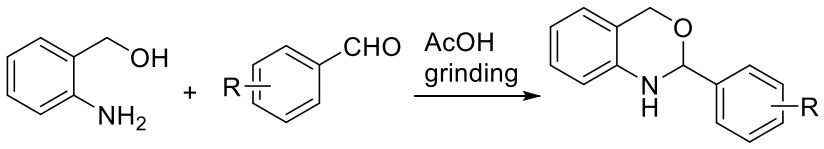
Scheme 18



Scheme 19

4.6 Green synthesis of benzoxazines and benzil diimines

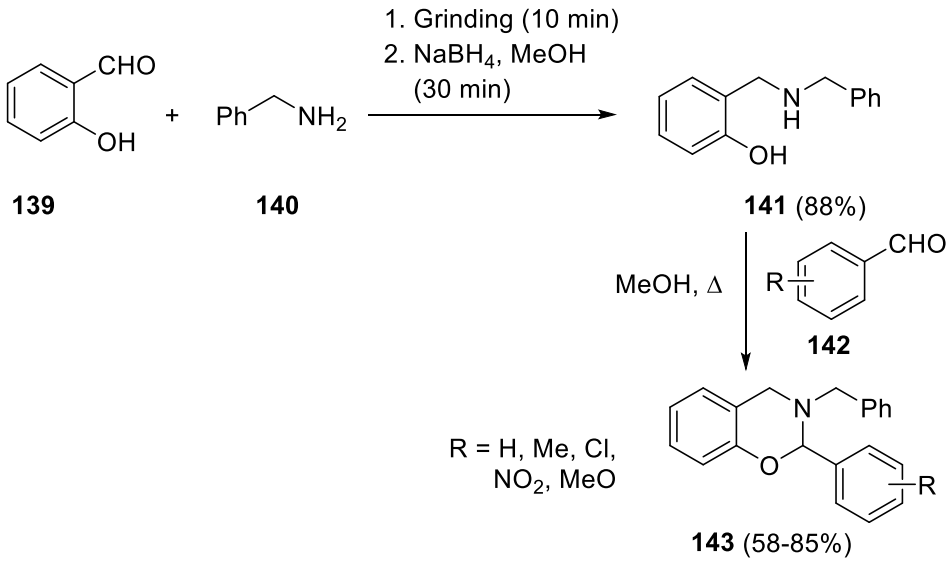
Our interest in benzoxazines was due to the ability of this class of compounds to polymerize upon heating to give thermosetting resins with wide applications ranging from adhesives to casting of airplane parts.[104] We were also intrigued by the general structural similarities between 2-arylbenzoxazines of type **138** and the naturally occurring flavans. The recognition that it should be possible to cyclize the imine of aminobenzyl alcohol **136** and benzaldehyde derivatives of type **137**, generated *in situ*, to give the corresponding benzoxazines is an elegant and central feature of our strategy. When benzaldehyde, *o*-chlorobenzaldehyde, *m*-nitrobenzaldehyde and *p*-nitrobenzaldehyde were mixed with aminobenzyl alcohol **136** in the presence of a catalytic amount of acetic acid and the mixtures grinded, the corresponding benzoxazines of type **138** were formed within 30 minutes in 96-99% yields and in high purity (Scheme 20).[101] It is noteworthy that the benzaldehyde derivatives discussed thus far carried electron withdrawing groups. The reactions of aminobenzyl alcohol **136** with benzaldehyde derivatives bearing electron donating hydroxyl or methoxy groups gave equilibrium mixtures of the corresponding intermediate imines and the benzoxazines.[105]



Scheme 20

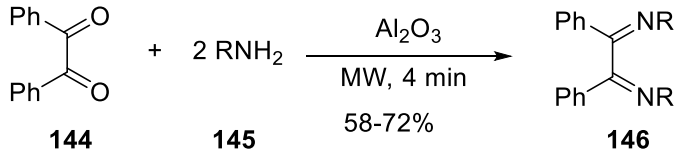
The isomeric benzoxazines with the oxygen at position 1 instead of 3 as in Scheme 21 were prepared by grinding benzylamine **140** and salicylaldehyde **139** followed by reduction of the intermediate imine to give 2-(aminomethyl)phenol **141** in 88% yield over the two steps. Subsequent reaction of 2-(aminomethyl)phenol **141** with benzaldehyde derivatives of type **142** gave the corresponding benzoxazines of type **143** in 58-85% yields (Scheme 21).[106] The last step of the procedure was found to be tolerant to electron withdrawing and electron

donating groups on the benzaldehyde. Indeed, nitro, chloro, methoxy and methylbenzaldehyde derivatives reacted with 2-(aminomethyl)phenol **141** to give the corresponding benzoxazines derivatives **143**.



Scheme 21

The microwave-assisted solvent-free reaction of benzil **144** with aromatic amines **145** (in 1:2 molar ratio) on the surface of alumina for four minutes afforded benzil diimines **146** (Scheme **22**).[107] An attempt to synthesize benzil monoimines by an equimolar reaction of benzil **144** with primary amines **145** under similar reaction conditions, however, afforded a complex mixture of products. It is worth mentioning that both mono- and diimines of 1,2-diketones such as benzil were known to be synthesized with difficulty requiring high temperature and longer time. Padwa had reported an equimolar reaction of benzil with amines at 175 °C in 2-3 h leading to the formation of benzil monoimines.[108]



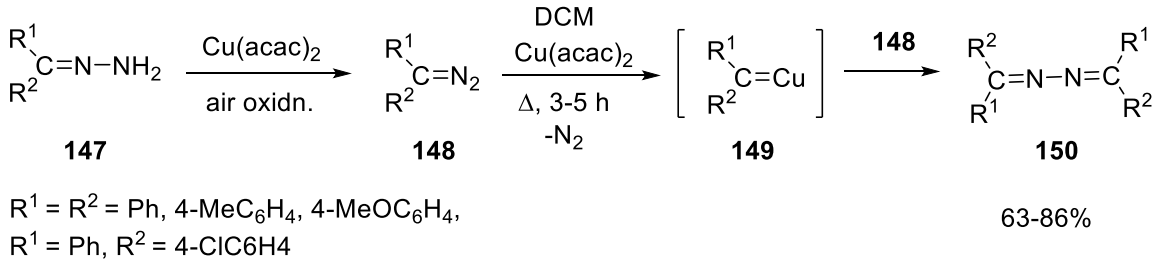
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 1-naphthyl

Scheme 22

4.7 Metal-catalyzed oxidation and hydrogenation reactions

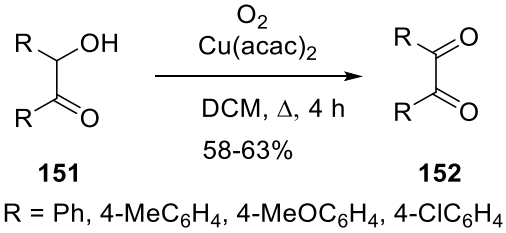
Transition metal salts and complexes are well known catalysts for oxidation of different functionalities in organic compounds. Among them, copper and cobalt salts and complexes have been thoroughly investigated.[109,110] Ibata and Singh reported in 1994 that bis(acetylacetonato)copper(II) worked as a catalyst for the oxidation of benzil monohydrazones furnishing 2-diazo-1,2-diarylethanones and benzil azines under different reaction conditions.[81] The usefulness of this catalyst in the oxidation of the hydrazones of aldehydes and ketones, and of alcohols (benzoins) was investigated at the University of Botswana. Treatment of benzophenone hydrazones **147** with bis(acetylacetonato)copper(II) afforded 1,2-bis(diarylmethylene)hydrazines **150** in good yields.[111] The

formation of the products was explained by i) a copper-catalyzed catalyzed aerial oxidation of hydrazones to the corresponding diaryl diazomethanes **148**, and ii) reaction of diaryl diazomethanes **148** with benzophenone hydrazones **147** through the intermediacy of copper-carbenoids **149** (Scheme 23). Similar reactions with hydrazones of aromatic aldehydes also yielded the corresponding azines.[112]



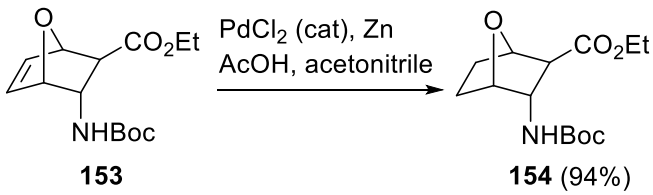
Scheme 23

With an objective to broaden the scope of bis(acetylacetonato)copper(II) as a catalysts in the oxidation of organic substrates, it was employed in the oxidation of hydroxyl group in α-hydroxyketones such as benzoins **151**. It catalyzed the oxidation of hydroxy group in benzoins leading to the formation of benzils **152** (**Scheme 24**).[113] The reaction took place both by conventional heating in solution and on solid support under microwave irradiation. The protocol was general to substrates having electron-donating and electron-withdrawing groups.



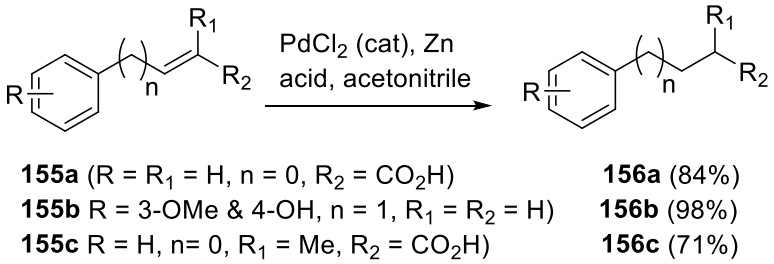
Scheme 24

The $PdCl_2$-catalyzed transfer hydrogenation of alkenes in the presence Zn powder and acetic acid was serendipitously discovered while studying the Pd-catalyzed reductive elimination of the oxygen bridge of products of the Diels-Alder reaction of furan with dienophiles.[114] When compound **153** was treated with a catalytic amount of $PdCl_2$ in the presence of Zn powder and acetic acid, the reduced form **154** was isolated in 94% yield (Scheme 25).[116] The reaction was successful when other acids such as formic acid, ammonium acetate and benzoic acid we used instead of acetic acid. Pd/C was found to be an alternative catalyst to $PdCl_2$.[115] The transfer hydrogenation is thought to proceed through the reduction of Pd(II) to Pd(0) by the Zn powder followed by oxidative addition of the organic acid to Pd(0) to give a palladium(II) hydride species which acts as the reducing agent.[115]



Scheme 25

The reduction procedure was extended to other alkenes such as cinnamic acid **155a**, eugenol **155b** and α-methylcinnamic acid **155c** and proceeded smoothly to give the corresponding reduced derivatives **156a-c** (Scheme 26).[114,115] Further, the reduction of α-methylcinnamic acid in the presence of L-(+)-tartaric acid instead of acetic acid proved to be highly asymmetric and gave the reduced product with 99% ee.[116]



155a (R = R_1 = H, n = 0, R_2 = CO_2H) **156a** (84%)
155b R = 3-OMe & 4-OH, n = 1, R_1 = R_2 = H) **156b** (98%)
155c R = H, n= 0, R_1 = Me, R_2 = CO_2H) **156c** (71%)

Scheme 26

4. Concluding Remarks

The organic chemistry research in Botswana has made tremendous progress during the last two decades. It has witnessed research developing in diverse areas of organic chemistry. It covers phytochemical studies of medicinally important plants, studies on oils, and synthesis of different heterocyclic compounds of biological relevance. Several novel alkaloidal and non-alkaloidal compounds have been isolated and characterized from eight different species of genus *Erythrina*. (+)-β–D-Gucoerysopine and (+)-15β–D-glucoerysopine are the two novel glycodienoid alkaloids isolated from *Erythrina latissima* seeds. Non-alkaloids isolated include, flavonoids, isoflavonoids, and aryl benzofuran, etc. Significant phytochemical work has also been reported on the monotypic genus *Bolusanthus speciousus*, as well as *Rhus sp*, *Bulbine sp*, *Scilla sp* and *Ledebouria sp* furnishing different classes of secondary metabolites with biological activities. Locally important seeds have been investigated for their oil value. *Tylosema esculentum* (morama) seeds furnished 48.2% oil yield and a high protein content. The extracts exhibited antioxidant, antibacterial, antifungal, antiviral and cytotoxic activities. Melon seed oil was found to be physicochemically comparable to sunflower oil.

Further, this review has demonstrated the versatility of adducts of the Diels-Alder reaction of furan and dienophiles in the synthesis of the reported structure of natural product oryzoxymycin and cyclohexyl β-amino acids. The results from work on use of enolate chemistry in the synthesis of flavans and aromatic acylation in the synthesis of flavanones were also summarized. The three-component reaction of benzaldehyde, malononitrile and resorcinol or phloroglucinol to give 4-arylchromenes was presented.

Using the reactions of α-diazoketones via diarylketenes, syntheses of β-lactams, spirooxindole-2-azetidinones, and 1,3,4-oxadiazolines have been achieved. The $Rh_2(OAc)_4$-catalyzed reaction of ethyl diazoacetate via rhodium-carbenoids with isatins yielded spirooxindole-oxiranes. Transformations of β-lactams have been carried out using sodium hydroxide, lithium aluminum hydride and cerium(VI) ammonium nitrate.

Different types of benzoxazines have been synthesized by grinding-induced condensation of appropriate amines with aldehydes. Microwave-assisted reaction of benzils with amines led to the synthesis of benzil diimines. Palladium-catalyzed hydrogenation of selected olefinic bonds has been carried out while bic(acetylacetonato)copper(II) has been employed as a catalyst in the oxidation of hydrazones and benzoins.

With the opening of new universities and research institutions in the country, we anticipate further diversification of the research areas keeping in mind the societal and economic needs of the nation.

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Authors' Biographies

Runner R. T. Majinda, a full professor of Organic Chemistry at the University of Botswana, is a researcher and Lecturer at the University of Botswana. He is a citizen of Botswana, born in 1961. He obtained his B.Sc. degree in Chemistry and Biology at the University of Botswana in 1987 and an M. Sc. degree in Pharmacology (with plant medicines option) from the University of Strathclyde in 1989. After lecturing at the University of Botswana for two years his employers granted him a scholarship in 1991 for a Ph.D. program in Natural Products Chemistry at the University of Strathclyde under the supervision of Professors Peter G. Waterman and Roger D. Waigh which he successfully completed in 1994.

Upon returning to Botswana, he embarked on a University teaching career and rose through the ranks to the post of full professor in 2006. His research interests have been in the area of bioactive natural products found in Botswana Medicinal plants, chief among which are plants from the genus *Erythrina*. He together with his colleagues in the Departments of Chemistry and Biological Sciences and collaborators overseas have looked at the various aspects of natural products such as isolation and structural elucidation, biological activity and synthesis.

He has co-authored over 86 publications which are published in reputable peer-reviewed international journals such as, among others, *Phytochemistry*, *Planta Medica*, and *Journal of Natural Products*. His work is impactful as testified by the over 1000 independent citations and books. He has also reviewed more than 1000 scientific papers for various journals such as *Phytochemistry*, *Journal of Natural Products*, *Biochemical Systematics & Ecology*, *Natural Product Research*, *RSC Advances*, *Phytochemical Analysis*, *Pharmaceutical Biology*, and *Phytochemistry Letters*. He is also on the Editorial Boards of several journals.

He has taught most the undergraduate Organic Chemistry content as well as graduate courses in Organic Spectroscopic, Biosynthesis of Secondary Metabolites and some advanced Organic Chemistry courses and has supervised several, M. Sc., M. Phil. and Ph. D. students.

Ishmael B. Masesane was born in Tutume, Botswana. He was awarded B. Sc. (Chemistry and Biology) and M. Sc. (Natural Products Chemistry) by the University of Botswana in 1996 and 1998 respectively. In 2004, he was awarded a Ph.D. (organic synthesis) by the University of Durham, UK. Ishmael was employed by the University of Botswana as a Staff Development Fellow after completion of his B.Sc. degree and as a lecturer after completion of his M.Sc. degree. He is currently a Professor of Chemistry at the University of Botswana and the Dean of the Faculty of Science. He is also the President of the Botswana Academy of Science, a Fellow of the Royal Society of Chemistry and an Executive Board member of Commonwealth Chemistry. To date, he has published 52 journal articles and 4 book chapters in the broad areas of Natural Products Chemistry and Organic Synthesis.

Girija S. Singh was born in Sasaram (Bihar), India. He received his B.Sc. and M.Sc. degrees from the U. P. College (then Gorakhpur University), Varanasi, India, in 1977 and 1979, respectively. He received his Ph.D. degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines and hydrazones in October 1984. Since then, he has occupied teaching and research positions in various universities such as Banaras Hindu University, India (JRF, SRF, PDF, Research Associate, Pool-Officer, Associate Professor), Osaka University, Japan (PDF), University of Zambia (Lecturer), and University of Botswana (Lecturer, Senior Lecturer, Associate Professor). He is currently working as Professor of Chemistry at the University of Botswana. He has authored 114 publications in books and in peer-reviewed journals. He is member of the American Chemical Society, Chemical Research Society of India, and Indian Chemical Society. He is on the editorial board of over half a dozen chemistry journals. His research interests include the study of synthesis and reactivity of biologically important heterocycles, reactions of carbenes and ketenes, metal-catalyzed oxidations, and organic chemistry education.