THE PREVALENCE OF NATURAL 3-ALK(EN)YL-SUBSTITUTED PHENOLS AND THEIR POTENTIAL SEMISYNTHESES FROM CASHEW NUT SHELL LIQUID

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ABSTRACT

The focus of this mini-review is to assemble an instructive sample of natural products possessing structural features present in phenolic constituents of Cashew Nut Shell Liquid (CNSL) and, thus, inspire researchers to undertake semisyntheses of these natural products using the relatively abundant phenolic components of CNSL as raw materials. In this review, the author attempts to identify (or point out to) a 3-alk(en)yl-substituted phenolic sub-structure embedded in a particular natural product and reveal the CNSL phenolic component that has the corresponding structural motif. In addition, the author prompts the reader into a thinking process that should eventually lead him/her to developing a comprehensive retrosynthesis of a particular natural product culminating to that CNSL phenolic component as the starting material. Thus, in some way this paper is a tutorial review to the newcomers in the field of natural product synthesis utilizing natural resources. The seasoned synthetic chemists will also benefit from this collection as they guide and inspire their research trainees to take up natural product synthesis. In this article, a brief introduction to the composition and applications of CNSL is presented. This is followed by a compilation from the literature of reported natural products possessing the 3-alk(en)yl-substituted phenolic moiety. Alongside this compilation, a diagnostic discussion is presented aiming at pinpointing CNSL phenols as prospective precursors for the semisyntheses of some selected natural products as illustrative examples.

Key words: Semisynthesis, CNSL phenols, 3-alk(en)yl-substituted phenolic sub-structure, natural products synthesis, natural resources

INTRODUCTION

Cashew Nut Shell Liquid/Oil (CNSL) is a by-product of the cashew processing industry; its chemical composition has been described as far back as 1967 (Akinhanmi and Atasie 2008). Based on the method of extraction from cashew nut shells, CNSL is classified into two types, solvent-extracted (Natural) CNSL and Technical CNSL. Usually, Natural CNSL contains cardol (15-20%) (Figure 1, **1**-**4**), anacardic acid (60-65%) (Figure 1, **5**-**8**), cardanol (10%) (Figure 1, **9**-**12**), and traces of methylcardol (Figure 1, **13**-**16**). Natural CNSL can also be obtained by physical pressing of the shells (extrusion method). Technical CNSL, obtained by roasting the shells, contains mostly cardanol (60-65%), cardol (15-20%), polymeric material (10%), and traces of methylcardol. Due to the high temperatures attained (*ca.* 200 °C) during the roasting process, anacardic acid decarboxylates to form cardanol (Kumar *et al*. 2002).

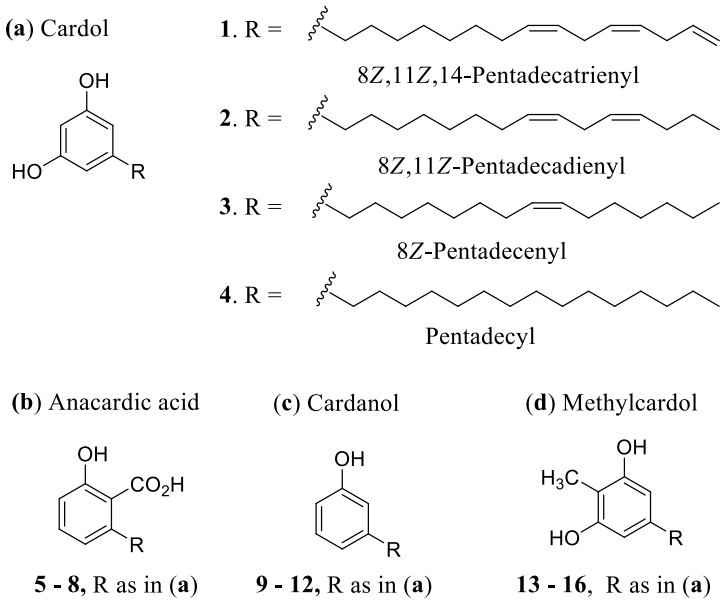


Figure 1. Structure of Cashew Nut Shell Liquid (CNSL) Constituents

The resourcefulness of CNSL and its individual phenolic constituents cannot be overemphasized. CNSL versatility is evident from its diverse uses as a mixture but also the numerous applications of its individual constituent phenols. For example, CNSL by itself finds applications as an insecticide, fungicide, larvicide, anti-termite, corrosion inhibitor, as well as an additive in many plastic formulations (Lubi and Thachil 2000, Asogwa *et al.* 2007, Buchweishaija 2009, Olotuah and Ofuya 2010, Mukhopadhyay *et al.* 2010, Mann and Kaufman 2012). CNSL also find applications in industry as a raw material for brake lining, as a water proofing agent, a preservative and in the manufacturing of paints and plastics (Akinhanmi and Atasie 2008). Moreover, CNSL is widely reported for its medicinal properties such as anti-bacterial, anti-oxidant, enzyme inhibition and other bioactivities (Himejima and Kubo 1991, Muroi *et al.* 2004, Kubo *et al.* 2006, Tsujimoto *et al.* 2007, Pereira *et al.* 2008, Stasiuk *et al.* 2008, de Jesus *et al.* 2011, Parasa *et al.* 2011). On the other hand, isolated constituent phenols from CNSL, especially cardanol and anacardic acid, have been extensively utilized in the syntheses of numerous polymeric materials (Jinhuo and Binghuan 1998, Lubi and Thachil 2000, Mkayula *et al.* 2004, Makame *et al.* 2005, Khaokhum *et al.* 2005, Gopalakrishnan and Sujatha 2010, Philip *et al.* 2012, Gopalakrishnan *et al.* 2012, Mwangi and Mbugua 2013).

Besides their being sources of polymeric products, the CNSL phenols form basic precursors for organic synthesis. For example, over the last one and a half decades cardanol has been used in the synthesis of products such as quaternary ammonium salts, hybrid materials, novel fulleropyrrolidines and porphyrins (de Avellar *et al.* 2000, Attanasi *et al.* 2009, Mele *et al.* 2009, and Vasapollo *et al.* 2011). Similarly, anacardic acid has also been utilized in the synthesis of numerous products including anacardic aldoximes, novel benzylamines and quinolines, as well as urea and thiourea derivatives that have

biological activities (Tyman and Iddenten 2005, Reddy *et al.* 2011, Vempati *et al.* 2011, Vempati *et al.* 2012). Cardol is also reported as a raw material in the synthesis of lasiodiplodin, a natural product isolated from the culture broth of the fungus *Botrydiplodia theobromae*, and a phosphorylated cardol compound with antioxidant activity (dos Santos and de Magalhães 1999, Maia *et al.* 2013).

The preceding brief introduction about the composition and reported applications of CNSL is certainly not exhaustive. Nevertheless, it provides a panoramic view of the importance of this cheap and renewable resource. In the section that follows, which is the focus of this review, the author compiles from the literature reported natural products possessing the 3-alk(en)yl-substituted phenolic pattern. Along with this compilation, analytical arguments pointing to CNSL phenolic constituents as prospective synthetic precursors for some selected natural products are given so as encourage sustained utilization of CNSL in natural product synthesis.

PREVALENCE AND PROJECTED SYNTHESES OF NATURAL 3-ALK(EN)YL-SUBSTITUTED PHENOLS FROM CNSL

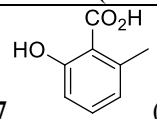
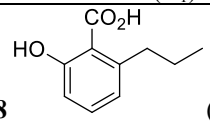
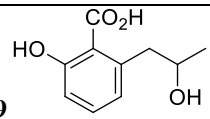
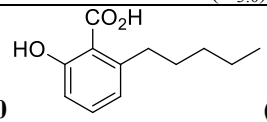
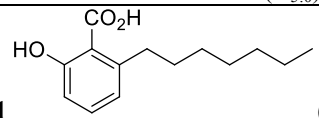
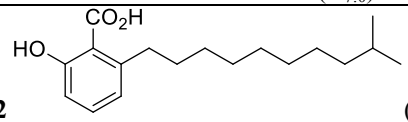
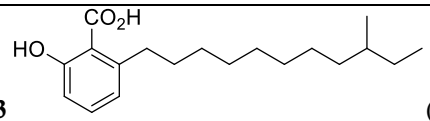
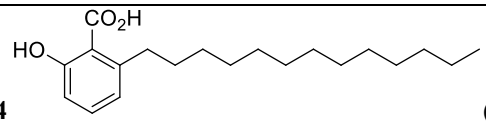
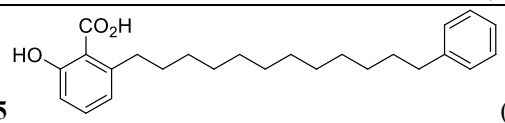
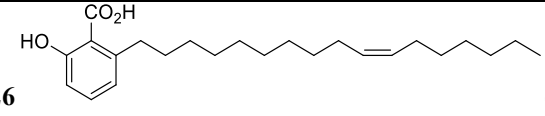
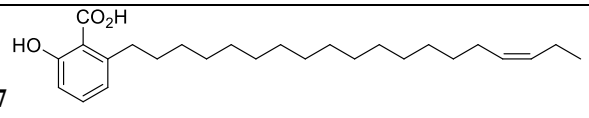
This section presents a wide array of reported natural products other than (*i.e.,* distinct from) the sixteen (16) CNSL constituents depicted in Figure 1. The presentation is divided into three sections namely: anacardic acid-, cardanol- and cardol-related natural products. This is done so as to facilitate discussions on the structural similarity between natural products being analyzed and the CNSL phenols. This arrangement makes it easier to provide suggestions on possible synthetic approach(es) toward a given 3-alk(en)yl-substituted phenolic natural product from a CNSL phenol. It must be emphasized that the categorization of any naturally occurring 3-alk(en)yl-substituted phenol into one of the three groups (*i.e.,* anacardic acid-, cardanol- and cardol-related) is based on the judgment and convenience of the author. It is certainly possible for a particular compound to possess structural features belonging to more than one group and that such a compound can therefore be classified into more than one class.

Anacardic Acid Related Natural Products

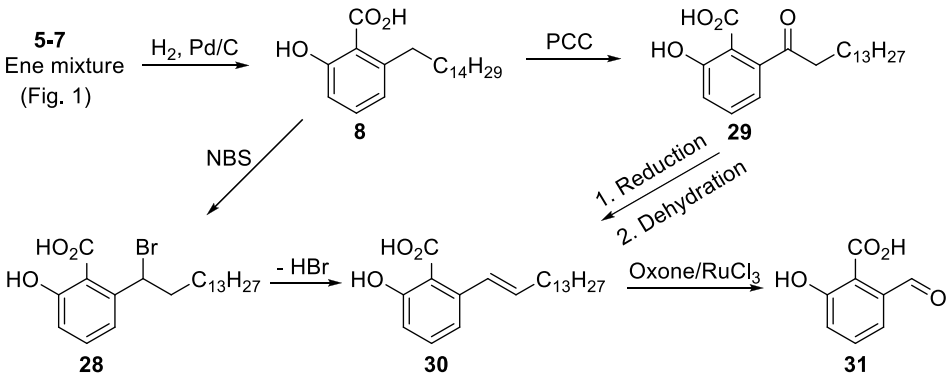
The literature abounds in naturally occurring 3-alk(en)yl-substituted phenolic compounds with structures similar to anacardic acids **5-8** shown in Figure 1 above. Before presenting examples it is important to take note of a nomenclatural clarification of compounds related to **5-8**. Since the carboxyl group in these compounds is given priority over the phenolic hydroxyl group, the anacardic acids are systematically named as 6-alk(en)yl-substituted salicylic acids. We shall endeavor to consistently refer to these compounds as 3-alk(en)yl-substituted phenols. However, when the designation 6-alk(en)yl-substituted salicylic acid (or simply 6-alk(en)ylsalicylic acid) is used it must be taken to refer to the same class of compounds.

Among the multitude of the anacardic acid related natural products, the aromatic antibiotic 6-methylsalicylic acid (**17**, Table 1) is the simplest. This compound was isolated, along with six other natural products, from *Aspergillus flavipes* (Nagia *et al.* 2012). Other examples of naturally occurring higher homologues of 6-methylsalicylic acid are shown in Table 1.

Table 1: Examples of Anacardic Acid Related Natural Products and Their Source

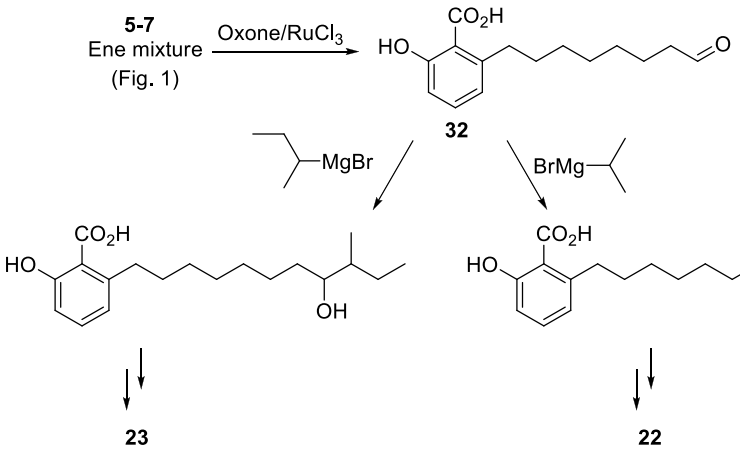
Structure (Side Chain Length and Unsaturation)	Source and Reference
 **17** (C_1)	*Aspergillus flavipes* (Nagia *et al.* 2012)
 **18** ($C_{3:0}$)	Metapleural gland of ants (Vander Meer 2012)
 **19** ($C_{3:0}$)	Fungal species (*Alternaria sp.*) associated with a sea cucumber (Xia *et al.* 2011)
 **20** ($C_{5:0}$)	Metapleural gland of ants (Vander Meer 2012)
 **21** ($C_{7:0}$)	Metapleural gland of ants (Vander Meer 2012)
 **22** ($C_{11:0}$)	*Streptomyces* strain (MS53), closely related to *Streptomyces laceyi* (Lee *et al.* 2006)
 **23** ($C_{12:0}$)	*Streptomyces* strain (MS53), closely related to *Streptomyces laceyi* (Lee *et al.* 2006)
 **24** ($C_{13:0}$)	*Ginkgo biloba* (He *et al.* 2000, Wang *et al.* 2009, Stasiuk and Kozubek 2010, Pszczolkowski *et al.* 2011)
 **25** (C_{12} + Ph)	*Knema elegans, K. furfuraceae* and *K. tunuinervia* (Pinto and Kijjoa 1990)
 **26** ($C_{17:1}$)	*Ginkgo biloba* (He *et al.* 2000, Wang *et al.* 2009, Stasiuk and Kozubek 2010, Pszczolkowski *et al.* 2011)
 **27** ($C_{19:1}$)	*Amphipterygium adstringens* (Rivero-Cruz 2011)

The structural similarity between compounds **17-27** (Table 1) and the anacardic acids **5-8** (Fig. 1) is very obvious. It is, therefore, quite possible to synthetically derivatize the relatively abundant anacardic acids (**5-8**) to compounds **17-27**. For compounds with the side chain shorter than C_8 (for example, **17-21**), one might saturate the olefinic bonds of the side chain of anacardic acid and thereafter carry out either benzylic oxidation or halogenation so as to set the stage for the eventual formation of a benzylic double bond as shown in compound **30** (Scheme 1). Cleavage of the benzylic double bond in compound **30** furnishes 2-formyl-6-hydroxybenzoic acid (**31**), which should act as the basic raw material for the semisyntheses of compounds **18-21** *via*, among others, a Grignard reaction or a Wittig reaction as a key step. The Grignard or Wittig reagent used should have an appropriate carbon chain such that when combined with the aldehydic carbon of compound **31** gives the required chain length in compounds **18-21**. Reductive manipulation of the aldehydic group of compound **31** should eventually result into the formation of **17**. The NBS route to a compound similar to **30** is reported in literature (Lograd*o et al.* 2005).



Scheme 1: Proposed synthesis of **31**, a raw material for the syntheses of compounds **17-21.**

For compounds with the side chain longer than C_8 (for example, **22-27**), it may be helpful to exploit the olefinic double bond at position 8 by cleaving it to obtain a C_8 carbon chain with aldehyde functionality as shown in compound **32** (Scheme 2). The aforementioned ozonolytic cleavage has already been reported (Lograd*o et al*. 2005). Once this is accomplished, the required chain length in compounds **22-27** may then be constructed through the reaction of aldehyde **32** obtained with, for example, a Grignard reagent having an appropriate number of carbon atoms. For example, an *iso*propylmagnesium bromide and *sec*-butylmagnesium bromide would lead to assemble the side chains of compounds **22** and **23**, respectively. The proposed synthetic approach summarized in Scheme 2 represents a general idea and, therefore, in a comprehensive synthetic planning some details and refinements may become necessary. These may include, for example, protection of the hydroxyl groups of both the phenolic and carboxyl functional groups as well as change of method in the construction of the side chain from compound **32**. In the latter case, one might decide to employ the Wittig instead of the Grignard method suggested in Scheme 2.



Scheme 2: Proposed synthesis of **32**, a raw material for the syntheses of compounds **22-27**.

In some cases the presence of a 3-alk(en)yl-substituted phenolic sub-structure imbedded in a particular natural product may be less obvious than it is in the examples discussed so far. For instance, it may be difficult to point out the similarity between anacardic acids **5-8** (Fig. 1) and some naturally occurring phenolic compounds such as the 8-hydroxy-3,4-dihydroisocoumarin (or 8-hydroxy-3,4-dihydro-1H-2-benzopyran-1-one) **33** and the two anthraquinones **34** and **35** depicted in Figure 2. Careful inspection of these natural products, however, reveals that a 3-alk(en)yl-substituted phenolic pattern, similar to that of anacardic acids **5-8**, forms part of their structures. This implies that it may be possible to obtain compounds **33-35** and similar compounds through synthetic manipulations of anacardic acids **5-8**. The 1,2,3-substitution pattern in the phenolic compounds **33-35** is indicated by the box on the left hand side of each structure. It must be noted that the 1,2,3-numbering in compounds **33-35** does not represent the standard way used for nomenclatural purposes of these compounds. In here the numbering indicates the relative positions of the three substituents on the left hand side aromatic ring. The intention of this numbering is to make easy the comparison of the sub-structures in the boxes to the substitution pattern in the anacardic acids **5-8**.

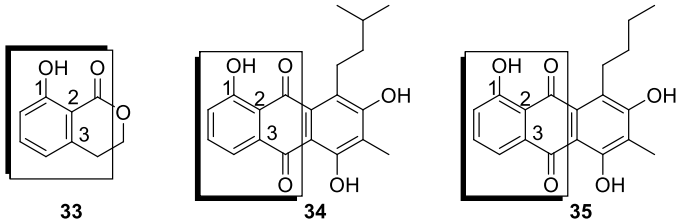
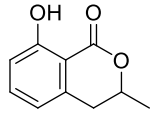
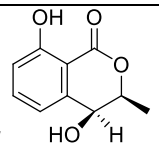
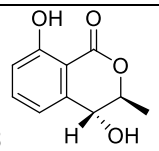
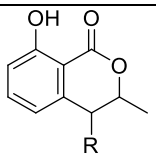
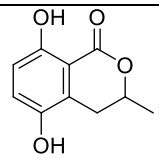
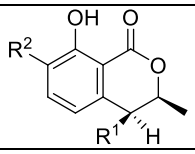
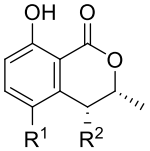


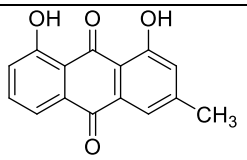
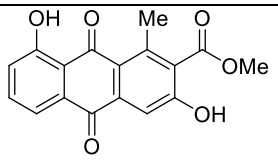
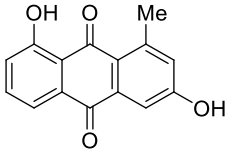
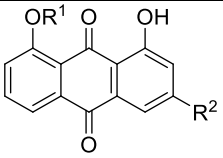
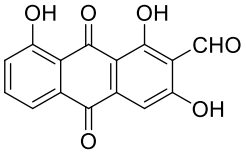
Figure 2. *Iso*coumarins and Anthraquinones with Structural Similarities to Anacardic Acids

Before discussing some potential semisynthetic manipulations of anacardic acids towards compounds similar to **33**, it would be prudent to point out that natural products with structures analogous to **33** have been reported in the literature and are known to be widely distributed in fungi and other organisms. In fact natural products that

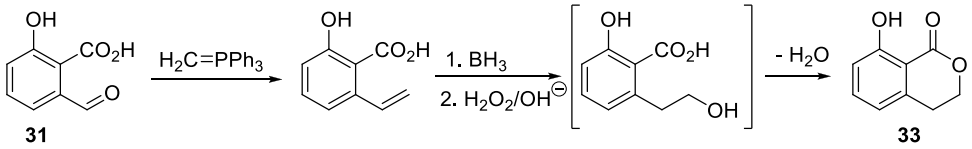
have various substituents on different positions of **33** are commonly known as melleins. On the other hand, anthraquinones analogous to **34** and **35** make up a class of ubiquitous naturally occurring compounds. Selected examples of melleins and anthraquinones are shown in Table 2.

Table 2: Examples of Melleins and Anthraquinones Structurally Related to Anacardic Acid.

Structure		**Source and Reference**
33 (See Figure 2)		Metapleural gland of ants (Vander Meer 2012)
34 (See Figure 2)		*Micromonospora lupini* (Actinomycete) Igarashi *et al.* 2007
35 (See Figure 2)		Same source as compound **34**
 **36**		Metapleural gland of ants (Vander Meer 2012) Stem bark of *Oroxylum indicum* (L.) Benth. ex Kurz (Maungjunburee 2010) Culture filtrates of *Botrosphaeria obtusa* (Djoukeng *et al.* 2009)
 **37**		Culture filtrates of *Neofusicoccum parvum* (Evidente *et al.* 2010)
 **38**		Culture filtrates of *Neofusicoccum parvum* (Evidente *et al.* 2010)
	**39**: R = CHO **40**: R = CH_2OH	Roots of *Rhus javanica* L. var. roxburghiana (Lee *et al.* 2005)
 **41**		*Botrosphaeria obtusa* (Venkatasubbaiah *et al.* 1991)
	**42**: R^1 = H; R^2 = OH **43**: R^1 = OH; R^2 = OH	Culture filtrates of *Botrosphaeria obtusa* (Djoukeng *et al.* 2009)
	**44**: R^1 = CO_2Me; R^2 = OH **45**: R^1 = CO_2Me; R^2 = H **46**: R^1 = Me; R^2 = H **47**: R^1 = CO_2H; R^2 = H	*Xylaria* sp. PSU-G12 (an endophytic fungi) (Rukachaisirikul *et al.* 2013)

 **48**		Medicinal Chinese herb – *Rumex japonicus* (Guo *et al.* 2011)
 **49**		Isolated from *Aloe saponaria* (Nogueira and Lopes 2011, Huo *et al.* 2009)
 **50**		Isolated from *Streptomyces coelicolor* A3 (2) (Bystrykh *et al.* 1997)
	**51**: R^1 = H; R^2 = H **52**: R^1 = H; R^2 = CH_2OH **53**: R^1 = CH_3 ; R^2 = CHO **54**: R^1 = H; R^2 = CO_2H **55**: R^1 = Gluc; R^2 = CO_2H	Isolated from *Cassia* species (Dave and Ledwani 2012)
 **56**		Isolated from *Cassia* species (Dave and Ledwani 2012)

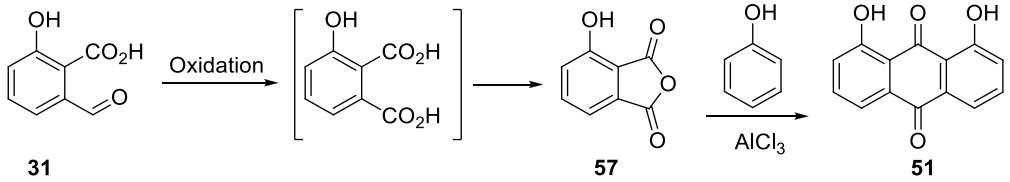
Retrosynthetic analysis of a mellein such as **33** (Fig. 1) could lead to aldehyde **31** (Scheme 1) as a key intermediate. Scheme 3 represents possible semisynthetic manipulations of **31** towards the targeted mellein **33**.With appropriate modifications and refinements, this general synthetic design can possibly be extended to the semisyntheses of other compounds related to **33**.



Scheme 3: Proposed synthesis of mellein **33** from the anacardic acid derived aldehyde **31**.

The coupling reaction between phthalic anhydride and its derivatives with other benzene derivatives is the most common method used to synthetically assemble an anthraquinone nucleus. With this idea in mind, one could possibly transform the anacardic acid derived aldehyde **31** to the phthalic anhydride **57** (Scheme 4) and,

thereafter, carry out a Friedel-Crafts acylation of a benzene derivative with **57** to obtain an anthraquinone. For example, a projected synthesis of anthraquinone **51** (Table 2) employing this idea is summarized in Scheme 4. The conversion of **57** to **51** has been reported by Dhananjeyan and co-workers (2005) although compound **57** was obtained from a different source.



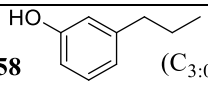
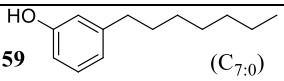
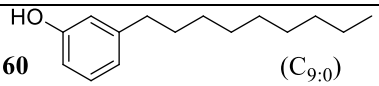
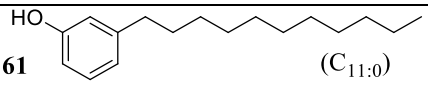
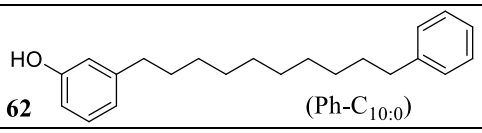
31 **57** **51**

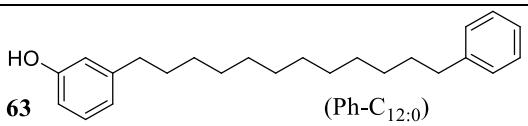
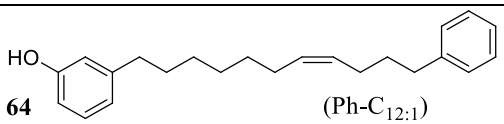
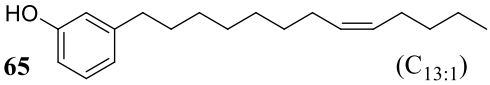
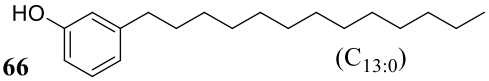
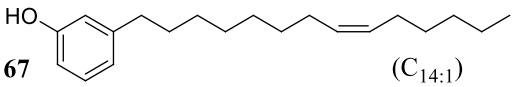
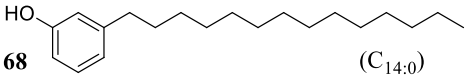
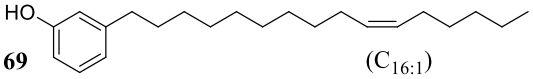
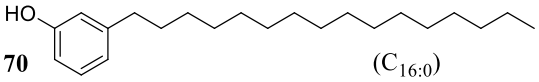
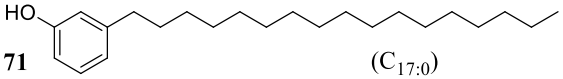
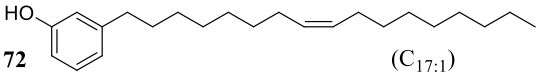
Scheme 4: Proposed synthesis of anthraquinone **51** from the anacardic acid derivative **31** (adapted from Dhananjeyan *et al*. 2005).

Cardanol Related Natural Products

From the chemotaxonomic point of view, naturally occurring phenols that are structurally related to the cardanols (*i.e.,* compounds **9-12**, Fig. 1) occur in fewer species compared to the anacardic acids and cardols, which are widely distributed. Apart from *Anacardium occidentale*, cardanols are also found in *Ginkgo biloba*, *Pistacia vera* and mycobacterial glycolipids (Tyman 2005, Saitta 2009). Table 3 lists some naturally occurring 3-alk(en)ylphenols and their sources.

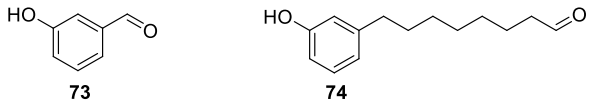
Table 3: Examples of 3-Alk(en)ylphenols Structurally Related to Cardanols **9-12**.

Structure	Source and Reference
 **58** ($C_{3:0}$)	Metapleural gland of ants (Vander Meer 2012); Urine of cattle and buffaloes (Mmongoyo *et al*. 2012)
 **59** ($C_{7:0}$)	Metapleural gland of ants (Vander Meer 2012)
 **60** ($C_{9:0}$)	Metapleural gland of ants (Vander Meer 2012)
 **61** ($C_{11:0}$)	From a Sumatran plant (Takaishi *et al.* 2004)
 **62** ($Ph\text{-}C_{10:0}$)	Detected in *Melanorrhoe austate* lacquer (Niimura and Miyakoshi 2003)

 **63** ($Ph\text{-}C_{12:0}$)	Same source as **62**;also isolated from *Knema furfuraceae* (Pinto and Kijjoa 1990)
 **64** ($Ph\text{-}C_{12:1}$)	Isolated from *Knema elegans* (Pinto and Kijjoa 1990)
 **65** ($C_{13:1}$)	Detected from kernels of *Pistacia vera* L. (Saitta *et al.* 2009)
 **66** ($C_{13:0}$)	From *Ginkgo biloba* (Wang *et al.* 2009, Stasiuk and Kozubek 2010)
 **67** ($C_{14:1}$)	Same source as **65**
 **68** ($C_{14:0}$)	Same source as **65**
 **69** ($C_{16:1}$)	Same source as **65**
 **70** ($C_{16:0}$)	Same source as **65**
 **71** ($C_{17:0}$)	Same source as **65**
 **72** ($C_{17:1}$)	Same source as **66**

The semisyntheses of the natural products listed in Table 3 can be achieved employing an approach that may require the derivatization of the CNSL cardanols **9-12** (Fig. 1) to aldehyde **73** and **74** (Fig. 3) in a manner analogous to the way aldehydes **31** (Scheme 1) and **32** (Scheme 2) were obtained. Further transformations of the key aldehyde intermediates **73** and **74** towards compounds **58-72** is expected to follow similar patterns as previously discussed for intermediates **31** and **32**.

3-Hydroxybenzadehyde (**73**) is commercially available and can also be synthesized from 3-nitrobenzalhehyde (Woodward 1945). On the other hand, Graham and Tyman (2002) obtained 8-(3-hydroxyphenyl)octanal (**74**) from ozonization of the CNSL cardanols (**9-12**)



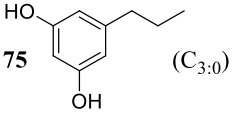
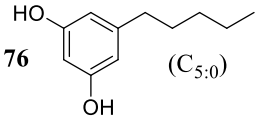
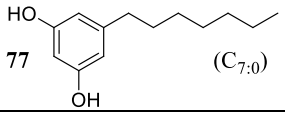
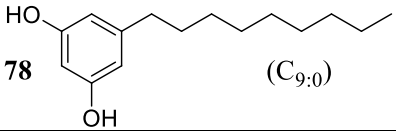
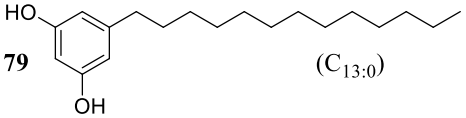
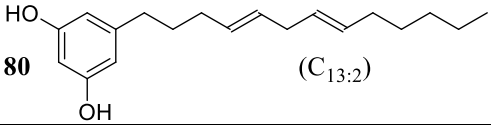
73 **74**

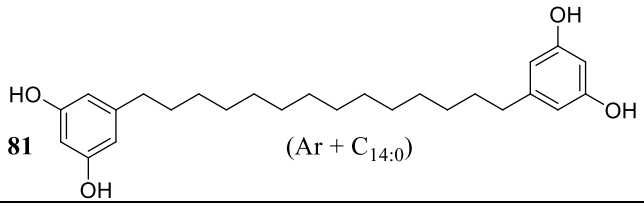
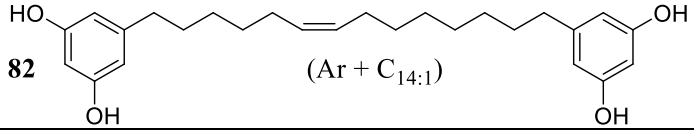
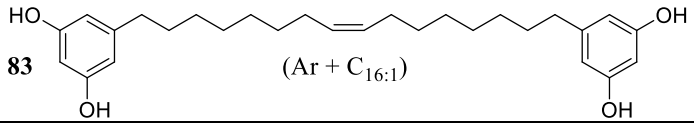
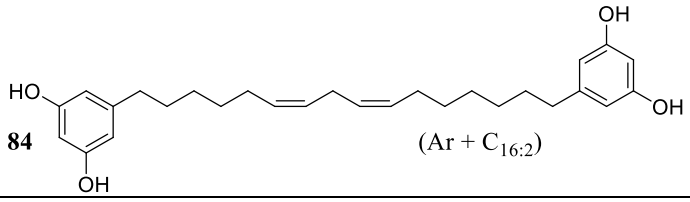
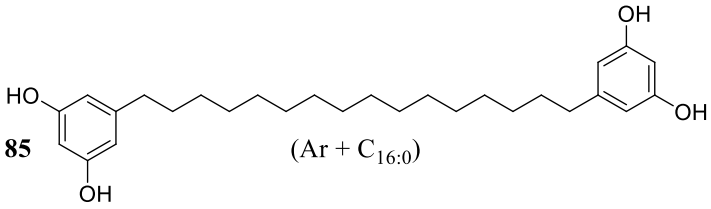
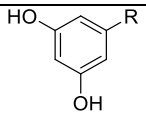
Figure 3. Aldehydes **73** and **74**, key intermediates for the syntheses of compounds **58-72.**

Cardol Related Natural Products

Phenolic compounds structurally related to the CNSL cardols **1-4** (Fig. 1) are commonly called 5-alkylresorcinols (or resorcinolic lipids). These natural products occur widely in plants, bacteria and in insect sources (Tyman 2005). 5-Alkylresorcinols are also found in mushrooms and other fungi. A list of more than 100 naturally occurring resorcinolic lipids has been compiled by Kozubek and Tyman (1999). The structures of a few known natural resorcinolic lipids are given in Table 4, which also provides the source of the resorcinolic lipids and references to earlier and recent studies.

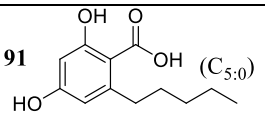
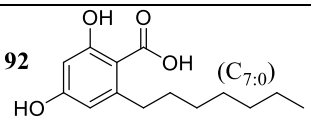
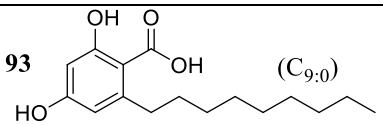
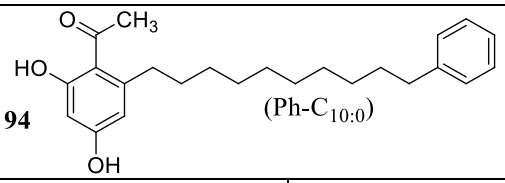
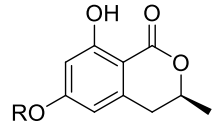
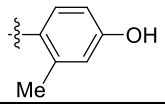
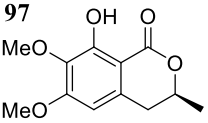
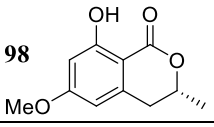
Table 4: Examples of 5-Alkylresorcinols Structurally Related to Cardols **1-4**

Structure	**Source and Reference**
 **75** ($C_{3:0}$)	Metapleural gland of ants (Vander Meer 2012)
 **76** ($C_{5:0}$)	Same source as **75**
 **77** ($C_{7:0}$)	Same source as **75**
 **78** ($C_{9:0}$)	Same source as **75**
 **79** ($C_{13:0}$)	Isolated from the West Australian shrub *Hakea trifurcata* (Füstner and Seidel 1997)
 **80** ($C_{13:2}$)	Isolated from an argentine medicinal plant *Lithraea melleoides* (López *et al.* 2005)

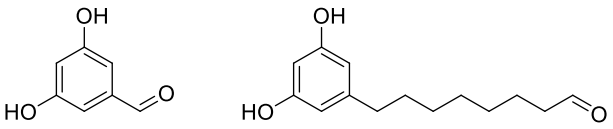
 **81** (Ar + $C_{14:0}$)		Same source as **79**
 **82** (Ar + $C_{14:1}$)		Same source as **79**
 **83** (Ar + $C_{16:1}$)		Same source as **79**
 **84** (Ar + $C_{16:2}$)		Isolated from the small tree *Grevillea whiteana* McGillivray (Wang *et al.* 2009)
 **85** (Ar + $C_{16:0}$)		Same source as **84**
	**86**: R = $C_{17:0}$ (Saturated) **87**: R = $C_{17:1}$ (Δ8*Z*) **88**: R = $C_{17:2}$ (Δ8*Z*,11*Z*) **89**: R = $C_{17:3}$ (Δ8*Z*,11*Z*,16) **90**: R = $C_{17:3}$ (Δ9*E*,11*Z*,16)	Isolated from the mushroom *Merulius incarnates* (Jin and Zjawiony 2006, Saleem *et al.* 2010)

In addition to 5-alk(en)ylbenzene-1,3-diols shown in Table 4, there are other cardol related natural products with substituents either in position 2 or 4 or both positions of the benzene ring. A few examples of such compounds are depicted in Table 5.

Table 5: Other Cardol Related Natural Products with Substituents in Position(s) 2 and/or 4.

Structure	**Source and Reference**
91 	Metapleural gland of ants (Vander Meer 2012)
92 	Same source as **91**
93 	Same source as **91**
94 	Isolated from *Knema elegans* and *K. tunuinervia* ssp. *setosa* (Pinto and Kijjoa 1990)
 **95**: R = Me **96**: R = 	Isolated from the fungus *Aspergillus terreus* (Choudhary *et al.* 2004)
97 	Same source as **95** & **96**
98 	Isolated from the fungus *Gilmaniella humicola* (Wanjiku 2009)

To accomplish the semisyntheses of the compounds listed in Tables 4 and 5, one can possibly make use of an approach that require the derivatization of the CNSL cardols **1-4** (Fig. 1) to aldehyde **99** and **100** (Fig. 4) in a manner corresponding to the way aldehydes **31** (Scheme 1) and **32** (Scheme 2) were obtained. Further synthetic manipulations of the key aldehyde intermediates **99** and **100** to compounds **75-98** are expected to follow analogous general patterns as the ones discussed earlier for intermediates **31** and **32**. In addition to this general synthetic strategy, detailed synthetic planning should include synthetic steps that address specific structural features of the target natural product. For example, awareness of the presence of extra substituents in positions 2 and/or 4 in compounds **91-98** (Table 5) should be reflected in the detailed synthetic plans for these compounds.



99 **100**

Figure 4. Aldehydes **99** and **100**, key intermediates for the syntheses of compounds **75-98.**

The organic intermediate 3,5-dihydroxybenzaldehyde (**99**) is commercially available whereas Graham and Tyman (2002) obtained 8-(3,5-hydroxyphenyl)octanal (**100**) from ozonization of the CNSL cardols (**1-4**, Fig. 1).

CONCLUSION

Based on structural resemblances with the major components of CNSL phenols, a categorized compilation of other naturally occurring 3-alk(en)yl-substituted phenolic compounds has been given in this mini-review. The selected summaries (Tables 1-5) undoubtedly indicate the extensive distribution and diversity of these compounds in plants, fungi, bacteria, insects, etc. Admittedly though, this review has not furnished an exhaustive compilation of all the available literature information in this field. This compilation, however, furnishes a useful source of and a lead to finding interesting natural products as synthetic targets. The briefly discussed potential semisynthetic strategies suggested in this review may serve as a source of inspiration for undertaking the semisyntheses of these natural products utilizing the relatively abundant CNSL phenols. In this article, the potential of CNSL phenols in the preparation of synthetically useful fine chemicals (such as the 3-substituted phenols **31**, **32**, **73**, **74**, **99** and **100**) has been highlighted. It is significant to note that 3-substituted phenols are difficult to prepare and, as a consequence, the commercially available products are generally expensive. In general, the author is of the view that this tutorial review will introduce the newcomers in the field of natural product synthesis utilizing natural resources. The experienced synthetic chemist will also benefit from this compilation as a tool for guiding and motivating research trainees to take up natural product synthesis.

ACKNOWLEDGEMENTS

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