

# Eudesmane sesquiterpenoids from the Asteraceae family†

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This review covers the structures and biological activities of eudesmane-type sesquiterpenoids from the plants of the Asteraceae family. Biosynthetic studies or chemical syntheses leading to the revision of structures or stereochemistries have also been included, and 593 references are cited.

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## 1 Introduction

The large family Asteraceae (= Compositae) contains 25 000–30 000 species belonging to over 1000 genera. Many species have been used as sources of rubber, medicines, edible oils, vegetables,

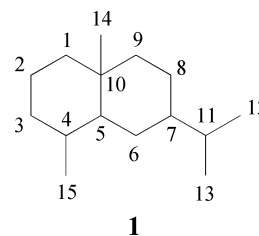
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pesticides and so on. Some are popular ornamental plants. The genera *Aster*, *Inula*, *Xanthium*, *Eupatorium*, *Carpesium*, *Saussurea* and *Taraxacum* are sources of various medicines; the whole plants of *Taraxacum kok-saghyz* and *Parthenium hysterophorus* are a source of rubber, and the seeds of *Helianthus annuus*, *Guizotia abyssinica* and *Xanthium sibiricum* are sources of edible oils. The extract from the leaves of *Blumea balsamifera* are used for the manufacture of borneol, and *Oxalis corymbosa* is used as a source of pyrethrum pesticides.<sup>1</sup> This family is a rich source of sesquiterpenoid natural products, especially those with the eudesmane framework.

The eudesmanoids are biosynthesised from farnesyl pyrophosphate,<sup>2</sup> and approximately 1000 natural eudesmanoids have been identified from the Asteraceae family, with many different oxygenation and cleavage patterns. The configuration and numbering of eudesmane (**1**, 2-isopropyl-4a,8-dimethyldecahydro-naphthalene) is shown below.



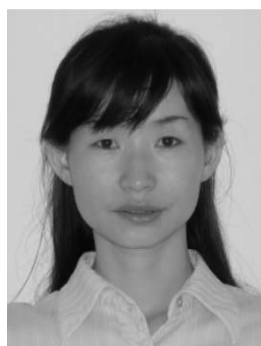
During the last two decades, eudesmane-type sesquiterpenoids and their biological activities from Asteraceae species have been the focus of numerous phytochemical, pharmacological and synthetic studies. Because the sesquiterpenoids exhibit a wide range of biological activities, and include compounds that are plant growth regulators, insect antifeedants, antifungals, anti-tumour compounds and antibacterials, there has been much interest in relating structure and oxygenation patterns to function.

This article reviews the structures and biological activities of novel eudesmane-type sesquiterpenoids from Asteraceae species. Studies involving biosynthesis and chemical synthesis and leading to a deeper chemical and biological understanding of these metabolites are discussed. The review highlights 972 compounds, and includes those with re-assigned structures or newly established stereochemistry where appropriate.

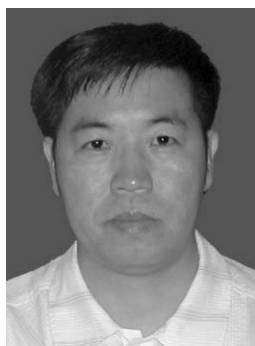
*Quan-Xiang Wu received her M.Sc. and Ph.D. degrees in Organic Chemistry from Lanzhou University, China. Her research interests focus on natural products chemistry, including isolation and structural elucidation of biologically active secondary metabolites, especially in the field of terpenes from the higher plants. She obtained a permanent position in Lanzhou University as Senior Lecturer in 2005.*

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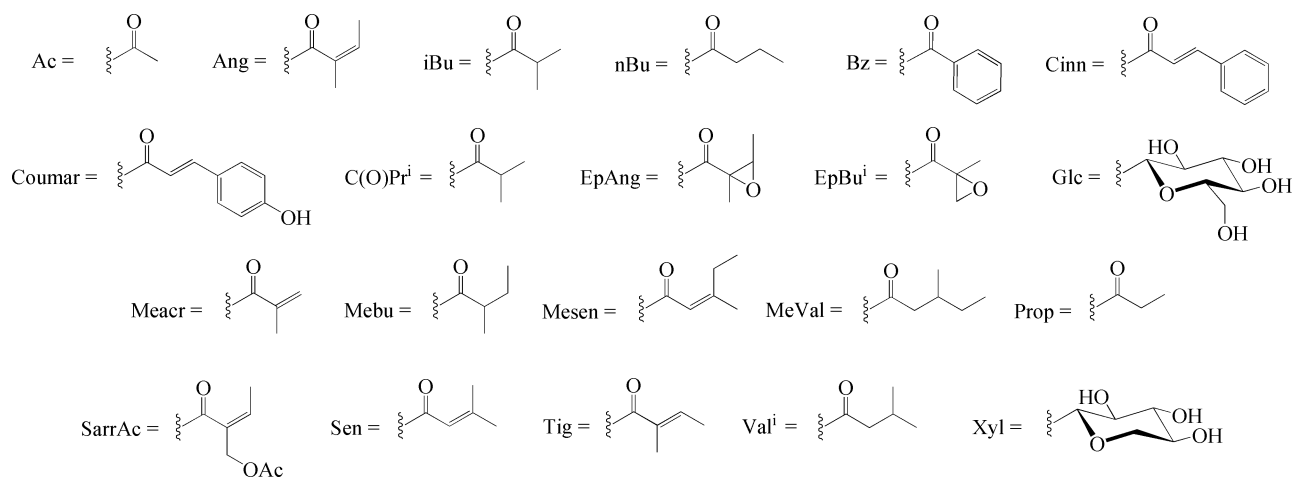
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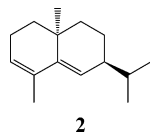


Zhong-Jian Jia



## 2 Eudesmenes

Non-oxygenated eudesmane sesquiterpenoids are hardly represented in the Asteraceae family. Eudesmene **2** was isolated from *Ursinia trifida*,<sup>3</sup> and its isomer, 10-*epi*-eudesma-3,5-diene, has been prepared from santonin.<sup>4</sup> The total syntheses of 4(15),7-dieneudesmane and (±)-vetiselinene have been reported.<sup>5</sup>



## 3 Oxygenated eudesmanes

Oxygenated eudesmanes form the major class of sesquiterpenoids in Asteraceae species, and include alcohols, ethers, epoxides, peroxides, aldehydes, ketones, carboxylic acids and lactones. The different functional groups are important in determining the individual biological activities of the various sesquiterpenoids. These compounds are discussed in more detail below.

### 3.1 Hydroxyl-substituted eudesmanes

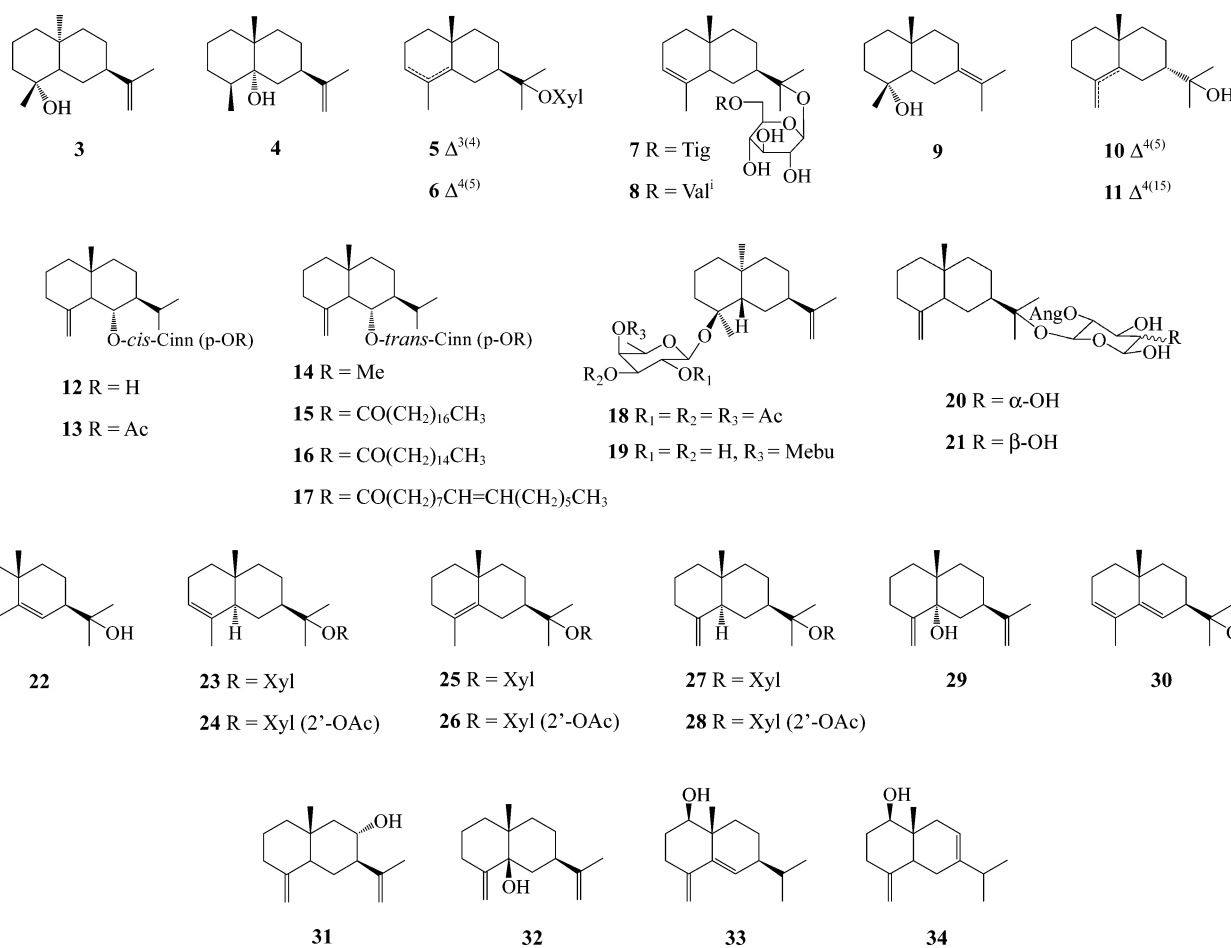
**3.1.1 Eudesmanols.** The novel eudesmanols **4–34** and their plant sources are detailed in Table 1. 4-Hydroxy-10-*epi*-eudesma-11-ene **3**<sup>23</sup> was synthesised from (–)-carvone, and the structure was established by X-ray analysis. The eudesmanols (±)-6-eudesmen-

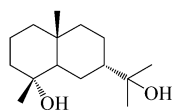
**Table 1** Sources of eudesmanols

Sources	Compounds
<i>Artemisia annua</i>	<b>29, 33, 34</b> <sup>18,19</sup>
<i>Calendula persica</i>	<b>20, 21</b> <sup>13</sup>
<i>Carthamus lanatus</i>	<b>18, 19</b> <sup>12</sup>
<i>Cassinia subtropica</i>	<b>29, 32</b> <sup>16</sup>
<i>Helichrysum italicum</i>	<b>22</b> <sup>14</sup>
<i>Iphiona mucronata</i>	<b>23, 24, 26, 28</b> <sup>15</sup>
<i>Iphiona scabra</i>	<b>5, 6, 25, 27</b> <sup>7</sup>
<i>Kleinia pendula</i>	<b>4</b> <sup>6</sup>
<i>Laggera alata</i>	<b>10, 11</b> <sup>10</sup>
<i>Laggera pterodonta</i>	<b>9</b> <sup>11</sup>
<i>Ligularia veitchiana</i>	<b>31</b> <sup>20–22</sup>
<i>Melampodium camphoratum</i>	<b>12–17</b> <sup>9</sup>
<i>Pegolettia oxydonta</i>	<b>7, 8</b> <sup>8</sup>
<i>Santolina rosmarinifolia</i>	<b>30</b> <sup>17</sup>

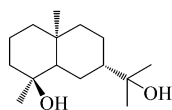
4 $\alpha$ -ol<sup>5</sup> and (±)-selina-3,11-dien-9-ol<sup>24</sup> have also been the subject of synthetic studies, as has been the synthesis of  $\alpha$ -dictyoptero<sup>25</sup> and platyllide.<sup>26</sup> A shorter route to the synthesis of (+)-junenol and isojunenol (together with their coumarate esters) starting from (–)-santonin has been developed, and (+)-junenol has been shown to be identical to 6-*epi*- $\beta$ -verbesinol.<sup>27</sup>

**3.1.2 Eudesmandiols.** New eudesmandiols **35–93** isolated from various plants are highlighted in Table 2. Kikkanol **B 88** showed inhibitory activity against rat lens aldose reductase.<sup>53</sup> The structure of teucdiol A was determined by X-ray analysis.<sup>57</sup> Eudesmane sesquiterpenes from the rhizomes of the Chinese

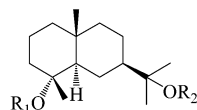
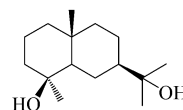




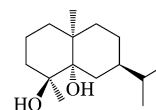
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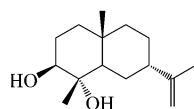
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37 R<sub>1</sub> = Glc, R<sub>2</sub> = H38 R<sub>1</sub> = H, R<sub>2</sub> = Glc

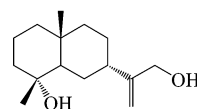
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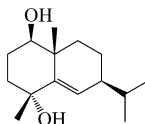
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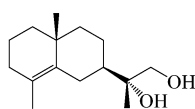
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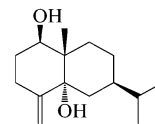
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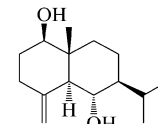
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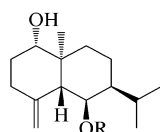
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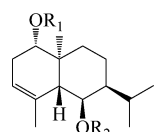
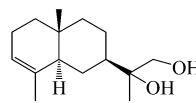


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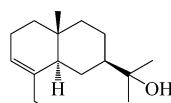


47 R = Ang

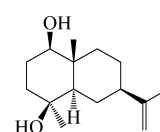
48 R = Cinn

49 R<sub>1</sub> = Cinn, R<sub>2</sub> = H50 R<sub>1</sub> = H, R<sub>2</sub> = Cinn51 R<sub>1</sub> = H, R<sub>2</sub> = Bz(*p*-OMe)52 R<sub>1</sub> = H, R<sub>2</sub> = Glc

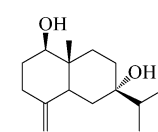
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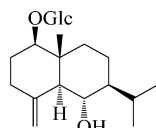
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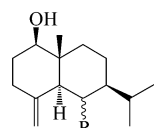
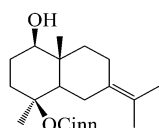
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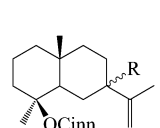
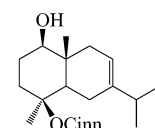
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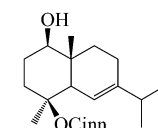
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58 R =  $\alpha$ -OH59 R =  $\beta$ -OH

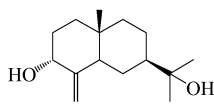
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61 R =  $\alpha$ -OH62 R =  $\beta$ -OH

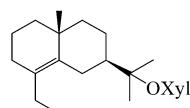
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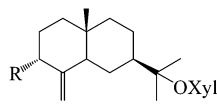
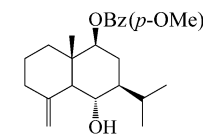
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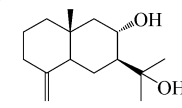
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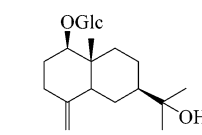
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67 R = H  
68 R = OH

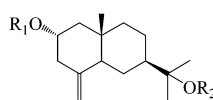
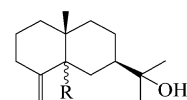
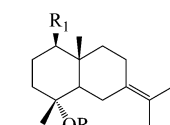
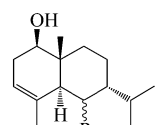
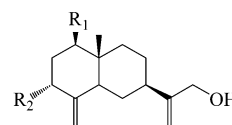
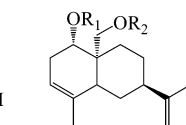
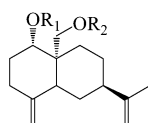
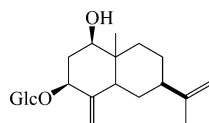
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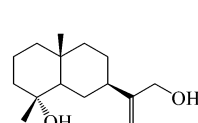
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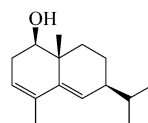
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72 R<sub>1</sub> = H, R<sub>2</sub> = Glc73 R<sub>1</sub> = Glc, R<sub>2</sub> = Glc74 R<sub>1</sub> = Glc-Glc, R<sub>2</sub> = Glc75 R<sub>1</sub> = Glc-Glc, R<sub>2</sub> = Glc-Glc76 R =  $\alpha$ -OH77 R =  $\beta$ -OH78 R<sub>1</sub> = OH, R<sub>2</sub> = Glc79 R<sub>1</sub> = OGlc, R<sub>2</sub> = H80 R =  $\alpha$ -OH81 R =  $\beta$ -OH82 R<sub>1</sub> = OH, R<sub>2</sub> = H83 R<sub>1</sub> = H, R<sub>2</sub> = OH84 R<sub>1</sub> = R<sub>2</sub> = H85 R<sub>1</sub> = H, R<sub>2</sub> = Ac86 R<sub>1</sub> = R<sub>2</sub> = H87 R<sub>1</sub> = H, R<sub>2</sub> = Ac88 R<sub>1</sub> = Ac, R<sub>2</sub> = H

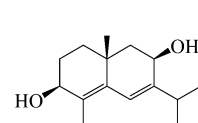
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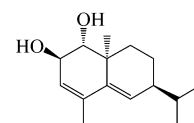
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**Table 2** Sources of eudesmandiols

Sources	Compounds
<i>Ageratina glechonophylla</i>	58 <sup>41</sup>
<i>Ambrosia artemisioides</i>	47–52 <sup>38</sup>
<i>Ambrosia elatior</i>	46, 69 <sup>37</sup>
<i>Artemisia arenaria</i>	43 <sup>35</sup>
<i>Artemisia eriopoda</i>	59 <sup>42</sup>
<i>Atractylodes lancea</i>	72–75 <sup>47</sup>
<i>Cassinia uncata</i>	53, 54 <sup>16</sup>
<i>Chrysanthemum indicum</i>	65, 44, 91 <sup>53</sup>
<i>Erigeron annuus</i>	55–57 <sup>39</sup>
<i>Gonospermum fruticosum</i>	82, 83, 90 <sup>50</sup>
<i>Hypochoeris radicata</i>	89 <sup>52</sup>
<i>Iphiaea scabra</i>	66, 67, 68 <sup>7</sup>
<i>Isodon grandifolia</i>	35 <sup>29</sup>
<i>Jasonia candicans</i>	42 <sup>34</sup>
<i>Jasonia glutinosa</i>	44 <sup>36</sup>
<i>Jasonia montana</i>	76, 77 <sup>48</sup>
<i>Laggera alata</i>	70 <sup>45</sup>
<i>Laggera crispata</i>	41 <sup>33</sup>
<i>Laggera pterodonta</i>	36–38, 78, 79 <sup>30,31</sup>
<i>Ligularia duciformis</i>	92 <sup>54,55</sup>
<i>Ligularia hodgsonii</i>	45 <sup>21</sup>
<i>Pluchea arguta</i>	35, 39 <sup>28,32</sup>
<i>Pluchea dioscoridis</i>	80, 81 <sup>49</sup>
<i>Pluchea indica</i>	71 <sup>46</sup>
<i>Polyachirus sphaerocephalus</i>	84–88 <sup>51</sup>
<i>Santolina insularis</i>	93 <sup>56</sup>
<i>Senecio microglossus</i>	58 <sup>40</sup>
<i>Ursinia trifida</i>	39, 40 <sup>3</sup>
<i>Verbesina oerstediana</i>	60–64 <sup>43</sup>

herb *Atractylodes ovata* have been shown to have cytotoxic activity against leukaemia cell lines.<sup>58</sup> The microbiological transformation of ilicic acid and kudtiol by cultures of *Cunninghamella echinulata* has been studied.<sup>59,60</sup> The microbiological transformations of 4 $\alpha$ - and 4 $\beta$ -hydroxyeudesmane derivatives by the filamentous fungus *Gliocladium roseum* have also been reported.<sup>61</sup>

A general enantiospecific approach to the synthesis of polyfunctional eudesmanes based on ring-closing metathesis has been reported.<sup>62</sup> (+)-Dihydrocarvone has been used as a starting point for the syntheses of (–)-10-*epi*-5 $\beta$ ,11-dihydroxyeudesmane and (–)-4,10-*epi*-5 $\beta$ ,11-dihydroxyeudesmane.<sup>63</sup> The first total synthesis of both C-11 epimers of 13-hydroxy- $\alpha$ -eudesmol has been completed. This work has permitted the absolute configuration of the natural diol to be established as **53**, and also the preparation of (+)- $\alpha$ -selinene to be accomplished.<sup>64</sup> The first enantioselective total syntheses of (+)-chrysanthemol,<sup>65</sup> (+)-selina-3,11-dien-9-ol<sup>66</sup> and (–)-rishitin<sup>67</sup> have been described, and racemic preparations of dehydrochamaecyneaol<sup>68</sup> and balanitol have been reported.<sup>69</sup>  $\alpha$ -Eudesmaol,<sup>70</sup> occidol<sup>71</sup> and tavaopallescensin<sup>72</sup> have been the subject of total synthesis, and a formal total synthesis of (–)-dehydrochamaecyneaol has been presented.<sup>73</sup> Eudesman-4-en-1 $\beta$ ,11-diol has been synthesised as its racemate.<sup>74</sup>

**3.1.3 Eudesmantriols.** Recently isolated eudesmantriols **94–138** and their plant sources are listed in Table 3. The structure of mucrolidin **104** was determined by X-ray analysis.<sup>79</sup> Kikkanol **A 118** showed inhibitory activity against rat lens aldose reductase.<sup>53</sup> The microbiological transformation of  $\beta$ -selinene by the plant pathogenic fungus *Glomerella cingulata* has been studied.<sup>91</sup> Enantioselective total syntheses of kudtriol, 5-*epi*-kudtriol and its C-11 epimer<sup>92–94</sup> have been accomplished.

**Table 3** Sources of eudesmantriols

Sources	Compounds
<i>Achillea clypeolata</i>	129 <sup>87</sup>
<i>Ainsliaea cordifolia</i>	124, 125 <sup>82</sup>
<i>Artemisia eriopoda</i>	96 <sup>42</sup>
<i>Artemisia monosperma</i>	132 <sup>88</sup>
<i>Atractylodes lancea</i>	114, 115, 131 <sup>47,86</sup>
<i>Chrysanthemum indicum</i>	118 <sup>53</sup>
<i>Erigeron brevicarpus</i>	127 <sup>84</sup>
<i>Iva frutescens</i>	103, 104 <sup>78</sup>
<i>Jasonia glutinosa</i>	108 <sup>86</sup>
<i>Laggera alata</i>	130 <sup>85</sup>
<i>Laggera pterodonta</i>	97–100, <sup>30,31</sup> 105, 106, <sup>11</sup> 109–112 <sup>80</sup>
<i>Pallenis spinosa</i>	121, 122 <sup>81</sup>
<i>Pluchea indica</i>	113, 123 <sup>46</sup>
<i>Polyachirus fuscus</i>	135–138 <sup>90</sup>
<i>Rhaponticum uniflorum</i>	134 <sup>89</sup>
<i>Santolina chamaecyparissus</i>	126 <sup>83</sup>
<i>Santolina insularis</i>	133 <sup>56</sup>
<i>Saussurea laniceps</i>	94 <sup>75</sup>
<i>Santolina rosmarinifolia</i>	119 <sup>17</sup>
<i>Tanacetopsis mucronata</i>	107 <sup>79</sup>
<i>Tessaria integrifolia</i>	101, 102 <sup>77</sup>
<i>Verbesina eggersii</i>	95 <sup>97</sup>
<i>Verbesina oerstediana</i>	116, 120, 128 <sup>43</sup>
<i>Verbesina virgata</i>	116, 117 <sup>76</sup>

**3.1.4 Polyhydroxylated eudesmanes.** 3,4,7,8-Tetrahydroxy eudesmanes **139** and **140** have been isolated from the methanolic extract of *Tessaria integrifolia*.<sup>77</sup> The tetrahydroxy eudesmanes **141**, **142** and **143** have also been found in the Asteraceaeous plants *Ainsliaea cordifolia*,<sup>82</sup> *Senecio flammeus*,<sup>95,96</sup> and *Verbesina eggersii*,<sup>97</sup> respectively. The pentahydroxy eudesmane **144** was isolated from *Calendula arvensis*.<sup>98</sup>

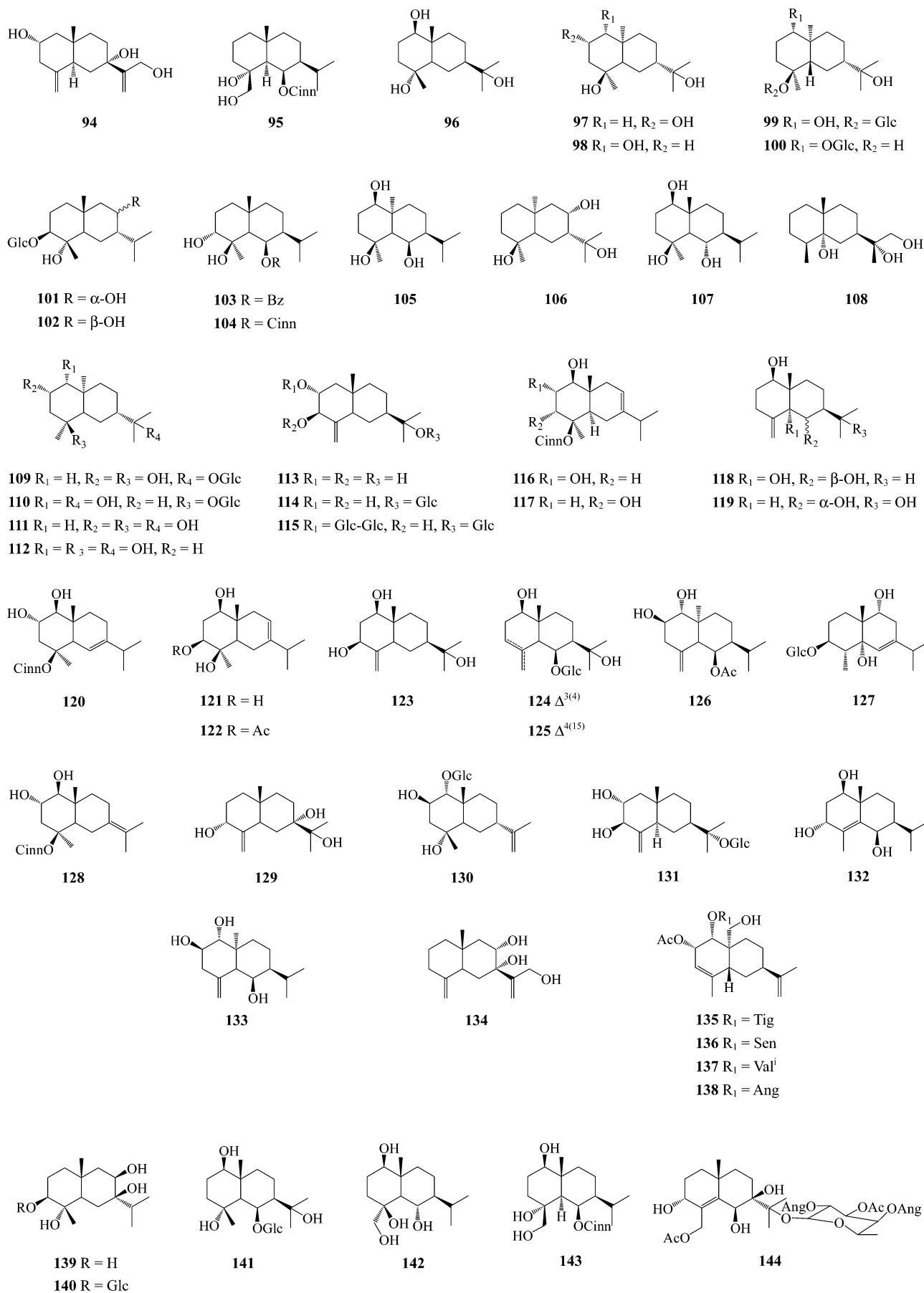
Two novel polyhydroxyl 7-*epi*-eudesmane derivatives have been isolated from the microbial transformation of a (1 $\alpha$ ,10 $\beta$ ),(4 $\beta$ ,5 $\alpha$ )-diepoxygermacrane using the hydroxylating fungus *Rhizopus nigricans*. The absolute configurations of these compounds was confirmed by single-crystal X-ray analyses.<sup>99</sup> The 1 $\alpha$ - and 2 $\alpha$ -hydroxyselinane derivatives have been prepared by chemical semi-synthesis and biotransformation with *Rhizopus nigricans*, using vulgarin as starting material.<sup>100</sup>

### 3.2 Eudesmane epoxides

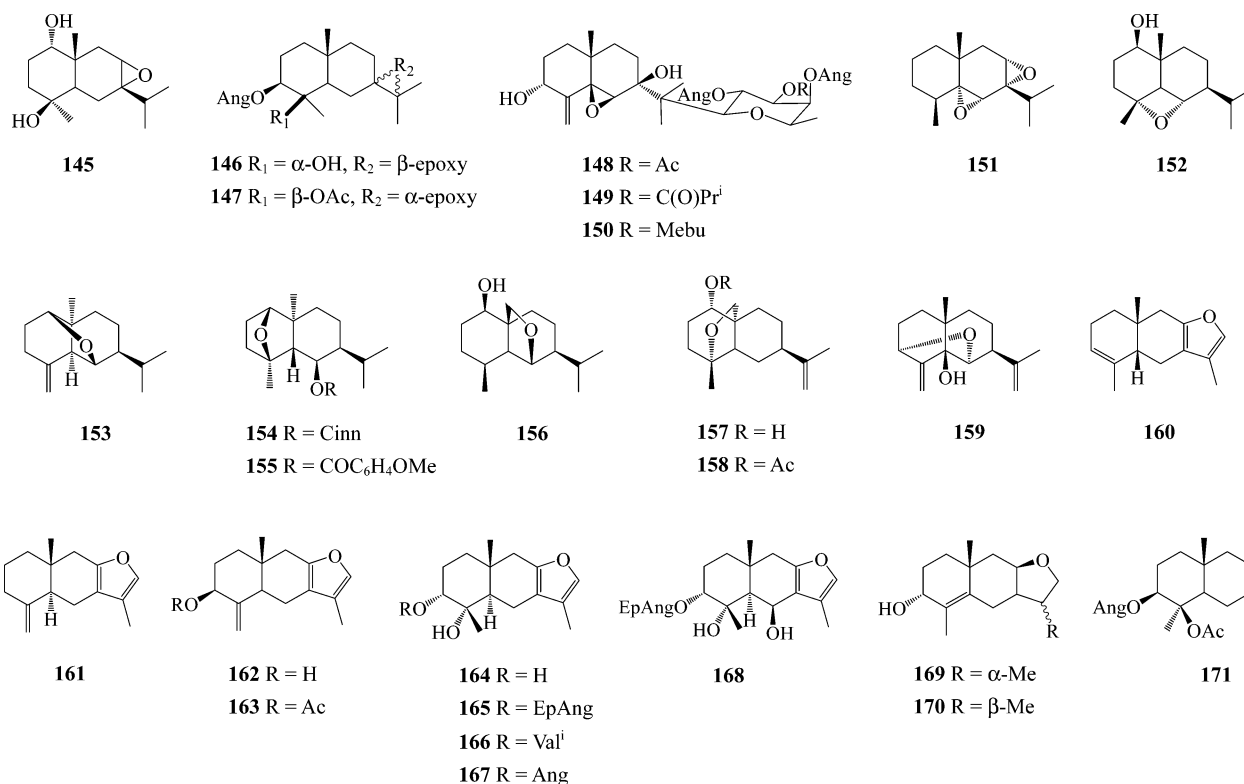
The eudesmane epoxides **146–171** and their corresponding plant sources are indicated in Table 4. The structure of epoxyplodiol **145** has been determined by single crystal X-ray diffraction

**Table 4** Sources of eudesmane epoxides

Sources	Compounds
<i>Ambrosia artemisioides</i>	154, 155 <sup>38</sup>
<i>Atractylodes japonica</i>	161 <sup>107</sup>
<i>Baccharis dracunculifolia</i>	153 <sup>103</sup>
<i>Calendula arvensis</i>	148, 149, 150 <sup>98</sup>
<i>Chrysanthemum indicum</i>	159 <sup>106</sup>
<i>Curculigo capitulata</i>	152 <sup>104</sup>
<i>Epilobium gariepina</i>	164–168 <sup>45</sup>
<i>Erigeron philadelphicus</i>	156 <sup>105</sup>
<i>Ixeris repens</i>	162, 163 <sup>108</sup>
<i>Liabum floribundum</i>	151 <sup>102</sup>
<i>Ondetia linearis</i>	169, 170 <sup>109</sup>
<i>Pluchea quitoc</i>	146, 147, <sup>101</sup> 171 <sup>110</sup>
<i>Polyachirus sphaerocephalus</i>	157, 158 <sup>51</sup>







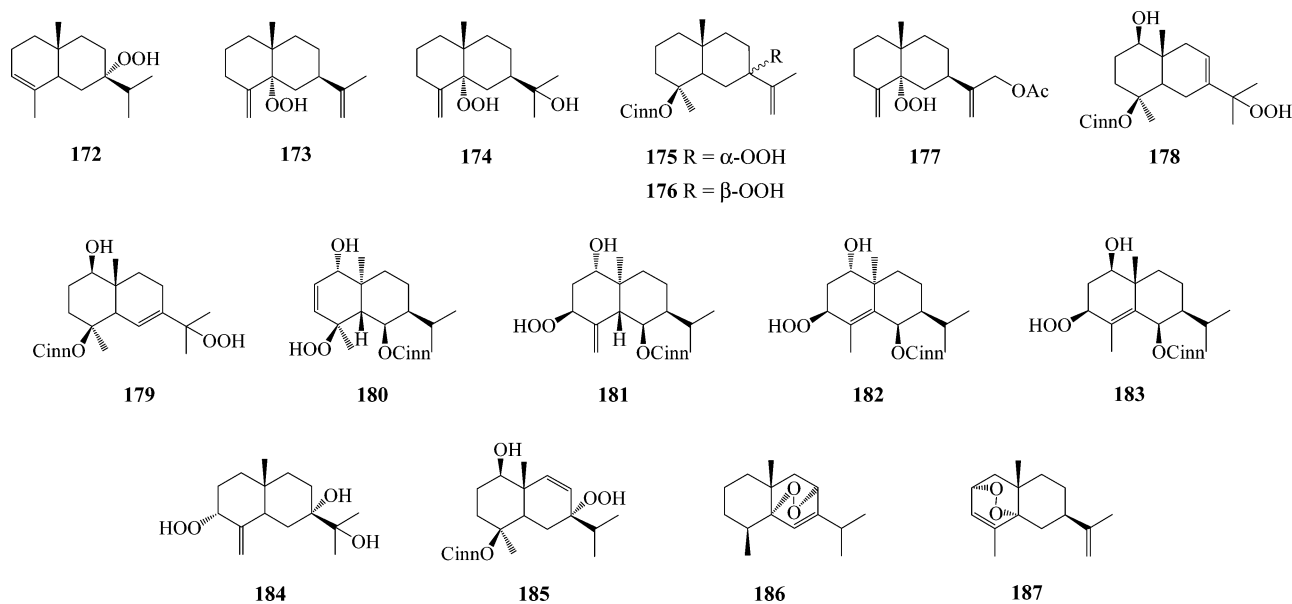
analysis.<sup>111</sup> The furanosesquiterpene atractylon showed moderate, but selective, 5-lipoxygenase inhibitory activity.<sup>112</sup> (+)-Dihydrocarvone has been used as a starting material for the first syntheses of (+)-5 $\alpha$ -hydroxy- $\beta$ -selinene and (-)-5 $\beta$ -hydroxy- $\beta$ -selinene.<sup>113</sup> The synthesis of (+)-1,2-dihydrotubipofuran **160**, starting from  $\alpha$ -santonin, has been completed.<sup>114</sup> Synthetic studies towards the furosesquiterpenes have been developed,<sup>115</sup> and a synthesis of both enantiomers of acetyltubipofuran has been reported.<sup>116</sup>

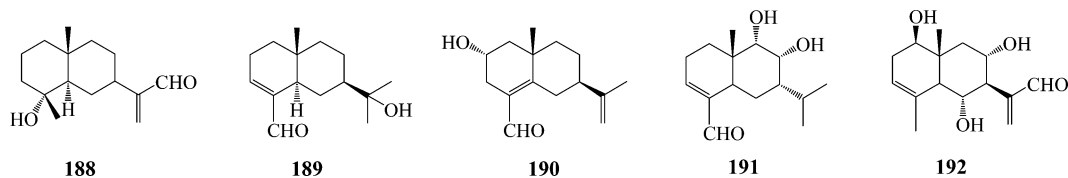
### 3.3 Eudesmane peroxides

Novel peroxide-substituted eudesmanes **172–187** and their corresponding plant sources are detailed in Table 5. There is very

**Table 5** Sources of eudesmane peroxides

Sources	Compounds
<i>Achillea clypeolata</i>	<b>184</b> <sup>121</sup>
<i>Ambrosia artemisioides</i>	<b>180–182</b> <sup>28</sup>
<i>Artemisia annua</i>	<b>173</b> <sup>19</sup>
<i>Artemisia douglasiana</i>	<b>174</b> <sup>118</sup>
<i>Aster oharai</i>	<b>172</b> <sup>117</sup>
<i>Brontonia discodea</i>	<b>183</b> , <b>185</b> <sup>120</sup>
<i>Calea prunifolia</i>	<b>177</b> <sup>119</sup>
<i>Dittrichia viscosa</i>	<b>187</b> <sup>123</sup>
<i>Isocoma coronopifolia</i>	<b>186</b> <sup>122</sup>
<i>Verbesina oerstediana</i>	<b>175</b> , <b>176</b> , <b>178</b> , <b>179</b> <sup>43</sup>





little literature on the bioactivity or synthesis of these structurally interesting eudesmane sesquiterpenoids.

### 3.4 Eudesmane aldehydes

The eudesmane aldehyde **188** has been found in *Vernonia glabra* var. *glabra*.<sup>124</sup> The other  $\alpha,\beta$ -unsaturated aldehydes **189**, **190**, **191** and **192** have been identified in *Cassinia uncata*,<sup>16</sup> *Tetragonotheca ludoviciana*,<sup>125</sup> *Chrysanthemum indicum*,<sup>53</sup> and *Tanacetopsis mucronata*,<sup>126</sup> respectively. The inhibitory activity of compound **191** against rat lens aldose reductase has been studied.<sup>53</sup> A series of sesquiterpene compounds possessing eudesmane carbon skeletons were tested as gastric cytoprotective agents on male Wistar rats. The presence of an  $\alpha,\beta$ -unsaturated aldehyde on the C-7 side chain together with a hydroxyl group at C-4 appears to be a prerequisite for their observed anti-ulcerogenic activity. In an attempt to establish new molecular structural requirements for this gastric cytoprotective activity, a structure–activity study has been performed.<sup>127</sup>

A new salen–manganese(III) complex bearing a sesquiterpene salicylaldehyde derivative has been used in the catalytic epoxidation of unfunctionalised olefins, with iodosylbenzene and molecular oxygen–pivalaldehyde as the terminal oxidant.<sup>128</sup>

### 3.5 Eudesmane ketones

A series of recently isolated eudesmane ketones **193–272** and their plant sources are highlighted in Table 6. The novel sesquiterpene ketone **194** was the isomer from the genus *Nepthta*.<sup>130</sup> The new cauthemone derivatives **212–218**, **220** and **221** have been identified from plants of the genus *Tessaria*, while **237**, **240**, **241**, **243** and **250** have been found in *Pluchea symphytifolia*, indicating that there is a phytochemical relationship between these two Asteraceae genera. The structure of 5-*O*-acetylcuahtemomyl-6-*O*-2,3'-epoxy-2-methylbutyrate, isolated from *Pluchea carolinensis*, has been determined by X-ray analysis.<sup>163</sup> Sesquiterpene **250**, which was isolated from *Pluchea suaveolens*<sup>164</sup> and *Epaltes brasiliensis*,<sup>165</sup> has been revised from the 11-hydroxy- to the 11-peroxy-derivative.<sup>142</sup> The structure of the sesquiterpene ketone carissone has been confirmed by X-ray analysis,<sup>166</sup> and the absolute configuration of cuahtemone has been revised to **210**.<sup>167</sup>

The antibacterial activities of **246**<sup>152</sup> and **263**<sup>159</sup> have been studied. The antiprotozoal activity of a range of known sesquiterpenes from *Jasonia glutinosa* has been explored and the antibacterial activities of carissone, dehydrocarissone and carindone have been evaluated.<sup>168</sup>

The biotransformation of 4 $\beta$ -hydroxyeudesmane-1,6-dione by the fungi *Gliocladium roseum* and *Exserohilum halodes* has been studied.<sup>169</sup> Alantolactone has been shown to induce apoptosis in jurkat leukaemia T cells.<sup>170</sup> A chemical–microbiological synthesis of 6 $\beta$ -eudesmanolides has been achieved with the fungus *Rhizopus nigricans*.<sup>171</sup> The microbiological transformation of

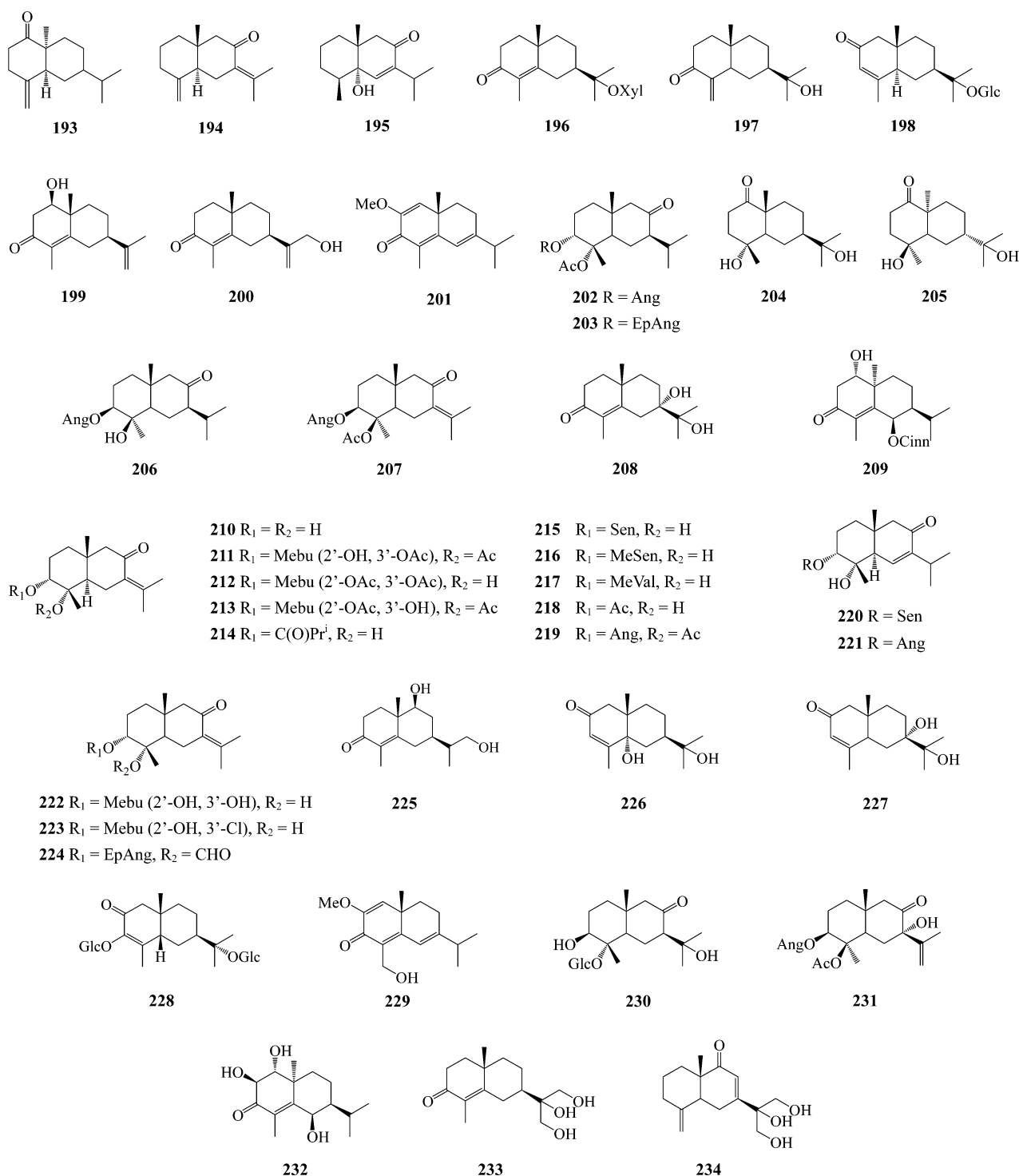
**Table 6** Sources of eudesmane ketones

Sources	Compounds
<i>Achillea clypeolata</i>	<b>208</b> , <b>227</b> <sup>121</sup>
<i>Achillea holosericea</i>	<b>233</b> <sup>155</sup>
<i>Ambrosia artemisioides</i>	<b>209</b> <sup>38</sup>
<i>Artemisia afra</i>	<b>200</b> <sup>136</sup>
<i>Artemisia caerulescens</i>	<b>199</b> , <b>268</b> <sup>133,134</sup>
<i>Artemisia eriopoda</i>	<b>204</b> , <b>226</b> <sup>42</sup>
<i>Artemisia herba-alba</i>	<b>269</b> <sup>161</sup>
<i>Atractylodes japonica</i>	<b>194</b> <sup>107</sup>
<i>Atractylodes lancea</i>	<b>198</b> , <sup>86</sup> <b>228</b> <sup>47,86</sup>
<i>Baccharis boliviensis</i>	<b>271</b> <sup>162</sup>
<i>Blumea alata</i>	<b>210</b> , <b>211</b> , <b>255–258</b> , <b>264</b> , <b>265</b> <sup>139</sup>
<i>Cassinia uncata</i>	<b>225</b> , <b>270</b> <sup>16</sup>
<i>Epaltes divaricata</i>	<b>219</b> <sup>143</sup>
<i>Epaltes mexicana</i>	<b>222</b> , <sup>144,145</sup> <b>241</b> , <sup>144</sup> <b>263</b> <sup>159</sup>
<i>Hypochoeris radicata</i>	<b>199</b> <sup>135</sup>
<i>Iphiona scabra</i>	<b>196</b> <sup>7</sup>
<i>Laggera alata</i>	<b>224</b> <sup>45</sup>
<i>Laggera crispata</i>	<b>235</b> <sup>33</sup>
<i>Laggera pterodonta</i>	<b>205</b> , <b>226</b> <sup>11</sup>
<i>Liabum floribundum</i>	<b>195</b> <sup>102</sup>
<i>Parthenium argentatum</i>	<b>201</b> , <b>229</b> , <b>272</b> <sup>137</sup>
<i>Pluchea arguta</i>	<b>213</b> , <sup>141</sup> <b>236</b> , <sup>147</sup> <b>238</b> , <sup>145</sup> <b>239</b> , <sup>149</sup> <b>245</b> , <b>246</b> , <sup>151,152</sup> <b>248</b> , <sup>32</sup> <b>250</b> , <sup>150</sup> <b>252</b> , <sup>153</sup> <b>253</b> , <sup>154</sup> <b>254</b> , <sup>151</sup> <b>260–262</b> , <sup>147,151,158</sup> <b>266</b> , <b>267</b> <sup>160,158</sup>
<i>Pluchea carolonesis</i>	<b>223</b> <sup>146</sup>
<i>Pluchea indica</i>	<b>212</b> <sup>140</sup>
<i>Pluchea odorata</i>	<b>237</b> , <sup>148</sup> <b>242</b> , <b>244</b> , <b>247</b> , <b>251</b> <sup>150</sup>
<i>Pluchea quitoc</i>	<b>243</b> , <b>249</b> , <sup>110</sup> <b>231</b> , <b>259</b> , <sup>101</sup> <b>206</b> , <b>207</b> <sup>101,110</sup>
<i>Pluchea symphytifolia</i>	<b>241</b> , <b>243</b> , <b>250</b> <sup>142</sup>
<i>Santolina insularis</i>	<b>232</b> <sup>56</sup>
<i>Saussurea lappa</i>	<b>230</b> <sup>45</sup>
<i>Saussurea parviflora</i>	<b>234</b> <sup>156,157</sup>
<i>Senecio bracteolatus</i>	<b>199</b> <sup>132</sup>
<i>Solidago gigantea</i>	<b>193</b> <sup>129</sup>
<i>Sphaeranthus indicus</i>	<b>197</b> <sup>131</sup>
<i>Tessaria integrifolia</i>	<b>202</b> , <b>203</b> , <sup>138</sup> <b>214–218</b> , <b>220</b> , <b>221</b> , <b>240</b> <sup>142</sup>

eudesmane derivatives by the fungus *Curvularia lunata* has also been reported.<sup>172</sup> The atractylon content of clonally propagated plants of *Atractylodes japonica* has been determined<sup>107</sup> and the allelochemical effects of eudesmane sesquiterpenes on *Tribolium castaneum* larvae have been investigated.<sup>173</sup>

A preparation of the HS-toxin A aglycone, starting from (–)-carvone, has been described.<sup>174</sup> (+)-Carvone has been used as the starting material in the synthesis of (+)- $\alpha$ -cyperone,<sup>175</sup> and the first total synthesis of (+)-5 $\alpha$ -hydroxyisoptercarpolone, starting from (+)-dihydrocarvone, has been described.<sup>176</sup> The hydroxylation of sesquiterpenes by enzymes from chicory roots has been investigated.<sup>177</sup> 3 $\beta$ -Angeloyloxy-4 $\beta$ -hydroxyeudesman-8-one **206** has been synthesised by an unambiguous route,<sup>178</sup> but its spectroscopic data was different from that of the natural product, to which this structure had been assigned.<sup>101,179</sup> An efficient and stereoselective synthesis of (+)- $\alpha$ -cyperone has been devised,<sup>180</sup> and the eudesmanolide artemisin has been used as a starting material in the preparation of 9-oxy-functionalised natural eudesmanes.<sup>181</sup> The total syntheses of ( $\pm$ )-cuahtemone<sup>182</sup>

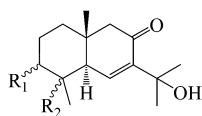




and (±)-eudesma-5,7(11)-dien-8-one has been reported.<sup>183</sup> The chemical transformation of  $\alpha$ -santonin into two 8-oxo- $\beta$ -cyperone derivatives has been reported.<sup>184</sup> A shorter, more efficient method for the preparation of 11,12-dihydroxyeudesmanolides, starting from  $\alpha$ -santonin, has been reported,<sup>185</sup> and a total synthesis of the naphthofurandione maturinone has been achieved.<sup>186</sup> Phytuberin has been synthesised starting from carvone.<sup>187</sup> A facile synthesis of 3-oxo-7 $\alpha$ H-eudesma-4 $\beta$ ,12-diol, previously isolated from *Casima uncata*, has been described.<sup>188</sup> An enantioselective synthesis of selina-1,3,7(11)-trien-8-one has been accomplished.<sup>189</sup>

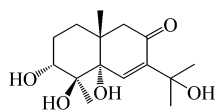
### 3.6 Eudesmane carboxylic acids

Recently isolated eudesmane carboxylic acids **273–423** from a number of different plants are listed in Table 7. The structure of vachanic acid<sup>258</sup> and **411**<sup>259</sup> have been conformed by X-ray studies. X-Ray crystallographic studies have also revealed catameric carboxyl-to-ketone hydrogen bonding in the bicyclic sesquiterpene keto acid **406**.<sup>242</sup> The aerial parts of *Flourensia thurifera* contain 3 $\beta$ -hydroxycostic acid **283** and a mixture of two acyl derivatives **284** and **285**. The toxicity of these substances toward *Artemia salina*

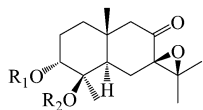
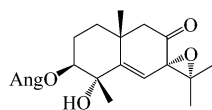


- 235  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-OH)}$ ,  $R_2 = \alpha\text{-OH}$   
 236  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-OH)}$ ,  $R_2 = \beta\text{-OH}$   
 237  $R_1 = \beta\text{-OMebu (2'-OH, 3'-OH)}$ ,  $R_2 = \alpha\text{-OH}$   
 238  $R_1 = \beta\text{-OMebu (2'-OH, 3'-Cl)}$ ,  $R_2 = \alpha\text{-OH}$   
 239  $R_1 = \beta\text{-OH}$ ,  $R_2 = \alpha\text{-OH}$   
 240  $R_1 = \alpha\text{-OSen}$ ,  $R_2 = \alpha\text{-OH}$   
 241  $R_1 = \alpha\text{-OAng}$ ,  $R_2 = \alpha\text{-OH}$   
 242  $R_1 = \alpha\text{-OAng}$ ,  $R_2 = \alpha\text{-OAc}$   
 243  $R_1 = \beta\text{-OAng}$ ,  $R_2 = \alpha\text{-OH}$

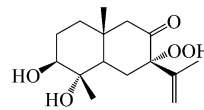
- 244  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-Cl)}$ ,  $R_2 = \alpha\text{-OAc}$   
 245  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-Cl)}$ ,  $R_2 = \beta\text{-OAc}$   
 246  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-Cl)}$ ,  $R_2 = \alpha\text{-OAc}$   
 247  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-Cl)}$ ,  $R_2 = \alpha\text{-OH}$   
 248  $R_1 = \alpha\text{-OMebu (2'-OH, 3'-OH)}$ ,  $R_2 = \alpha\text{-OAc}$   
 249  $R_1 = \beta\text{-OAng}$ ,  $R_2 = \beta\text{-OAc}$   
 250  $R_1 = \alpha\text{-OEpAng}$ ,  $R_2 = \alpha\text{-OH}$   
 251  $R_1 = \alpha\text{-OEpAng}$ ,  $R_2 = \alpha\text{-OAc}$   
 252  $R_1 = \alpha\text{-OEpAng}$ ,  $R_2 = \beta\text{-OAc}$   
 253  $R_1 = \beta\text{-OMebu (2'-OH, 3'-Cl)}$ ,  $R_2 = \beta\text{-OAc}$



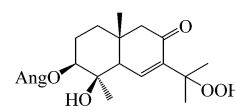
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255  $R_1 = \text{Ang}$ ,  $R_2 = \text{H}$ 

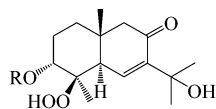
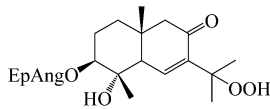
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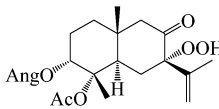
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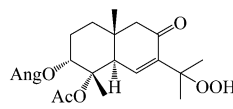
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256  $R_1 = \text{Ang}$ ,  $R_2 = \text{Ac}$ 257  $R_1 = \text{EpAng}$ ,  $R_2 = \text{H}$ 258  $R_1 = \text{EpAng}$ ,  $R_2 = \text{Ac}$ 262  $R = \text{Mebu (2'-OH, 3'-Cl)}$ 

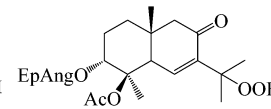
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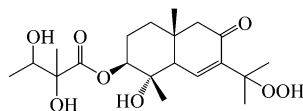
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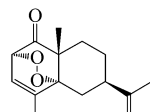
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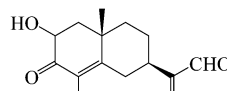
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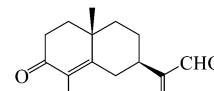
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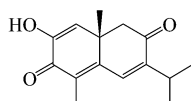
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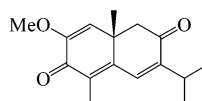
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and their antifeedant properties against *Spodoptera littoralis* have been evaluated.<sup>199</sup> Compound 411 exhibited potent antimicrobial activity against the six bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Bacillus cereus* and *Salmonella enteritides*.<sup>260</sup> The sesquiterpene 12-carboxyudesma-3,11(13)-diene and the xanthnolide tomentosin were the major compounds responsible for the ichthyotoxicity shown by *Dittrichia graveolens*.<sup>261</sup> A mechanistic approach to study the *in vivo* anti-inflammatory activity of various sesquiterpenes isolated from *Inula viscosa* has been carried out.<sup>262</sup> The anti-inflammatory properties of other sesquiterpenes from *Jasonia glutinosa*<sup>263</sup> have also been tested.

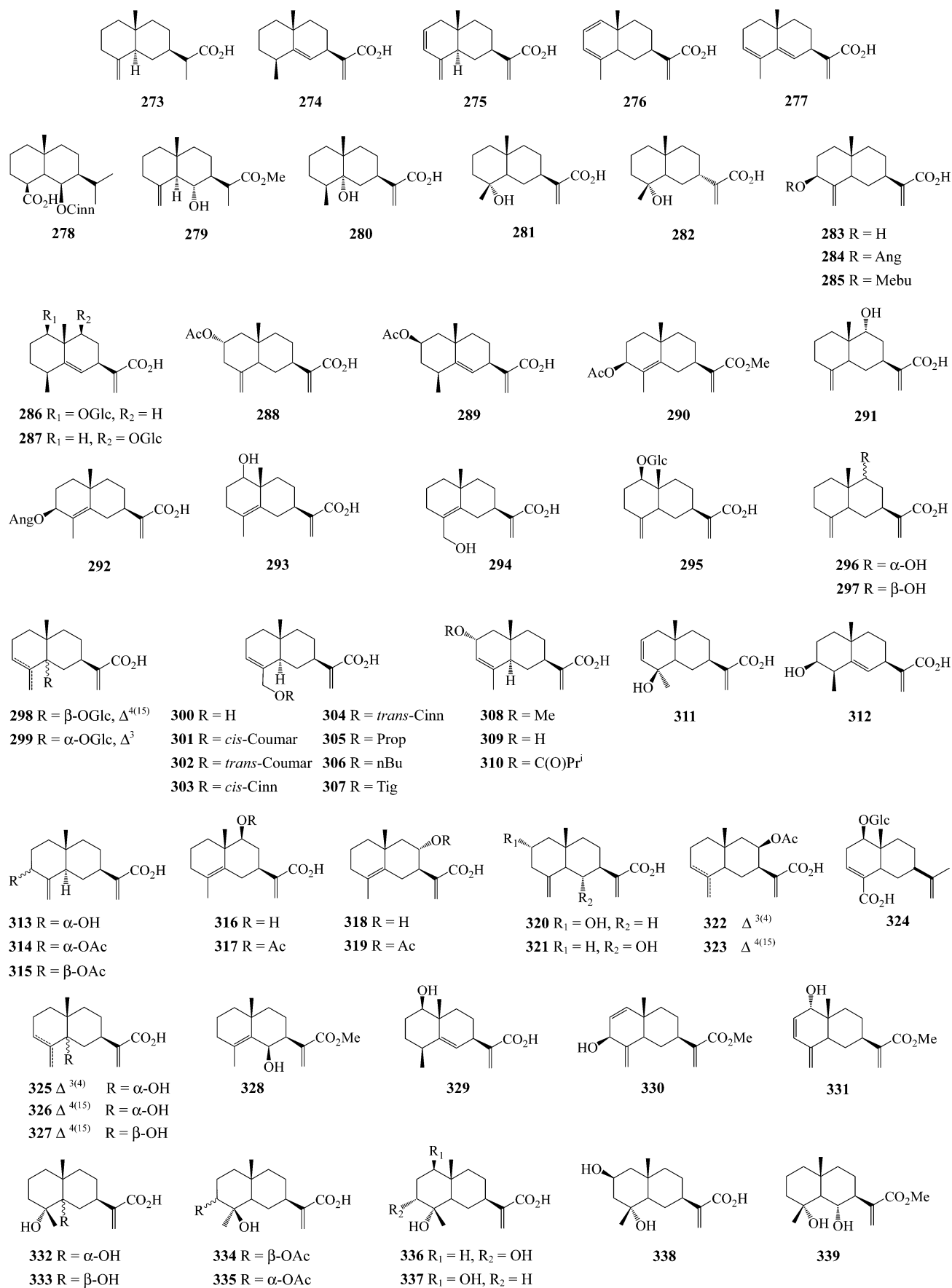
The bioconversion of several eudesmane derivatives using the fungi *Rhizopus nigricans* and *Curvularia lunata* has been studied.<sup>264,265</sup> The microbiological transformation of the eudesmane sesquiterpenes ilicic acid and plectranthone by the fungi *Aspergillus niger*<sup>266</sup> and *Beauveria bassiana*,<sup>267</sup> respectively, have been described, and the microbiological transformation of ilicic

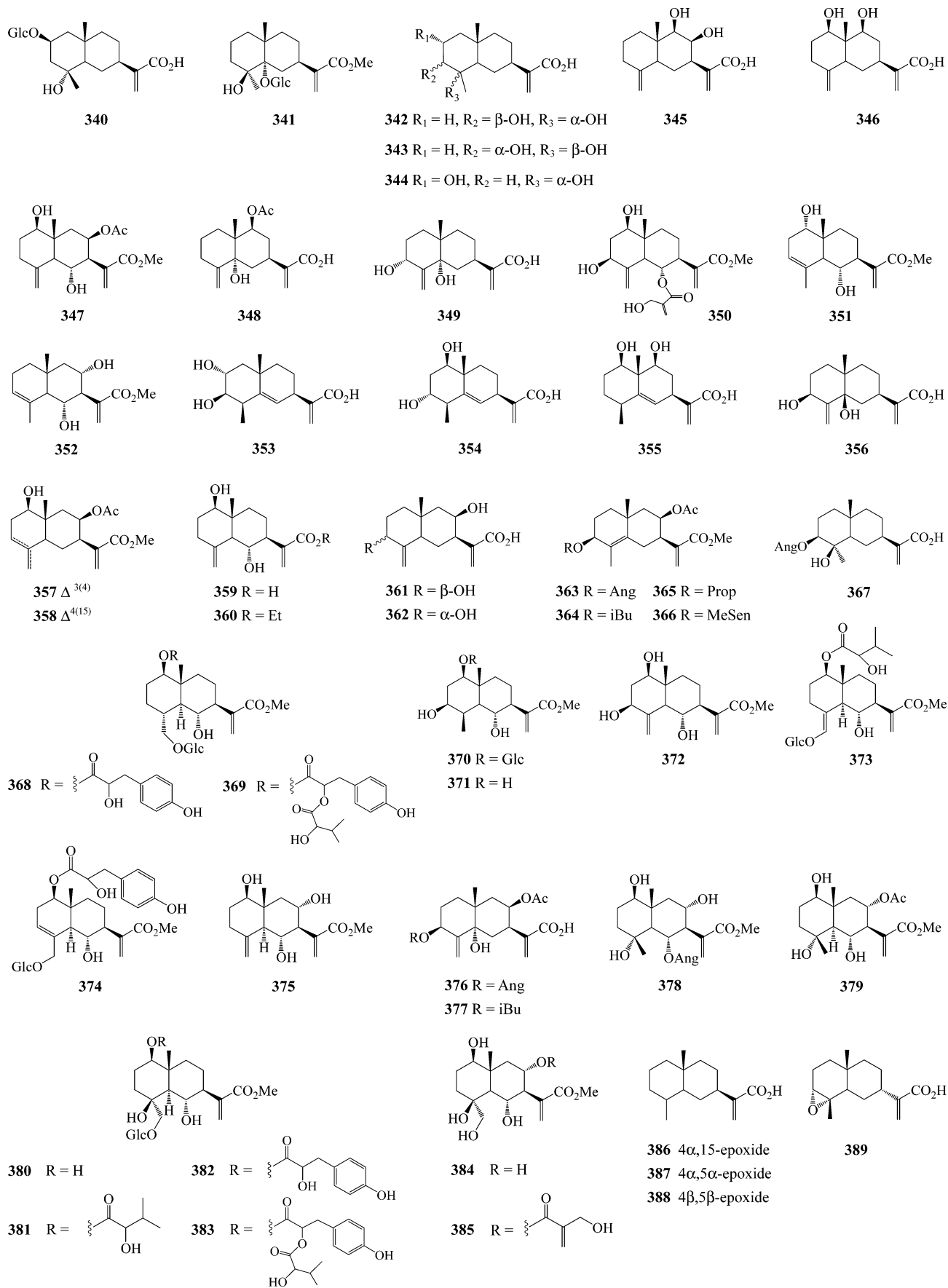
acid by cultures of *Cunninghamella echinulata* has also been evaluated.<sup>59,60</sup>

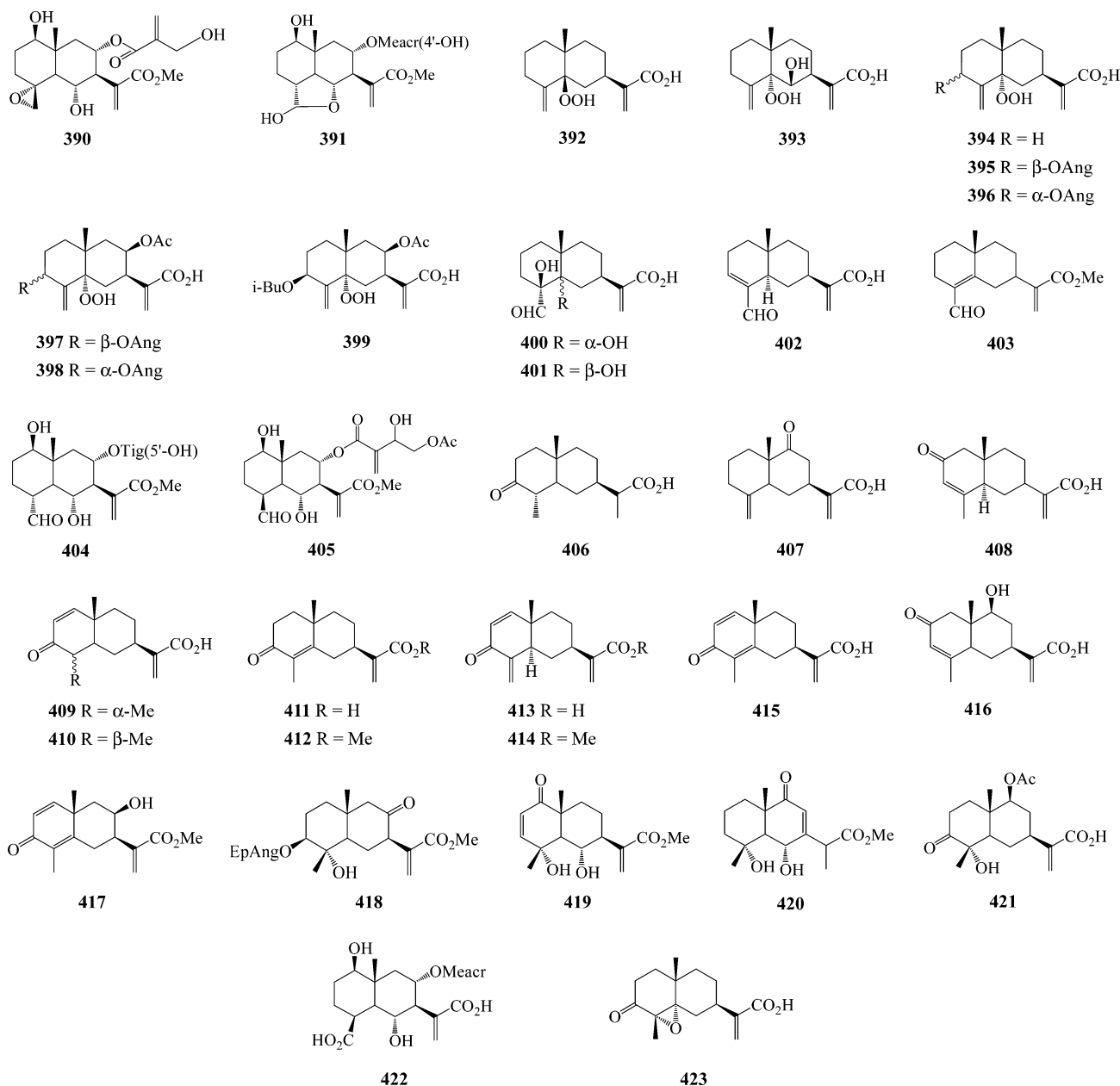
(±)-Dihydrocarvone has been used as the starting material in the synthesis of (+)-3-oxoudesma-4,11(13)-dien-12-oic acid,<sup>268</sup> and santonin has been employed in the preparation of furanoedesma-1,3-diene and tubipofurane.<sup>269</sup> The total synthesis of the eudesmanic acid 415, starting from (+)-dihydrocarvone, has been achieved.<sup>249,250</sup> An enantioselective total synthesis of eudesma-3,11(13)-dien-12-oic acid.<sup>270</sup> has also been completed. The recombinant sesquiterpene synthases from grand fir  $\delta$ -selinene synthase produces more than 30 sesquiterpene olefins from the acyclic precursor farnesyl diphosphate.<sup>271</sup>

### 3.7 Eudesmanolides

**3.7.1 Eudesmane-12,6-olides.** A wide range of structurally diverse eudesmane-12,6-olides have been reported from the Asterceae family, and a good deal of biological activity,







biotransformation and chemical syntheses studies about those lactones have been completed.

The lactones **424–742** and their corresponding plant sources are outlined in Table 8. Lasolide **506** and isolasolide **507** have been obtained from plants of the genus *Lasera*, and the structure of **506** has been revised.<sup>314</sup> The structures of 7 $\alpha$ -hydroxycostunolide<sup>338</sup> badkhisinin **443** and oopodin **660** have been determined by X-ray analysis,<sup>395</sup> and the stereochemistry of tauremisin **707** has been determined by single-crystal X-ray diffraction analysis.<sup>201</sup> The structure of torrentin, an eudesmanolide isolated from *Artemisia herba-alba*, has been revised to **487**.<sup>399</sup> The lactone **432**, also obtained from *Artemisia herba-alba*,<sup>279</sup> has had its structure revised, as the original configuration assigned at C-11 was erroneous.<sup>278</sup> Conformational analyses of 6 $\alpha$ - and 6 $\beta$ -eudesmanolides, as well as 8 $\alpha$ - and 8 $\beta$ -eudesmanolides, have been carried out.<sup>396</sup> The structure of 1-*O*-acetylbritannilactone

has been determined by X-ray analysis,<sup>397</sup> whilst the absolute configuration of glaucescenolide has been confirmed by chemical synthesis.<sup>398</sup> The known eudesmanolide magnolialide has been obtained from *Cichorium intybus* and shown to be identical to cichoriolide (another eudesmanolide), and cichopumilide (a guaianolide). Consequently, the structures of these last two lactones must be corrected. Moreover, the structures of their natural 11 $\beta$ ,13-dihydro derivatives and the glycosides cichorioside and sonchuside C should also be amended.<sup>399</sup> The structures of the alkaline reduction products of santonin have been determined.<sup>400</sup> A straightforward procedure for the introduction of a double bond between C-7 and C-11 in the eudesmanolide skeleton has been described.<sup>401</sup>

Sphaeranthanolide **498** exhibited immunostimulant activity in the jerne plaque assay.<sup>402</sup> The toxicity and antifeedant activity of several eudesmanolides from two *Encelia* species against larvae of

**Table 7** Sources of eudesmane carboxylic acids

Sources	Compounds
<i>Achillea schischkinii</i>	420 <sup>254</sup>
<i>Ambrosia elatior</i>	293 <sup>37</sup>
<i>Apalochlamys spectabilis</i>	325–327, <sup>48,197</sup> 280, 386–388 <sup>197</sup>
<i>Arctotis aspera</i>	413 <sup>247</sup>
<i>Artemisia altaiensis</i>	412 <sup>246</sup>
<i>Artemisia genus</i>	406 <sup>242</sup>
<i>Artemisia herba-alba</i>	281, <sup>198</sup> 326 <sup>218</sup>
<i>Artemisia mongolica</i>	352 <sup>229</sup>
<i>Artemisia pectinata</i>	318, 319 <sup>213</sup>
<i>Artemisia phaeolepis</i>	421 <sup>255</sup>
<i>Artemisia rutifolia</i>	350, <sup>227</sup> 372 <sup>236</sup>
<i>Artemisia tournefortiana</i>	316, <sup>211</sup> 316, 317, <sup>212</sup> 348, <sup>31</sup> 407 <sup>211</sup>
<i>Artemisia vulgaris</i>	331, 415 <sup>220</sup>
<i>Brocchia cinerea</i>	378 <sup>237</sup>
<i>Cassinia uncata</i>	283, 290, 300–307, 375, 379, 402 <sup>16</sup>
<i>Centaurea arguta</i>	330, 414 <sup>219</sup>
<i>Centaurea attica</i>	405 <sup>241</sup>
<i>Centaurea chilensis</i>	291 <sup>201</sup>
<i>Centaurea tweediei</i>	422 <sup>257</sup>
<i>Cratystylis conocephala</i>	320 <sup>215</sup>
<i>Dittrichia viscosa</i>	275, <sup>192</sup> 309, 313 <sup>207</sup>
<i>Eriocephalus pauperrimus</i>	292, 361–367, 376, 377, 392, 394–399, 423 <sup>202</sup>
<i>Eupatorium quadrangulare</i>	279 <sup>196</sup>
<i>Ferreyranthus fruticosus</i>	417 <sup>251</sup>
<i>Flourensia macrophylla</i>	296, 297, 345, 346, 407 <sup>204</sup>
<i>Flourensia thurifera</i>	283–285 <sup>199</sup>
<i>Geigeria rigida</i>	322, 323 <sup>217</sup>
<i>Haeckeria punctulata</i>	314, 315, <sup>210</sup> 334, 335 <sup>223</sup>
<i>Helianthus annuus</i>	276 <sup>193</sup>
<i>Holocarpa virgata</i>	273 <sup>190</sup>
<i>Hydropectis aquatica</i>	347 <sup>226</sup>
<i>Hypochoeris radicata</i>	295, 324 <sup>52</sup>
<i>Inula japonica</i>	357, 358 <sup>231,232</sup>
<i>Inula viscosa</i>	310, <sup>208</sup> 308, 311, <sup>205</sup> 313, <sup>209</sup> 389, <sup>209</sup> 416, 342–344 <sup>225</sup>
<i>Ixeris debilis</i>	368, 369, 373, 374, 380 <sup>108</sup>
<i>Jasonia candicans</i>	282 <sup>34</sup>
<i>Jasonia montana</i>	327, 349, <sup>48</sup> 411 <sup>244</sup>
<i>Laggara pterodonota</i>	338 <sup>31,200</sup>
<i>Laggara alata</i>	298, 299, 340, <sup>85</sup> 277, 336, 341, <sup>194</sup> 333, <sup>222</sup> 337, <sup>224</sup>
<i>Laggara pterodonta</i>	274, 312, 329, 353, <sup>191</sup> 286, <sup>191</sup> 287, <sup>200</sup> 288, 289, <sup>11</sup> 332, <sup>221</sup> 354, 355, <sup>31,200</sup> 412 <sup>245</sup>
<i>Montanoa speciosa</i>	413 <sup>248</sup>
<i>Onopordon acaulon</i>	384, 385, <sup>238</sup> 390 <sup>239</sup>
<i>Onopordon illyricum</i>	391, 404 <sup>240</sup>
<i>Perymenium featherstonei</i>	409, 410 <sup>243</sup>
<i>Pluchea arguta</i>	418 <sup>252</sup>
<i>Pluchea dioscoridis</i>	294, 403, <sup>203</sup> 400, 401 <sup>49</sup>
<i>Rudbeckia grandiflora</i>	321, 339 <sup>216</sup>
<i>Saussurea lappa</i>	360 <sup>234</sup>
<i>Schistostephium rotundifolium</i>	309, 408 <sup>206</sup>
<i>Sphaeranthus indicus</i>	320, <sup>214</sup> 370 <sup>131</sup>
<i>Tanacetum praeteritum</i>	351, <sup>228</sup> 419 <sup>253</sup>
<i>Taraxacum laevigatum</i>	371 <sup>235</sup>
<i>Tessaria absinthioides</i>	356 <sup>230</sup>
<i>Tessaria integrifolia</i>	316 <sup>138</sup>
<i>Ursinia eckloniana</i>	392 <sup>3</sup>
<i>Ursinia tenuifolia</i>	328, 393 <sup>3</sup>
<i>Verbesina turbacensis</i>	278 <sup>195</sup>
<i>Warionia saharae</i>	359 <sup>233</sup>

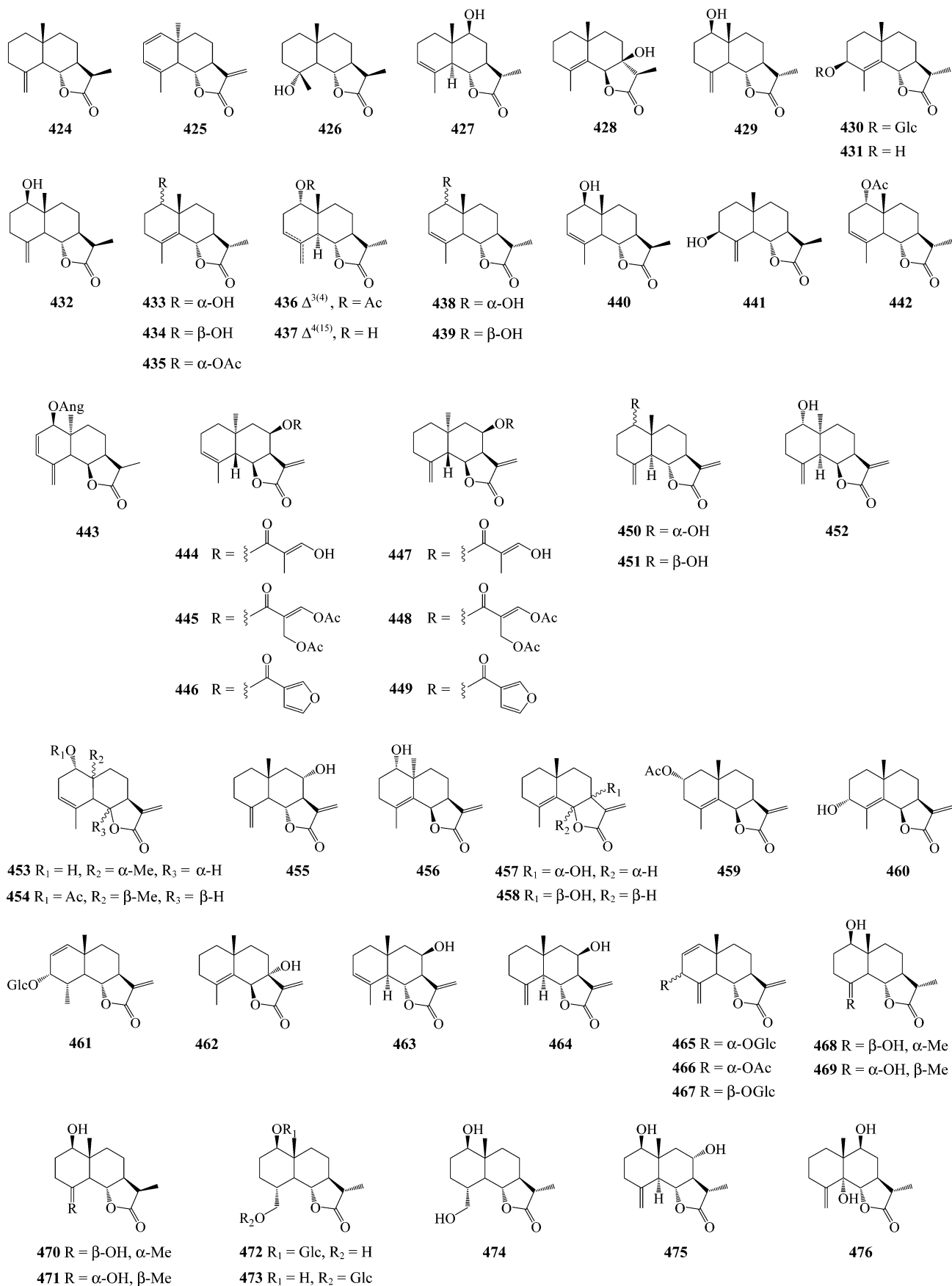
*Spodoptera littoralis* have been determined.<sup>403</sup> A structure–activity relationship study of the sesquiterpene lactones that stimulate the germination of witchweed *Striga asiatica* has been described. The highest activity was observed with a mixture of santamarin and reynosin.<sup>404</sup> The cytotoxic and antibacterial activities of the

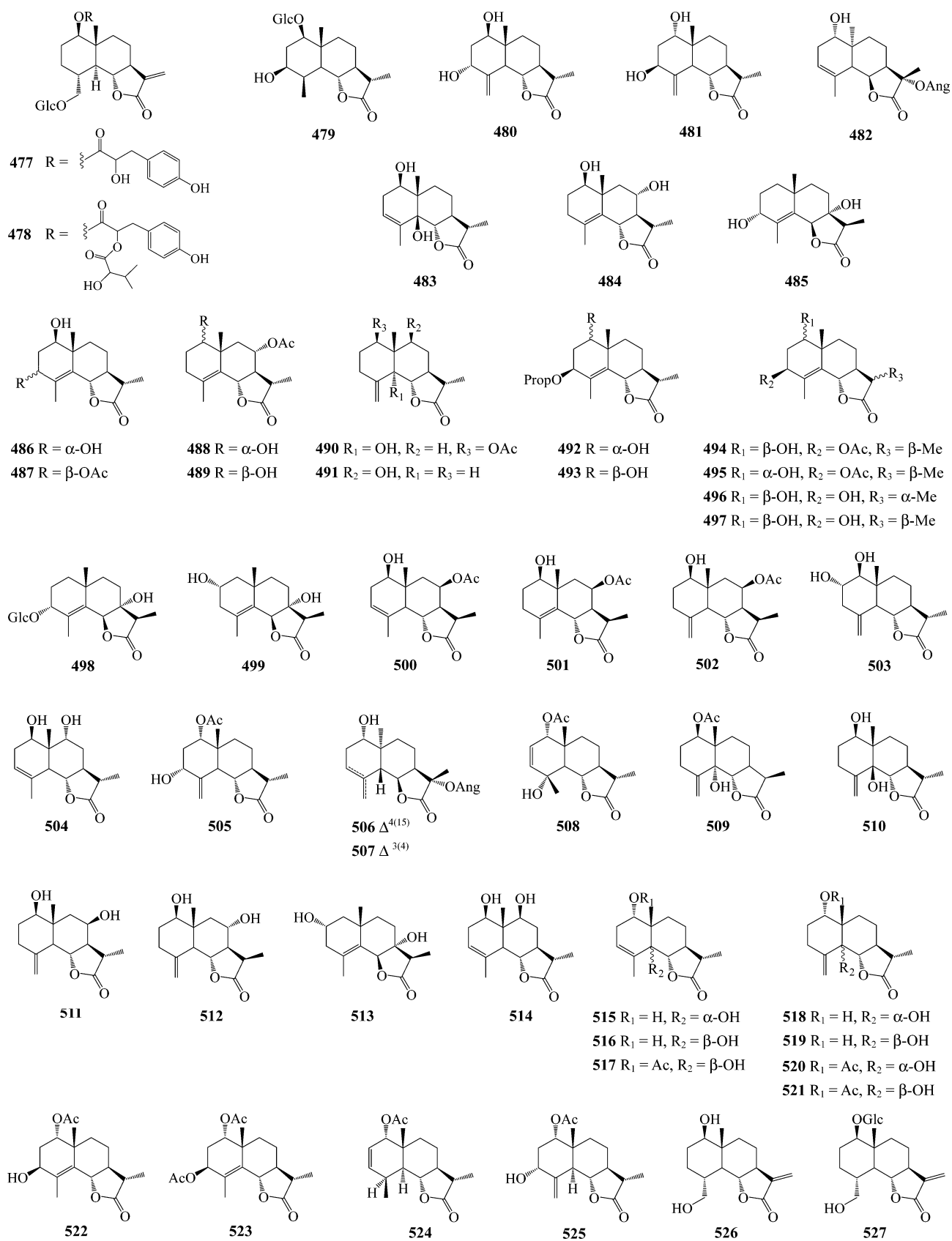
sesquiterpene lactones isolated from *Tanacetum praeteritum* has been evaluated.<sup>405</sup> The cytotoxic properties of the known eudesmane lactones from *Artemisia princeps* have been examined,<sup>406</sup> and the pharmacological activity of reynosin<sup>407,408</sup> and santamarine<sup>408</sup> has been studied. The *in vitro* activity of compounds **687**, **688**, **689** and **695** against three Gram-positive and three Gram-negative bacteria was evaluated using a microdilution method, and their cytotoxic activity was determined against a panel of human tumour cell lines.<sup>374</sup> Preliminary studies using the mycelial growth method indicated that the synthetic eudesmanolides **675**, **676**, **677**, **678** and **702** had inhibitory activities of against pathogenic fungi such as *Pythiumaphami dermatum*, *Phytophthora capsici*, *Fusarium oxysporum*, *Rhizoctonia solani* and *Botrytis cinerea* of 100–200 mg L<sup>-1</sup>.<sup>409</sup> Antiproliferative sesquiterpene lactones have been obtained from the roots of *Inula helenium*.<sup>410</sup> The effect of yomogin, an eudesmanolide with anti-inflammatory activity, has been investigated in human promyelocytic HL-60 leukaemia cells,<sup>411</sup> whilst the antiplasmodial activity of the lactones isolated from *Eupatorium semialatum* has been studied.<sup>412</sup> The antimicrobial activities of several lactones obtained from *Inula helenium*, *Rudbeckia subtomentosa*<sup>413</sup> and *Hemiteptia lyrata*<sup>414</sup> have been studied. The known lactones magnolialide and artemisin have been obtained from *Cichorium intybus*;<sup>415</sup> magnolialide has been shown to inhibit the growth of several tumour cell lines, but artemisin was inactive.<sup>416</sup> Studies of the inhibition of nitric oxide production by the lactone yomogin have been carried out.<sup>417</sup>

The biotransformation of  $\alpha$ -santonin by the fungus *Botrytis cinerea* afforded its 11 $\beta$ -hydroxy derivatives in very good yield.<sup>418</sup> The microbiological transformation of deoxyvulgarin by *Rhizopus nigricans* and *Aspergillus ochraceus* has been reported,<sup>419</sup> and the microbiological transformation of  $\alpha$ -santonin by *Pseudomonas cichorii*<sup>420</sup> and *Aspergillus niger*<sup>421</sup> has also been studied. A biogenetic synthesis of vulgarin and peroxyvulgarin has been devised.<sup>422</sup> During the preparation of 4-*epi*-6 $\beta$ -vulgarin, a biotransformation with the fungus *Rhizopus nigricans* was utilised in one of the synthetic steps.<sup>424</sup> The biomimetic cyclisation of cnicin led to a new lactone, malactanolide **741**.<sup>425</sup> The microbiological transformation of several sesquiterpene lactones by the fungi *Cunninghamella echinulata* and *Rhizopus oryzae* has been reported,<sup>426</sup> and transformations of  $\alpha$ -santonin, and  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclocostunolide with various fungi have been investigated.<sup>427</sup> The microbiological transformations of 7 $\alpha$ -hydroxyfrullanolide<sup>428</sup> and 11,13-dehydrosantonin<sup>429</sup> by *Aspergillus niger* have been reported. The microbial transformations of 6 $\alpha$ - and 6 $\beta$ -eudesmanolides by cultures of the fungus *Rhizopus nigricans* have been examined,<sup>430</sup> and the microbiological transformation of  $\alpha$ -santonin by several fungi has been studied.<sup>431</sup> A biomimetic synthesis of the bisessquiterpene lactones ( $\pm$ )-biatractylolide and ( $\pm$ )-biepiasterolide has been accomplished.<sup>432</sup> A *Pseudomonas* strain has been utilised in the biotransformation of  $\alpha$ -santonin to 1,2-dihydrosantonin and the dihydroxy derivative **743**.<sup>433</sup> The high photoreactivity of isoalantolactone with thymine to give photoadducts, involving the 5,6-double bond of thymine and the exomethylene double bond of the lactone, has been studied. This reaction may provide an explanation of the progressive evolution of contact dermatitis into chronic actinic dermatitis as an effect of the action of sesquiterpene lactones on the skin.<sup>434</sup>

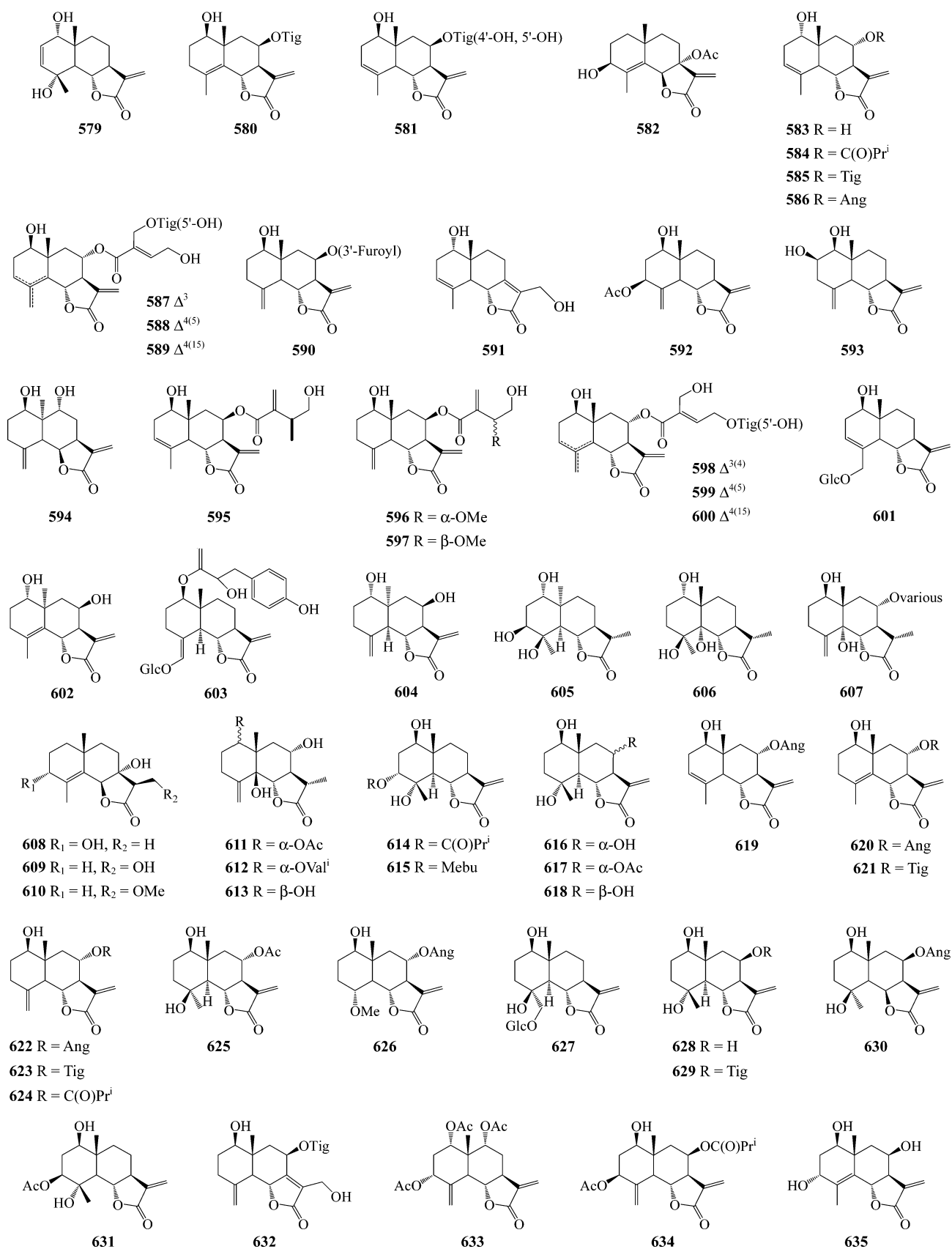
A review of approaches towards the synthesis of *cis*-decalins has been reported. The *cis*-decalin framework is present in various classes of natural products.<sup>435</sup> A review of the conversion of

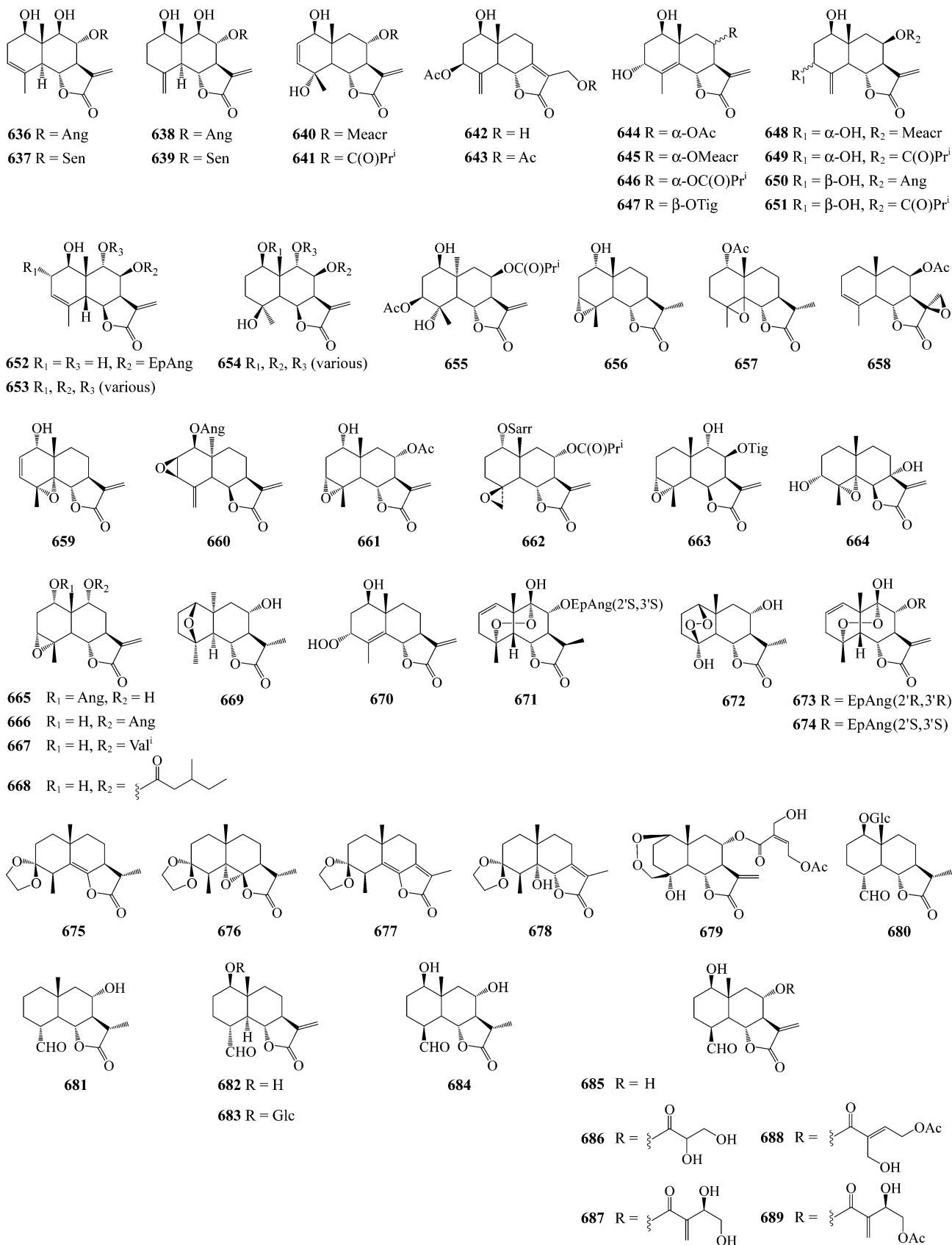


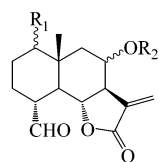






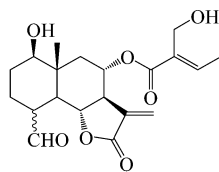




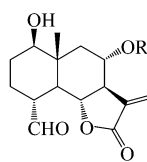


690  $R_1 = \alpha\text{-OH}$ ,  $R_2 = \alpha\text{-Meacr}(4'\text{-OH})$

691  $R_1 = \beta\text{-OH}$ ,  $R_2 = \beta\text{-Meacr}$

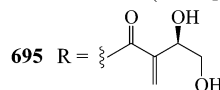


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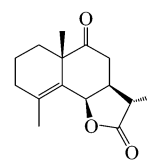


693  $R = \text{H}$

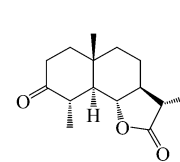
694  $R = \text{Meacr}(3'\text{-CH}_2\text{OAc}, 3'\text{-OH})$



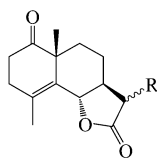
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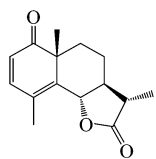


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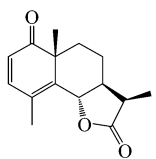


698  $R = \alpha\text{-Me}$

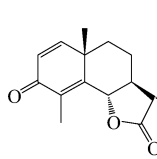
699  $R = \beta\text{-Me}$



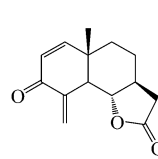
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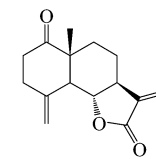
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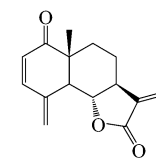
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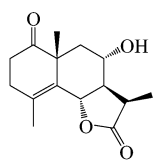
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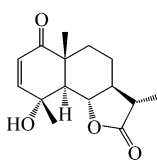
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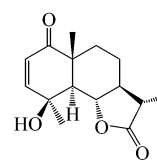
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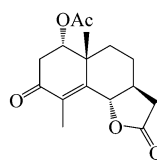
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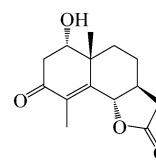
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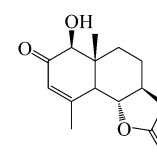
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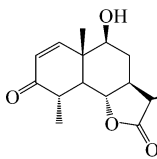
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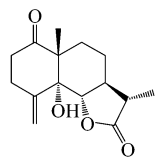
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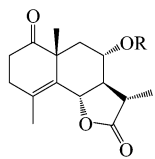
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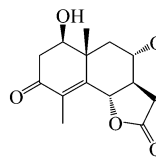
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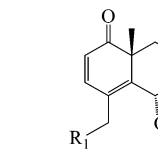
714  $R = \text{various}$



715  $R = \text{Ac}$

716  $R = \text{Meacr}$

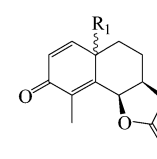
717  $R = \text{C(O)Pr}^i$



718  $R_1 = \text{OH}$ ,  $R_2 = \text{H}$ ,  $R_3 = \beta\text{-Me}$

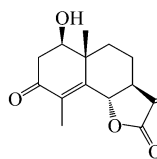
719  $R_1 = \text{OH}$ ,  $R_2 = \text{H}$ ,  $R_3 = \alpha\text{-Me}$

720  $R_1 = \text{H}$ ,  $R_2 = \text{OH}$ ,  $R_3 = \alpha\text{-Me}$

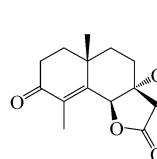


721  $R_1 = \alpha\text{-Me}$ ,  $R_2 = \text{Ang}$

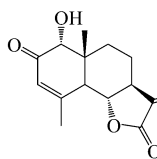
722  $R_1 = \beta\text{-Me}$ ,  $R_2 = \text{H}$



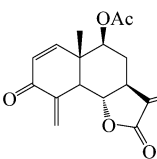
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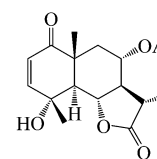
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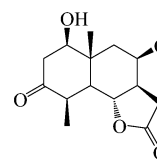
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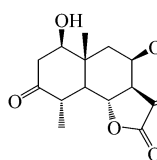
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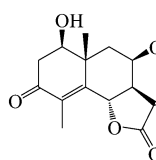
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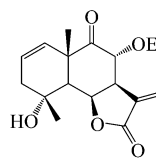
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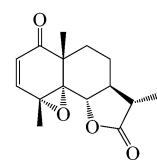
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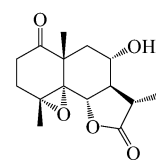
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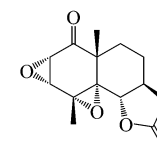
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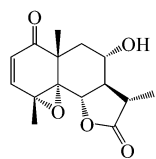
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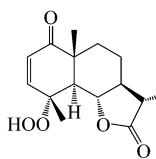
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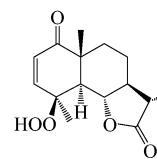
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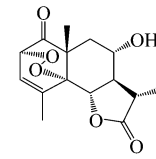
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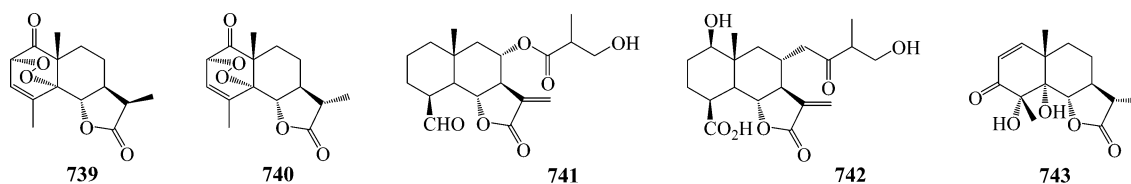


737



738





$\alpha$ -santonin into other sesquiterpene lactones, such as eudesma-12,6-olides and eudesma-12,8-olides, has been published.<sup>436</sup> Chemical, enzymatic and microbiological methods have been used in the transformation of santonin into sivasinolide and yomogin analogues.<sup>437</sup> Ultrasound has been used to enhance the rate of the reductive cleavage of sesquiterpene  $\gamma$ -enone-lactones.<sup>438</sup> An interesting procedure for the SmI<sub>2</sub>-catalyzed rearrangement of a 5 $\alpha$ ,6 $\alpha$ -epoxy-11,13-dihydroeudesmanolide to an eudesm-5,7(11)-dienolide has been reported.<sup>439</sup>

The synthesis of deuterium-labelled eudesmanolides, starting from lactones isolated from *Inula helenium*, has been described.<sup>440</sup> The partial syntheses of 7 $\beta$ -hydroxyeudesmanolide,<sup>442</sup> erivanin, and 1-*epi*-erivanin<sup>443</sup> has been reported. The syntheses of artepaulin, tuberin, oopodin, and vulgarin derivatives, starting from  $\alpha$ -santonin, has been reported.<sup>444</sup> The sesquiterpene lactone costunolide has been used in an efficient partial synthesis of several eudesmanolides.<sup>445</sup> A synthesis of (+)-colartin and (+)-arbusculin together with their C-4 epimers has been devised, and the plant growth regulating activity of these lactones has been studied.<sup>446</sup> A novel approach towards the stereocontrolled synthesis of eudesmanolides has been developed following a quasi-biomimetic strategy starting from a functionalised oxabicyclic template, by which the first total syntheses of gallicadiol and isogallicadiol were achieved.<sup>447</sup> Another lactone, **722**, has been synthesised as a racemate,<sup>448</sup> which implied a revision of the structure previously assigned.<sup>449</sup> An enantioselective synthesis of (+)-decipienin A has been achieved.<sup>450</sup> The syntheses, using free-radical chemistry, of (+)-3 $\alpha$ -hydroxyreynosin, (+)-reynosin and (+)-11 $\beta$ ,13-dihydroreynosin, starting from 1,10-epoxy-11 $\beta$ ,13-dihydrocostunolide, have been accomplished.<sup>451</sup>

The syntheses of dehydrobrachylaenolide, isodehydrochamaecynone and *trans*-isodehydrochamaecynone, starting from tuberiferine, have been reported. Eudesmanolides possessing an  $\alpha$ -methylene- $\gamma$ -lactone moiety, such as dehydrobrachylaenolide, exhibited significant inhibitory activity toward the induction of the intercellular adhesion molecule-1 (ICAM-1).<sup>452</sup> The total synthesis<sup>453</sup> of (+)-decipienin A **721** has been carried out, confirming the stereochemistry proposed by the Czech authors<sup>454</sup> and correcting the original structure.<sup>455</sup> (+)-Stobenolide has been prepared starting from (+)-salonitenolide.<sup>456</sup> A short synthesis of the sesquiterpene lactone 1-oxoeudesma-2,4-dien-11 $\beta$ -hydro-12,6 $\alpha$ -olide has been achieved,<sup>457</sup> and a synthesis of 11 $\beta$ -angeloyloxy- $\alpha$ -santonin has been devised. In this work, the X-ray structure of 11 $\beta$ -hydroxy- $\alpha$ -santonin was described.<sup>458</sup> The partial synthesis of 6 $\beta$ -eudesmanolides and 6 $\beta$ -guaianolides from 6 $\alpha$ -eudesmanolides has been reported,<sup>459</sup> and a synthesis of the reported structure of herbolide I has been devised, showing that the assigned structure is erroneous.<sup>460</sup>

A short synthesis of (+)-colarin and (+)-arbusculin, starting from  $\alpha$ -santonin, has been accomplished.<sup>461</sup> The syntheses of the eudesmanolides torrentin and dihydrosantamarine, and the elemanolide saussaurea lactone have been reported,<sup>462</sup> and a synthetic

strategy whereby 6 $\beta$ -eudesmanolide isomers are converted into the 6 $\alpha$ -analogues in modest yield has been developed.<sup>463</sup> Artemisin has been used as the starting material in the preparation of herbolide E, showing that the previously proposed structure for this compound must be revised.<sup>464</sup> Syntheses of 4 $\alpha$ ,5 $\alpha$ - and 4 $\beta$ ,5 $\beta$ -epoxy-eudesmanolides<sup>465</sup> and the bioactive lactones (–)-arbusclin D **529** and (–)-*epi*-arbusclin D have been reported.<sup>323</sup> A formal synthesis of (–)- $\alpha$ -santonin has been achieved using an optically active key intermediate, prepared by asymmetric hydrolysis of its racemate.<sup>466</sup> Santonin and other sesquiterpene lactones react with pyrrolidine at room temperature to afford  $\gamma$ -hydroxyalkylamides,<sup>467</sup> and the unexpected selective formation of a  $\delta$ -lactone after the ozonolysis of a santonin derivative has been reported.<sup>468</sup>

A first total synthesis of ( $\pm$ )-diplophyllin has been devised,<sup>469</sup> and a highly stereoselective synthesis of ivangulin has been achieved.<sup>470</sup> A modified synthesis of racemic occidentaol has been reported,<sup>471</sup> as well as the synthesis and *in vitro* activity of 3-hydroxyencelin.<sup>425</sup> An easy route to racemic 11-hydroxy-eudesmanolides, such as decipienin A, has been described,<sup>472</sup> and short syntheses of dehydroisoerivanin, isoerivanin, ludovicin C and 1 $\alpha$ ,3 $\alpha$ -dihydroxyarbusculin B have been described.<sup>473</sup> (–)- $\alpha$ -Santonin has been used as starting material in the synthesis of phytuberin,<sup>474</sup> and other studies towards the biomimetic synthesis of these sesquiterpene lactones have been described.<sup>475</sup> Syntheses of (–)-isobaimuxinol and (–)-baimuxinol have been reported,<sup>476,477</sup> and cytotoxic  $\alpha$ -aminomethyl-substituted eudesmanolides have been prepared by stereoselective Michael-type addition of amines to alantolactone and isoalantolactone.<sup>478</sup>

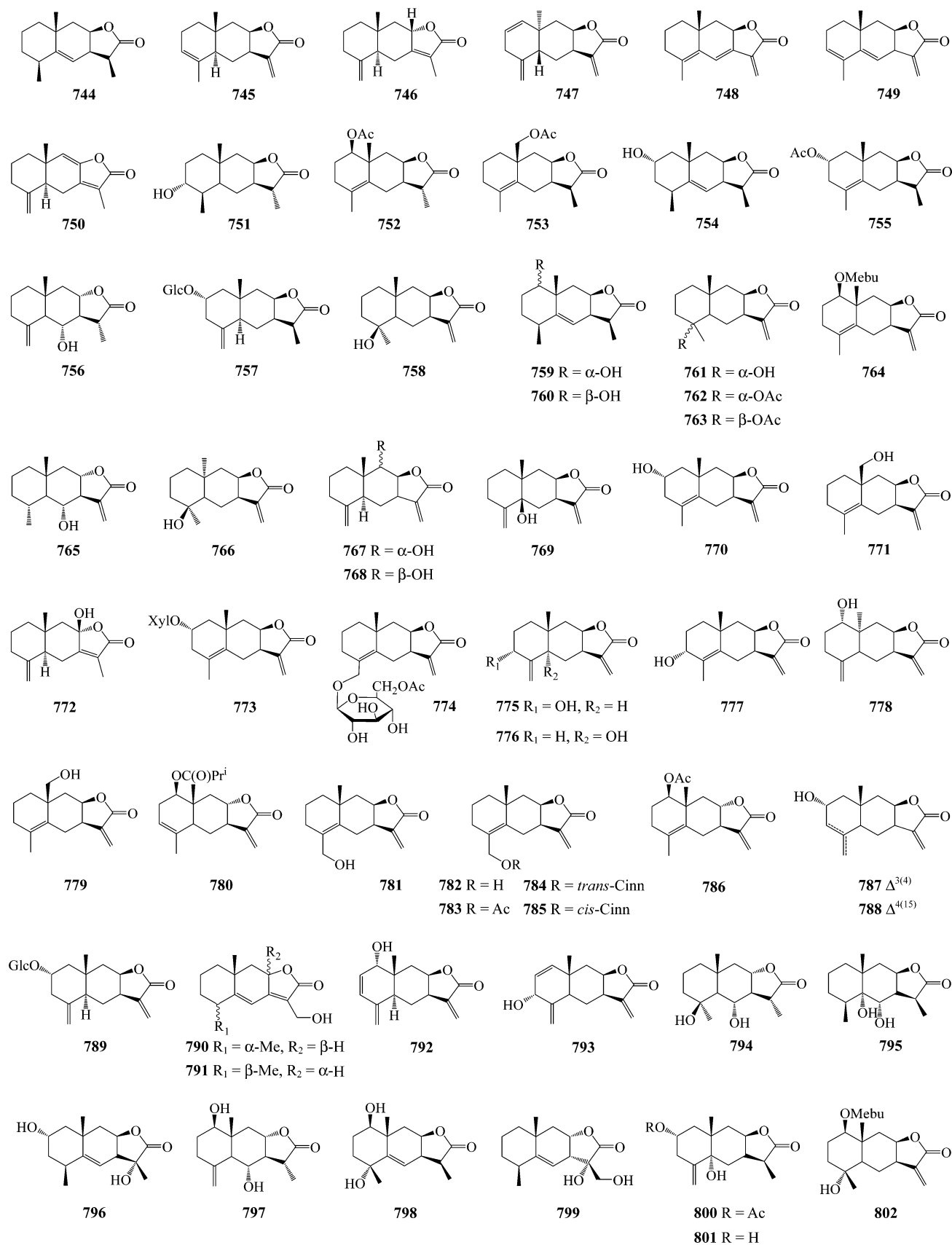
**3.7.2 Eudesmane-12,8-olides.** The new eudesmane-12,8-olides **744–917** and their plant sources are summarised in Table 9. Single crystal X-ray diffraction analysis has been used to establish the structures of sesquiterpene lactones **849**, **850** and **851**<sup>522</sup> obtained from *Steiractinia*, the telekin epimers **769** and **887**,<sup>538</sup> as well as isogallicadiol,<sup>543</sup> gazanniolide<sup>544</sup> and compound **813**.<sup>508</sup> The structure of eudesmanolide, isolated from *Lasiolanea santosi*<sup>503</sup> and *Mikania goyazensis*,<sup>504</sup> has been revised to **797**,<sup>545</sup> and the stereochemistry of septuplinolide **761** has been revised, correcting the stereochemistry of the 4-OH group from  $\beta$  to  $\alpha$ .<sup>490</sup>

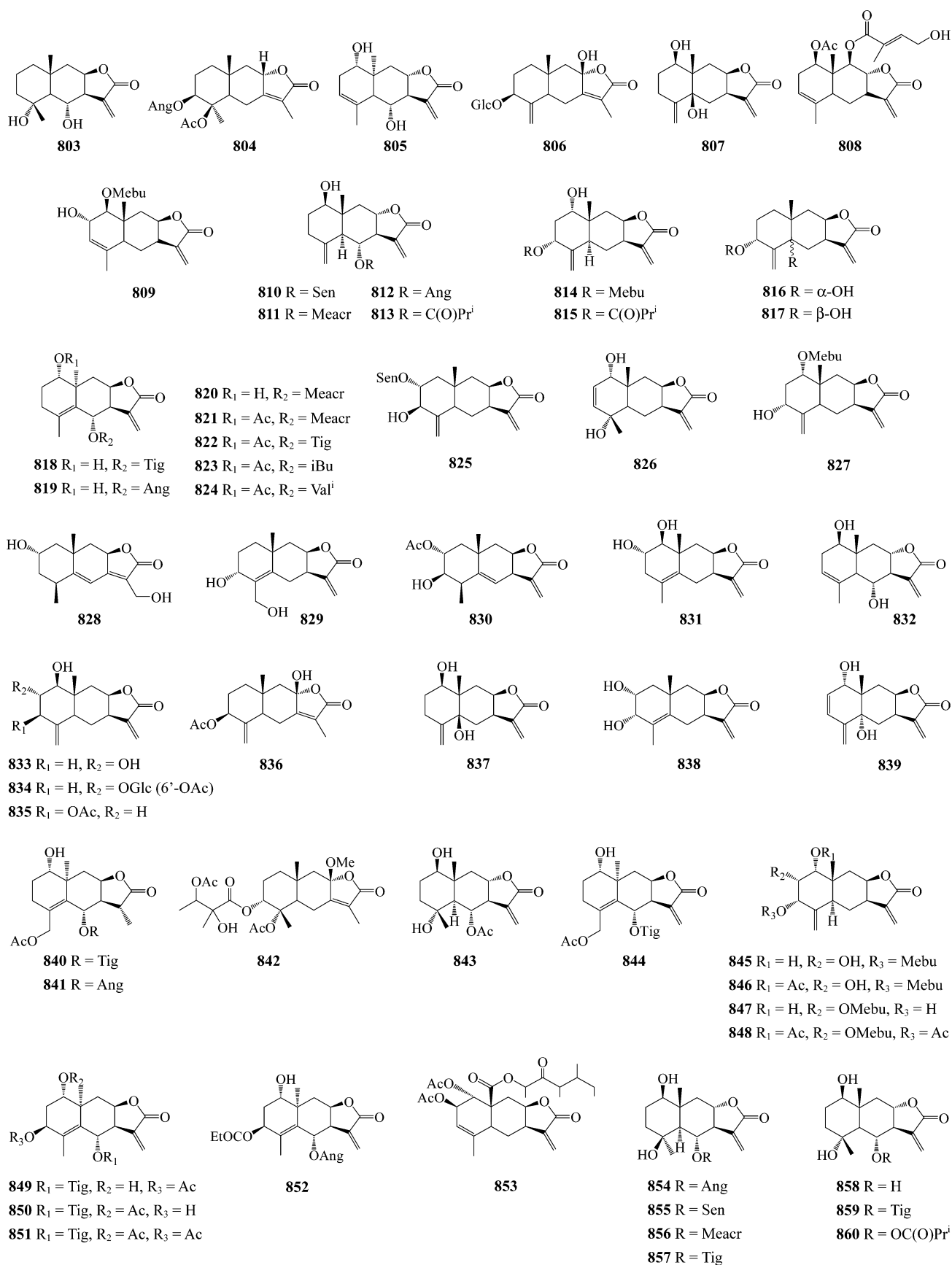
Inunal **745** and isoalalantolactone **897** are biologically active as plant growth regulators, promoting the formation of adventitious roots.<sup>481</sup> The biotransformation of pyrenthrosin by *Rhizopus nigricans* has been investigated to generate eudesmanolide-type metabolites, which exhibited cytotoxic, antifungal, and antiprotzoal activities.<sup>546</sup>

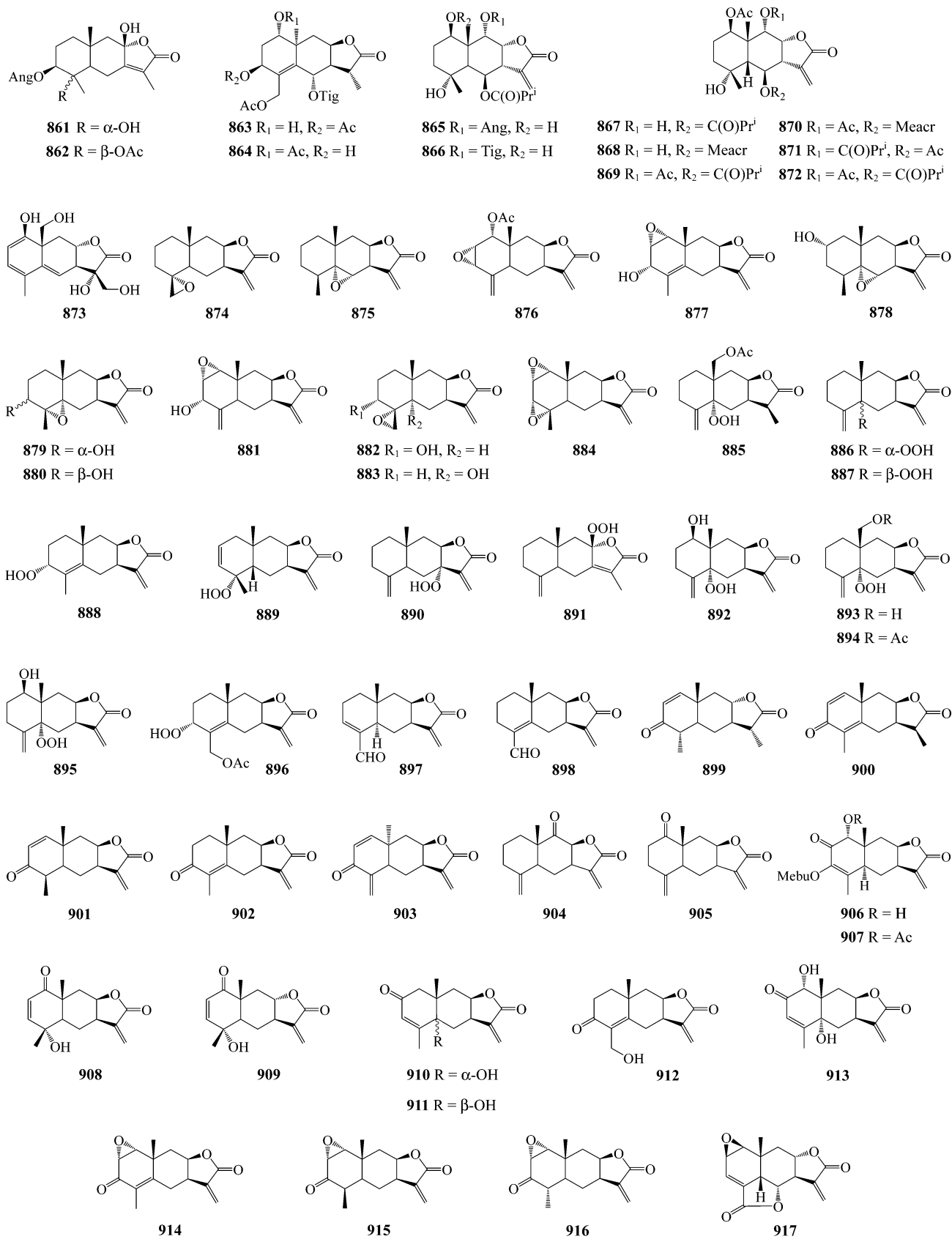
The chemical and microbiological transformation of (–)- $\alpha$ -santonin into 8-*epi*-artemisin has been carried out,<sup>441</sup> and the synthesis of 8-*epi*-ivangustin and 8-*epi*-isoivangustin starting from santonin has been explored.<sup>444</sup> The synthesis of deuterium-labelled eudesmanolides, starting from lactones isolated from *Inula helenium*, has also been described.<sup>547</sup> A partial synthesis

**Table 8** Sources of eudesmane-12,6-olides

Sources	Compounds	Sources	Compounds
<i>Anthemis carpatica</i>	583–586 <sup>345</sup>	<i>Grangea maderaspatana</i>	485 <sup>308</sup>
<i>Arctotheca calendula</i>	703 <sup>247</sup>	<i>Greenmaniella resinosa</i>	536, 541, 651, 728, 729 <sup>328</sup>
<i>Argyranthemum foeniculaceum</i>	697 <sup>380</sup>	<i>Gutenbergia cordifolia</i>	726 <sup>294</sup>
<i>Artemisia afra</i>	643 <sup>136</sup>	<i>Helipterum roseum</i>	619–624, 626 <sup>354</sup>
<i>Artemisia caerulescens</i>	488, 489, <sup>134</sup> 669 <sup>211,366</sup>	<i>Hieracium intybaceum</i>	461, 467 <sup>295</sup>
<i>Artemisia caerulescens</i> subsp. <i>gallica</i>	709 <sup>387</sup>	<i>Inula graveolens</i>	460, 724 <sup>293</sup>
<i>Artemisia caerulescens</i> var. <i>cretacea</i>	433 <sup>280</sup>	<i>Inula salsoloides</i>	511 <sup>316</sup>
<i>Artemisia canariensis</i>	532, 575, 704, 705, <sup>325</sup> 727 <sup>393</sup>	<i>Ixeris dentata</i>	465 <sup>297</sup>
<i>Artemisia cretacea</i>	698 <sup>381</sup>	<i>Ixeris repens</i>	477, 478, 601, 603, 627 <sup>108</sup>
<i>Artemisia diffusa</i>	437, 710 <sup>283</sup>	<i>Laser trilobum</i>	482, <sup>306</sup> 506, 507 <sup>314</sup>
<i>Artemisia fragrans</i>	438, <sup>285</sup> 475 <sup>304</sup>	<i>Leucanthemopsis actinata</i>	429 <sup>275</sup>
<i>Artemisia giraldui</i>	706 <sup>385</sup>	<i>Liabum floribundum</i>	712 <sup>389</sup>
<i>Artemisia gracilescens</i>	698 <sup>382</sup>	<i>Liatris laevigata</i>	565–567, <sup>339</sup> 629 <sup>239</sup>
<i>Artemisia herba-alba</i>	469, 481, 492, 493, <sup>218</sup> 424, 426, 440, 470, 471, 699, <sup>198</sup> 490, 491, <sup>161</sup> 700, 701, 718–720, 732, 734, 735, 738–740, <sup>383</sup> 427, 476, <sup>272</sup> 429, 434, 436, 484, <sup>276</sup> 432, <sup>279</sup> 487, <sup>309</sup> 494–497, <sup>310</sup> 514, <sup>319</sup> 656 <sup>361</sup>	<i>Mikania guaco</i>	552, <sup>336</sup> 564, 644 <sup>336</sup>
<i>Artemisia hugueti</i>	435, 437, 510, 515–523, 611 <sup>282</sup>	<i>Montanoa frutescens</i>	636–639 <sup>357</sup>
<i>Artemisia ifranensis</i>	606 <sup>282</sup>	<i>Montanoa hibiscifolia</i>	671, 673, 674, 731 <sup>367</sup>
<i>Artemisia inculta</i>	512 <sup>317</sup>	<i>Onopordon myriacanthum</i>	692 <sup>376</sup>
<i>Artemisia judaica</i>	480, 486, 642, 707, <sup>305</sup> 708, 736, <sup>386</sup> 737 <sup>394</sup>	<i>Onopordon ambiguum</i>	690 <sup>375</sup>
<i>Artemisia lehmanniana</i>	524, 525 <sup>321</sup>	<i>Onopordon tauricum</i>	684, 742 <sup>371</sup>
<i>Artemisia lehmannianoda</i>	442 <sup>288</sup>	<i>Pegolettia oxydonta</i>	534, 560 <sup>8</sup>
<i>Artemisia lerchiana</i>	592, 631 <sup>348</sup>	<i>Pegolettia senegalensis</i>	444–449, 534 <sup>289</sup>
<i>Artemisia leucotricha</i>	514 <sup>320</sup>	<i>Perymenium mendezii</i>	455 <sup>290</sup>
<i>Artemisia lucentica</i>	425, 593 <sup>273</sup>	<i>Picris aculeata</i>	462, 480, 486 <sup>296</sup>
<i>Artemisia ludoviciana</i>	576 <sup>342</sup>	<i>Picris spinifera</i>	711 <sup>388</sup>
<i>Artemisia maritima</i>	483, <sup>307</sup> 547, 661, 715 <sup>333</sup>	<i>Pluchea dioscoridis</i>	504, 548, 666–668, <sup>312</sup> 549, <sup>334</sup> 594, <sup>49</sup> 665 <sup>312,365</sup>
<i>Artemisia nitrosa</i>	509 <sup>315</sup>	<i>Podochaenium eminens</i>	531 <sup>324</sup>
<i>Artemisia pauciflora</i>	697 <sup>379</sup>	<i>Pyrethrum santolinoides</i>	605 <sup>350</sup>
<i>Artemisia pontica</i>	607, 612, 613 <sup>351</sup>	<i>Ratibida latipalearis</i>	659 <sup>364</sup>
<i>Artemisia rutifolia</i>	439 <sup>227</sup>	<i>Schistostephium crataegifolium</i>	538 <sup>206</sup>
<i>Artemisia salina</i>	441 <sup>87</sup>	<i>Schistostephium heptalobum</i>	454, 546 <sup>206</sup>
<i>Artemisia santolinifolia</i>	713 <sup>390</sup>	<i>Schistostephium rotundifolium</i>	450 <sup>206</sup>
<i>Artemisia santonicus</i>	714, 733 <sup>391</sup>	<i>Senecio chrysanthemoides</i>	505, 508 <sup>313</sup>
<i>Artemisia spicigera</i>	437 <sup>284</sup>	<i>Sonchus asper</i>	472, 473, 527, 680, 683 <sup>301</sup>
<i>Artemisia splendens</i>	434 <sup>281</sup>	<i>Sonchus macrocarpus</i>	474, 526, <sup>302</sup> 682 <sup>370</sup>
<i>Artemisia tenuisecta</i>	657 <sup>362</sup>	<i>Sonchus oleraceus</i>	430, 431, 451 <sup>277</sup>
<i>Artemisia tournefortiana</i>	696 <sup>211</sup>	<i>Sphaeranthus indicus</i>	428, 458, 462, <sup>274</sup> 457, <sup>291</sup> 498, <sup>166</sup> 513, <sup>318</sup> 573, <sup>341</sup> 582, 664, <sup>131</sup> 608–610 <sup>352</sup>
<i>Athanasia calva</i>	569, 572 <sup>340</sup>	<i>Sphaeranthus suaveolens</i>	459, 499, 568, 570, 571 <sup>292</sup>
<i>Bartlettina karwinskiana</i>	658 <sup>363</sup>	<i>Squmoappus skutchii</i>	539 <sup>329</sup>
<i>Bishopanthus soliceps</i>	614, 615 <sup>353</sup>	<i>Stevia aff. tomentosum</i>	500–502 <sup>311</sup>
<i>Calea trichomata</i>	542, 545, 632, 650, <sup>331</sup> 647 <sup>359</sup>	<i>Stevia alpina</i>	580, 581 <sup>344</sup>
<i>Calostephane divaricata</i>	630, 652–654, 663 <sup>355</sup>	<i>Stevia breviaristata</i>	578 <sup>343</sup>
<i>Cassinia subtropica</i>	558, 635 <sup>16</sup>	<i>Tanacetum ferulaceum</i>	528 <sup>322</sup>
<i>Cassinia uncata</i>	463, 464, 537, 538, 540, 574, 602, 604, 616–618, 625, 730 <sup>16</sup>	<i>Tanacetum parthenium</i>	540, <sup>330</sup> 579, 591, 670, <sup>228</sup> 725 <sup>253</sup>
<i>Centaurea aspera</i>	672, 679 <sup>368</sup>	<i>Tanacetum vulgare</i>	723 <sup>392</sup>
<i>Centaurea attica</i>	687 <sup>241</sup>	<i>Taraxacum hallaisanensis</i>	479, 530 <sup>303</sup>
<i>Centaurea deusta</i>	694 <sup>378</sup>	<i>Taraxacum</i>	533, 577 <sup>326</sup>
<i>Centaurea granata</i>	681 <sup>369</sup>	<i>linearisquameum</i>	
<i>Centaurea malacitana</i>	686, 741 <sup>373</sup>	<i>Tithonia diversifolia</i>	634, <sup>356</sup> 655 <sup>360</sup>
<i>Centaurea ornata</i>	432 <sup>278</sup>	<i>Tithonia rotundifolia</i>	543, 544, 557, 559, 561 <sup>332</sup>
<i>Centaurea spinosa</i>	687, 688, 689, 695 <sup>374</sup>	<i>Ursinia abrotanoides</i>	628 <sup>3</sup>
<i>Centaurea thessala</i>	685 <sup>241,372</sup>	<i>Vladimiria souliei</i>	469, 503 <sup>300</sup>
<i>Centaurea tweediei</i>	691 <sup>257</sup>	<i>Zexmenia lantanifolia</i>	535 <sup>327</sup>
<i>Centaurea zuccariniana</i>	693 <sup>377</sup>		
<i>Chamaemelum fuscum</i>	550, 551, 645, 646, 716, 717, <sup>335</sup> 640, 641, 648, 649 <sup>358</sup>		
<i>Cratystylis conocephala</i>	633 <sup>215</sup>		
<i>Decachaeta ovatifolia</i>	562, 563 <sup>338</sup>		
<i>Dendroseris neriifolia</i>	468 <sup>299</sup>		
<i>Dicoma macrocephala</i>	466 <sup>298</sup>		
<i>Dimerostemma asperatum</i>	662 <sup>337</sup>		
<i>Dimerostemma bishoppii</i>	553–556 <sup>337</sup>		
<i>Disynaphia multicrenulata</i>	590 <sup>347</sup>		
<i>Echinops spinosissimus</i>	440 <sup>286</sup>		
<i>Eupatorium semialatum</i>	587–589, 598–600, <sup>346</sup> 595–597 <sup>349</sup>		
<i>Geigeria rigida</i>	452, 453, 456, 534, 560 <sup>217</sup>		







**Table 9** Sources of eudesmane-12,8-olides

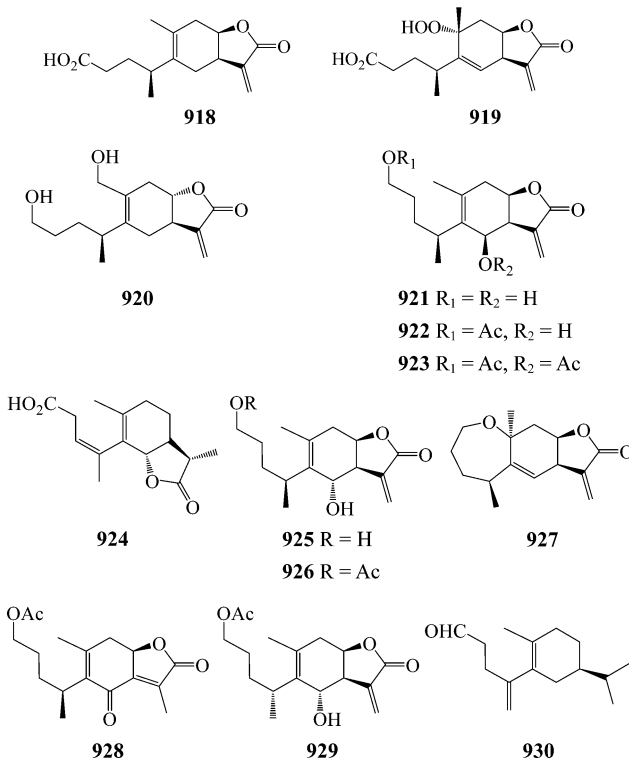
Sources	Compounds
<i>Ambrosia artemisioides</i>	782, 783, 784, 785, 829, 874, 879, 896, 912 <sup>38</sup>
<i>Anthemis altissima</i>	805 <sup>506</sup>
<i>Artemisia argyi</i>	762, 763 <sup>491</sup>
<i>Artemisia feddei</i>	884, 536, 915 <sup>542</sup>
<i>Artemisia iwawayomogi</i>	745, 775–777, 816, 817, 879, 880, 888, 889, 902 <sup>280</sup>
<i>Artemisia umbelliformis</i>	886, 887 <sup>537</sup>
<i>Artemisia xerophytica</i>	826 <sup>512</sup>
<i>Aspilia pluriseta</i>	849–851 <sup>522</sup>
<i>Atractylodes japonica</i>	746, 750, 772, 107, 806 <sup>507</sup>
<i>Atractylodes macrocephala</i>	836, 519, 891 <sup>539</sup>
<i>Bahia absinthifolia</i>	774 <sup>497</sup>
<i>Blumea afrakiana</i>	827 <sup>513</sup>
<i>Blumea densiflora</i>	814, 815, 845–848, 906, 907 <sup>509</sup>
<i>Calea septuplinerva</i>	761, 490, 758 <sup>488</sup>
<i>Calea subcordata</i>	780, 498, 813, 508, 909 <sup>541</sup>
<i>Carpesium cernuum</i>	791 <sup>501,502</sup>
<i>Carpesium macrocephalum</i>	755, 800, 801, 485, 757, 789, 487, 755, 795 <sup>486</sup>
<i>Cassinia subtropica</i>	843 <sup>16</sup>
<i>Eriocephalus africanus</i>	837, 885, 892–895 <sup>202</sup>
<i>Eriocephalus pauperrimus</i>	771, 807 <sup>202</sup>
<i>Eriocephalus scariosus</i>	752–753, 779 <sup>202</sup>
<i>Ferreyranthus fruticosus</i>	792, 793, 839, 877, 881, 884, 900, 908, 913, 914, 916 <sup>251</sup>
<i>Flourensia macrophylla</i>	767, 768, 904, 905 <sup>204</sup>
<i>Flourensia riparia</i>	766 <sup>494</sup>
<i>Gnephosis arachnoidea</i>	786, 831 <sup>500</sup>
<i>Gochmatia vernonioides</i>	857 <sup>525</sup>
<i>Greenmaniella resinosa</i>	910, 911 <sup>328</sup>
<i>Guizotia scabra</i>	876 <sup>533</sup>
<i>Hyaloseris salicifolia</i>	833, 834 <sup>517</sup>
<i>Inula britannica</i>	803 <sup>505</sup>
<i>Inula caspica</i>	825 <sup>511</sup>
<i>Inula japonica</i>	760 <sup>231</sup>
<i>Inula macrophylla</i>	744, 873, 479, 744, 480, 790, 799 <sup>479</sup>
<i>Inula montana</i>	835 <sup>518</sup>
<i>Inula racemosa</i>	745, 481, 748, 749, 483, 781, 874, 875, 898, 499, 882, 883, 890, 535, 897 <sup>481</sup>
<i>Inula thapsoides</i>	759, 760, 798 <sup>489</sup>
<i>Lasiolanea santosii</i>	797 <sup>503</sup>
<i>Mikania cynanchifolia</i>	917 <sup>551</sup>
<i>Mikania goyazensis</i>	797 <sup>504</sup>
<i>Ondetia linearis</i>	754, 787, 788, 796 <sup>109</sup>
<i>Pegolettia oxydonta</i>	808 <sup>8</sup>
<i>Perymenium featherstonei</i>	901 <sup>243</sup>
<i>Pluchea dioscordis</i>	773 <sup>496</sup>
<i>Pluchea quitoc</i>	804, 861, 862 <sup>101</sup>
<i>Pulicaria crispa</i>	878 <sup>534</sup>
<i>Pulicaria undulata</i>	770, 828 <sup>495</sup>
<i>Schistostephium crataegifolium</i>	810–813, 854–856 <sup>206</sup>
<i>Senecio flammeus</i>	853 <sup>524</sup>
<i>Spilanthes acmella</i>	899 <sup>540</sup>
<i>Spilanthes leiocarpa</i>	747 <sup>482</sup>
<i>Stevia achalensis</i>	751, 778, 903 <sup>484</sup>
<i>Tanacetopsis mucronata</i>	832 <sup>515</sup>
<i>Tanacetum argenteum</i>	859 <sup>527</sup>
<i>Tanacetum densum</i>	832, 516, 837, 520, 858 <sup>526</sup>
<i>Tanacetum ferulaceum</i>	756, 794, 322, 765 <sup>493</sup>
<i>Tanacetum parthenium</i>	859 <sup>529</sup>
<i>Tessaria ambigua</i>	842 <sup>138</sup>
<i>Vicoa pentanema</i>	830, 838 <sup>514</sup>
<i>Wedelia grandiflora</i>	818–824 <sup>410</sup>
<i>Wedelia hispida</i>	863, 864 <sup>528</sup>
<i>Wedelia paludosa</i>	871, 872 <sup>532</sup>
<i>Wedelia pinetorum</i>	840, 841, 844 <sup>521</sup>
<i>Wedelia prostata</i>	867–870 <sup>531</sup>
<i>Wedelia prostrata</i>	865, 866 <sup>530</sup>
<i>Wunderlichia mirabilis</i>	764, 802, 809 <sup>492</sup>
<i>Zexmenia virgulata</i>	852 <sup>523</sup>

of (+)-ivalin has been achieved,<sup>423</sup> and a general procedure for the synthesis of both 12,6- and 12,8-eudesmanolides has been described.<sup>548</sup> Partial syntheses of (+)-isoalantolactone and (+)-isoalloalantolactone have been devised,<sup>549</sup> and the synthesis of (–)-dehydrobaimuxinol has been reported.<sup>550</sup>

## 4 Secoeudesmanes

### 4.1 1,10-Secoeudesmanes

1,10-Secoeudesmanes **918** and **919** have been found in *Gnephosis arachnoidea*.<sup>500</sup> Metabolite **920** has been isolated from *Calostephane divaricata*,<sup>555</sup> **921** and **923** have been identified from *Inula britannica*,<sup>552</sup> and the secoeudesmanes **922**, **925** and **926** have been found in *Inula japonica*.<sup>553</sup> Compound **924** has been isolated from *Artemisia hugueti*,<sup>282</sup> **927–929** have been found in *Inula britannica*,<sup>554</sup> and **930** has been isolated from *Solidago gigantea*.<sup>129</sup>

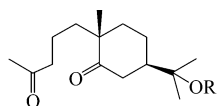


Studies on the semi-synthesis, structure determination and biotransformation of cyclic sulfinated eudesmane derivatives have been described.<sup>555</sup> The structures of deacetylinulicin and inulicin, two secopseudoguaianolides extracted from *Inula japonica*, have been revised to the secoeudesmanolides **921** and **922** respectively.<sup>552,553</sup> An enantioselective synthesis of the 1,10-secoeudesmanolides eriolanin and eriolangin has been achieved.<sup>556</sup>

### 4.2 4,5-Secoeudesmanes

4,5-Secoeudesmanolide **935**<sup>480</sup> has been identified from *Inula macrophylla*. The diketone eudesmanes **931**,<sup>202</sup> **932**,<sup>7</sup> **933**<sup>108</sup> and **934**<sup>3</sup> have been found in *Eriocephalus africanus*, *Iphiona scabra*, *Ixeris repens* and *Ursinia eckloniana*, respectively. 6,7-Secoeudesmane, (–)- $\alpha$ -eudesmol<sup>557</sup> and 7-*epi*- $\gamma$ -eudesmol<sup>558</sup> have been described, and a racemic synthesis of balanitol has been reported.<sup>69</sup> The enantioselective total syntheses of chrysanthemol,<sup>559,560</sup>

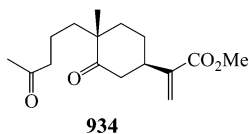




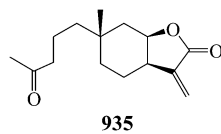
931 R = H

932 R = Xyl

933 R = Xyl(2'-OAc)



934

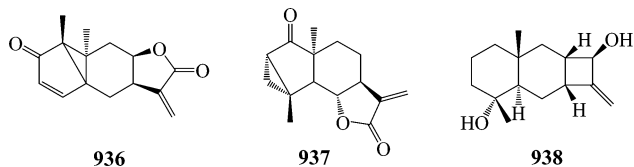


935

4,5-dioxo-*seco*- $\gamma$ -eudesmol, 5 $\beta$ ,11-dihydroxyiphionan-4-one<sup>561</sup> and the *seco*eudesmane glutinone,<sup>320,562</sup> have been reported. The total syntheses of 4,5-*seco*eudesmane-type sesquiterpenes, such as 4,5-dioxo-10-*epi*-4,5-*seco*- $\gamma$ -eudesmane and 4,5-dioxo-10-*epi*-4,5-*seco*- $\gamma$ -eudesmanol, have also been reported.<sup>563</sup>

## 5 Cycloeudesmanes and isomeric eudesmanes

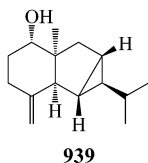
The cycloeudesmanes are few in the Asteraceae family. For example, the methyl-transferred 1,5-cycloeudesmane **936** has been identified from *Ferreyranthus fruticosus*<sup>251</sup> and 2,4-cycloeudesm-12,6-olide **937**, the structure of which was confirmed by X-ray analysis, is a constituent of *Ratibida latipalearis*.<sup>564,565</sup> 8,12-Cycloeudesmene **938** has been isolated from *Jasonia candicans*,<sup>34</sup> 6,8-cycloeudesmene **939** has been identified from *Solidago gigantea*,<sup>129</sup> and 2,4-cycloeudesm-12,8-olide **940** is a constituent of *Ondetia linearis*.<sup>109</sup> The isomeric eudesma-13-acids **941**<sup>566</sup> and **942**<sup>560</sup> have been found in *Tithonia diversifolia*, and **943–947** were obtained from *Inula macrophylla*.<sup>480</sup>



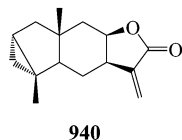
936

937

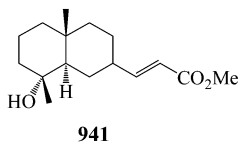
938



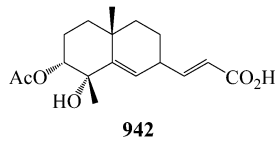
939



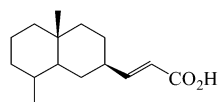
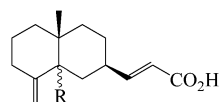
940



941



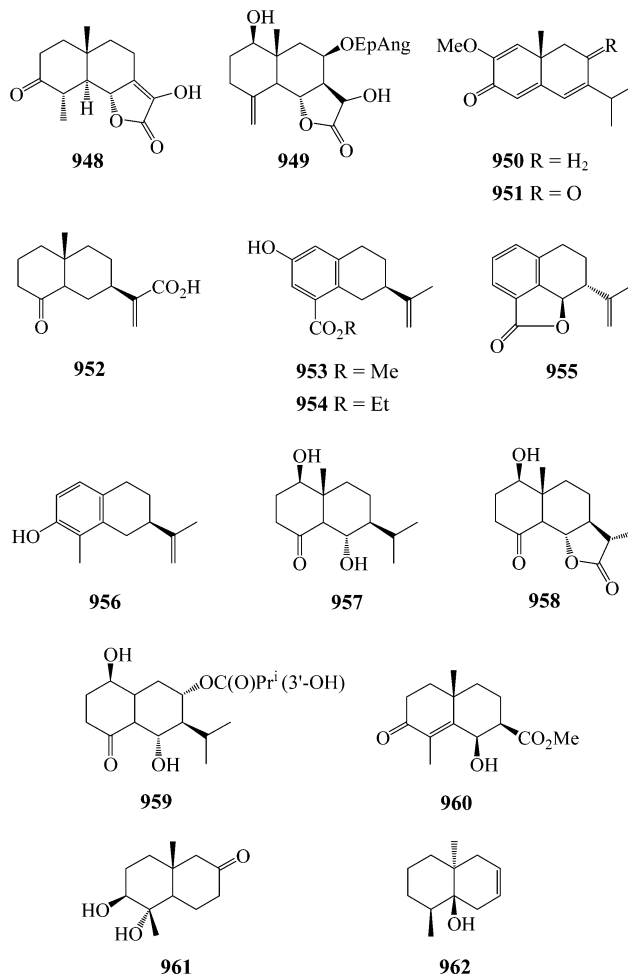
942

943  $\Delta^{(5)}$ 944 4 $\alpha$ ,5 $\alpha$ -epoxy945 4 $\beta$ ,5 $\beta$ -epoxy946 R =  $\alpha$ -OH947 R =  $\beta$ -OH

## 6 Noreudesmanes

15-Noreudesmanes **950** and **951** are elaborated by *Parthenium argentatum*,<sup>137</sup> and eudesmanes **952** and **958** have been isolated from *Apalochlamys spectabilis*<sup>197</sup> and *Microlabium polymniodes*<sup>384</sup> respectively. Sesquiterpene **959** has been elucidated from *Onopordon ambigum*,<sup>256</sup> and compound **957** is a constituent of *Erigeron annuus*.<sup>39</sup> A stereoselective synthesis of the norsesquiterpene platyphyllide has been achieved.<sup>567</sup>

14-Noreudesmanes **953**, **954**<sup>568</sup> and **956**<sup>133</sup> have been identified from *Ligularia dentata*, and **955** has been isolated from *Senecio gilliesianus*.<sup>569</sup> The 13-noreudesmanes **948** and **949** have been found in *Crepis pygmaea*<sup>570</sup> and *Tithonia pedunculata*,<sup>571</sup> respectively. The norsesquiterpenolide **948** has been synthesised from  $\alpha$ -santonin.<sup>572</sup> Di-noreudesmane **960** has been isolated from *Jasonia montana*,<sup>48</sup> and trinoreudesmanes **961** and **962** have been found in *Pluchea arguta*<sup>252</sup> and *Rebutia marsoneri*,<sup>573</sup> respectively. A practical synthesis of enantiomerically pure (–)-geosmin has been achieved,<sup>574</sup> and the eudesmane sesquiterpene (+)-dehydrogeosmin **962** has been prepared by synthesis.<sup>575</sup> The biosynthesis of the trinorsesquiterpene geosmin in a *Streptomyces* species and also in the liverwort *Fossombronina pusilla* has been investigated. This work revealed that the bacterium produces geosmin *via* 1-deoxy-D-xylose, whilst the liverwort uses the mevalolactone pathway.<sup>576</sup> An efficient procedure for creating precise gene replacements in *Streptomyces coelicolor* has permitted the identification of a protein domain required for the biosynthesis of the trinorsesquiterpene geosmin,



948

949

950 R = H<sub>2</sub>

951 R = O

952

953 R = Me

954 R = Et

955

956

957

958

959

960

961

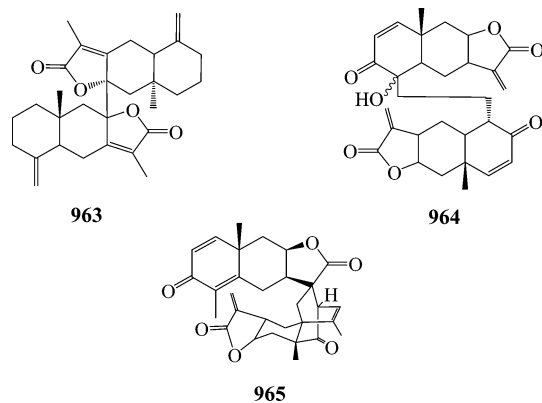
962

the metabolite responsible for the musty-earthly odour of soil.<sup>577</sup> Moreover, the expression and mechanistic analysis of a germacadienol synthase from this *Streptomyces* species, implicated in the biosynthesis of geosmin, has been described.<sup>578</sup> The quantitative determination of this norsesquiterpene in red beets and wheat grain<sup>579</sup> has also been reported.

## 7 Dimers

### 7.1 Dieudesmanes

The bis-sesquiterpene biatractylode **963** has been found in an extract of the Chinese medicinal herb *Atractylodes macrocephala*.<sup>580,581</sup> A biomimetic synthesis of the bis-sesquiterpenes biatractylolide and biepiasterolide has been achieved.<sup>582,583</sup> A dimeric eudesmanolide, hydroxyl-bis-dihydroencelin **964**, has been found as a component of the aerial parts of *Montanoa speciosa*,<sup>584</sup> and the structure of 2(11'),5(13')-dieudesmane **965** from *Ferreyranthus fruticosus* has been elucidated.<sup>251</sup> The structure of the dimeric lactone biatractylolide has been determined by X-ray analysis.<sup>585</sup>



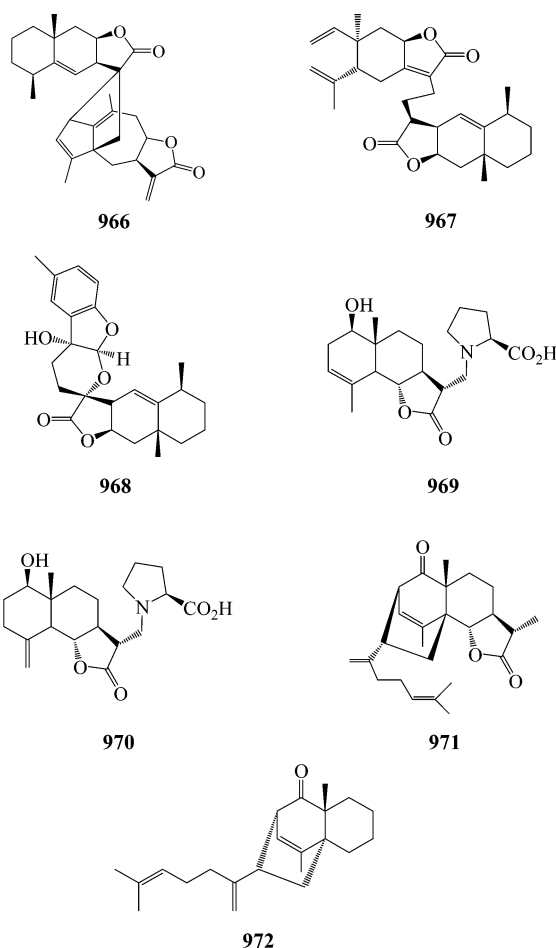
### 7.2 Iso-dimers

Rudbeckiolide **966**, a new dimeric sesquiterpene lactone with a eudesmane and a guaiane skeleton, has been obtained in low yield from *Rudbeckia laciniata*.<sup>586</sup> Compound **968** and macrophyllidimer A **967** are two novel sesquiterpenes, which have been found in an extract from the bark of *Inula macrophylla*.<sup>587,588</sup> Sausureamines D (**969**) and E (**970**), formed from a eudesmanolide and an alkaloid, have been isolated from *Saussurea lappa*.<sup>589</sup> Two new compounds, **971** and **972**, adducts of a eudesmene lactone with a monoterpene, and of a trinoreudesmane with a monoterpene, have been obtained from *Artemisia herba-alba*.<sup>383</sup>

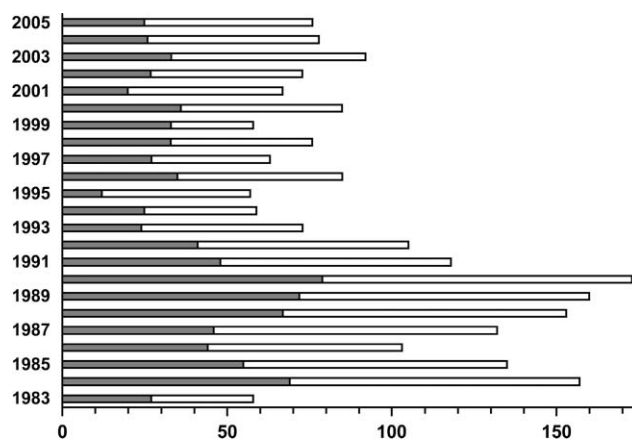
## 8 Conclusions

The Asteraceae family includes many species with a variety of uses, some of which are economically important.<sup>1</sup> The majority of eudesmanolides described in this report were isolated from either the aerial parts or the whole plants, mainly by "traditional" methods, but also by HPLC. The stereochemistry of many compounds was determined conclusively – molecular mechanics methods were also used in a number of cases to calculate conformations and relative stabilities.<sup>590</sup>

The 972 compounds described in this review were isolated from 247 species (of 110 genera), 523 of these compounds belonging to



the eudesmanolide group – a field in which Chinese researchers have been very active. The phytochemistry studies were focused on the large genera: *Artemisia*, *Centaurea*, *Inula*, *Pluchea*, etc. Our literature search has shown that interest in eudesmanoids from the Asteraceae is decreasing (see Fig. 1), although many researchers are still engaged in this area. For the period 1983–1989, the number of eudesmanes reported from the Asteraceae species was 75% of the number from the other higher plants and marine organisms.



**Fig. 1** Distribution of the total number of eudesmanes from 1983 to 2005. The grey part of each bar shows the number of eudesmanes reported from the Asteraceae species. The white part of each bar shows the number of eudesmanes reported from the other higher plants and marine organisms.

For the period 1990–1999, this proportion fell to 65%, and for the period 2000–2005, it fell again to 50%.

In the early years of eudesmanoid research there was less emphasis on biological testing, but increasingly there has been a focus on the biological properties of these compounds. Therefore the starting point for many investigations is the use of plants in traditional medicine, followed by the isolation and biological testing of their active principles. The broad and often very promising biological properties of eudesmanoids are very well known. Studies on the semi-synthesis, total synthesis and biotransformation of eudesmane derivatives have been described and have been increasing in number. Structure–activity relationships of sesquiterpene lactones have also been undertaken.<sup>591</sup> However, systematic structure–activity studies with cell cultures or other biological models, which might give insight into the mechanism of activity of eudesmanoids on the molecular level, seem to be absent. This might be a promising direction in which work in the field of eudesmanoids from the Asteraceae may proceed.

Recently, there has been great interest in the study of chemotaxonomy based on secondary metabolites from the Asteraceae family. In these studies, sesquiterpene lactones, which are used as taxonomic markers, are the most studied class of secondary metabolites. More than 4000 sesquiterpene lactones with around 30 different skeletons have so far been reported from several tribes of Asteraceae,<sup>592</sup> from which it is clear that eudesmanoids are particularly widespread, and have special trends of accumulation in particular Asteraceae tribes and subtribes.<sup>593</sup>

## 9 Acknowledgements

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