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The Synthesis of 5-, 6-, 7- and 8-Membered Oxygen-containing Benzo-fused Rings using Alkene Isomerization and Ring-closing Metathesis Reactions

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ABSTRACT

A number of benzo-fused oxygen-containing heterocycles were synthesized from allyl-3-isopropoxy-4-methoxybenzaldehyde using metathesis or an alkene isomerization-metathesis sequence as key synthetic steps. Benzo-fused compounds thus formed included a 3,6-dihydro-1*H*-2-benzoxocine, 1,3-dihydro-benzo[*c*]oxepine, 1*H*-isochromene, 2,3-dihydro-benzo[*b*]oxepine, benzofuran and 2*H*-chromene skeleton, demonstrating the versatility of this methodology.

KEYWORDS

Ring-closing metathesis, isomerization, ruthenium, benzo-fused compounds.

1. Introduction

There are many examples of benzo-fused oxygen-containing heterocycles described in the chemical literature. Examples of 5-, 6-, 7- and 8-membered oxygen-containing benzo-fused rings include the 1- and 2-benzoxepine **1** and **2**, the chromane **3**, the isochromene **4**, the 1-benzofuran **5** and the 2-benzoxocine **6** skeletons (Fig. 1).

Benzo-fused naturally-occurring products with an oxygen atom in the 1-position and unsaturation in the hetero-aromatic ring are known and some representative examples are shown in Fig. 2. Cnidioside B **7**, a substituted 1-benzofuran isolated from the aerial parts of the plant *Ruta graveolens,* was found to possess antimicrobial and cytotoxic activities.[1] Dalbergichromene **8** with a 2*H*-chromene skeleton was isolated from the stem bark and heartwood of the timber tree *Dalbergia sissoo*.[2] Finally, the 1-benzoxepine class of compounds is represented by radulanin L **9**, an interesting bibenzyl isolated from *Radula complanata*.[3]

On the other hand, unsaturated naturally-occurring benzo-fused compounds with the oxygen atom in the 2-position are much more scarce and seem to only occur in more highly oxidized forms; e.g. drypemolundein A **10** isolated from the Cameroonian plant *Drypetes molunduana*.[4] Of interest is that this compound also contains the 1-benzofuran skeleton.

Benzo-fused oxygen-containing heterocycles have also been frequently used as pharmaceutical templates and four examples are highlighted in Fig. 3. An SAR investigation showed that the 2-methyl-1-benzofuran, as shown for general compound **11**, was a critical binding element for a range of orally active FXa inhibitors.[5] 2*H*-chromen-7-yl sulfamate **12** was synthesized as a potential inhibitor of the enzyme steroid sulfatase and is thus important for the treatment of hormone-dependent tumours, e.g. of the breast.[6] Another example in this series is the 1*H*-isochromene compound **13** synthesized by Wünsch and co-workers[7] in their studies of tricyclic amine compounds with potential CNS activity. This research group has also synthesized other substituted 1*H*-isochromene derivatives in their investigations.[8] Finally a lobatamide C analogue **14**, with a large lactone ring, was synthesized as an analogue of the naturally occurring compound and tested for V-ATPase inhibition.[9]

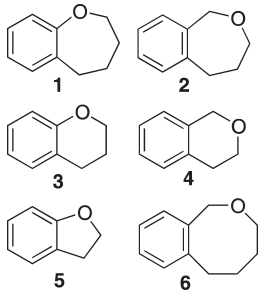

Figure 1

It should therefore not be surprising that there are many published methods for the generation of these types of benzo-fused structural units. One of these potential approaches is by way of ring-closing metathesis (RCM). RCM is a very useful reaction and this methodology needs little introduction.[10] However, the use of base- or metal-mediated isomerization reactions to generate precursors with the alkenes in the required positions for metathesis has only seen modest application in synthesis. This phenomenon of pre- or post-metathesis isomerization is,

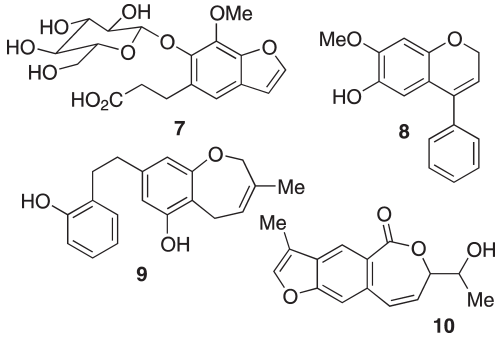

Figure 2

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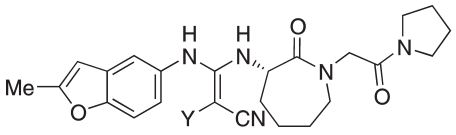
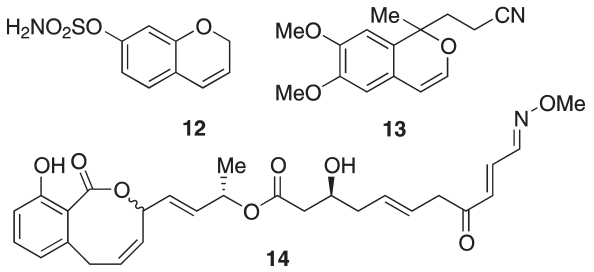
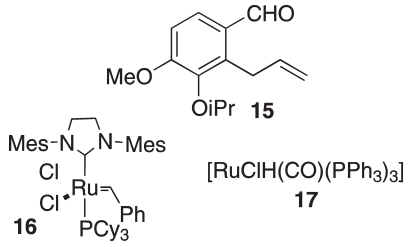


11 Y = wide range of functional groups



12 **13** **14**

Figure 3



15 **16** **17** [RuClH(CO)(PPh$_3$)$_3$]

Figure 4

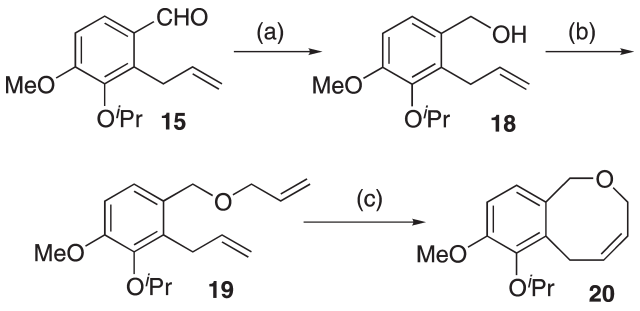
however, very useful and its occurrence in the literature has been high-lighted in recent reviews and accounts by Schmidt.[11] Our group[12a–h] and others[13] have made extensive use of isomerization, followed by ruthenium-mediated metathesis, to synthesize a range of benzo-fused compounds.[12i]

In this paper we aim to demonstrate the power of alkene isomerization reactions coupled to the use of RCM reactions by generating examples of the *O*-containing benzo-fused compounds **1–6**, of different ring sizes, from the same precursor **15**.[14] This compound has been extensively used in our work before as a scaffold for the formation of other benzo-fused compounds.[15] The organometallic catalysts that we used in this study were the ruthenium based Grubb's second-generation catalyst **16** and the isomerization catalyst **17**.[16]

2. Results and Discussion

The initial synthetic work focused on the synthesis of the 8-membered 3,6-dihydro-1*H*-2-benzoxocine skeleton, communicated earlier.[12a] To this end compound **15** was converted into the bis-allyl precursor **19** by initial reduction of the aldehyde group with lithium aluminum hydride to afford the substituted benzyl alcohol **18**. This reaction was followed by an allylation of the primary alcohol to give the desired compound **19**. The subsequent metathesis reaction on this substrate afforded the desired 1*H*-2-benzoxocine **20** in a moderate yield of 52%. The ^{1}H NMR spectrum of compound **20** depicted the alkene peaks of the heterocyclic ring as multiplets at δ 5.54–5.61 and 5.82–5.91 and the HRMS molecular ion for the compound, 248.1413, compared well with the calculated value for $C_{15}H_{20}O_3$: 248.1412. Finally, confirmation of the structure of **20** was provided by comparison of our NMR data with data for a number of other 3,6-dihydro-1*H*-2-benzoxocines generated by metathesis.[17]

To synthesize the 7-membered 1,3-dihydro-2-benzoxepine ring system **22**, we needed to access a precursor that contained a styrene functionality rather than the allyl found at C-2 of compound **19**. Therefore we attempted to isomerize the allyl group of compound **19** with [RuClH(CO)(PPh$_3$)$_3$] **17** but this led to mixtures of desired product **21** and a partially characterized benzaldehyde, probably formed by the deallylation of the benzyl alcohol followed by oxidation. As a satisfactory solution to this problem we found that treatment of the bis-allyl compound **19** with potassium *t*-butoxide, under very mild conditions, resulted in the formation of product **21**. Inspection of the NMR spectra of this compound proved that **21** was a mixture of *E,Z*-isomers and it was clear that a selective isomerization to afford the styrene had occurred. To the best of our knowledge, this type of selective isomerization process with potassium *t*-butoxide is not well known[12d] and confirmation of precisely which allyl group had isomerized was readily provided by NMR spectroscopy. It was clear, from the respective ^{1}H NMR spectra, that the ArCH$_2$ peak (a multiplet at ~δ 3.5 in the spectrum of **19**) had disappeared while the OCH$_2$ peak (a multiplet at ~δ 4.0) was still evident in both the ^{1}H NMR spectra of compounds **19** and **21**. Furthermore, the ArCH$_2$ peak in the ^{13}C NMR spectrum of **19** (δ 30.6) had been replaced in the corresponding spectrum of **21** by a peak for the newly formed methyl group at δ 19.2.

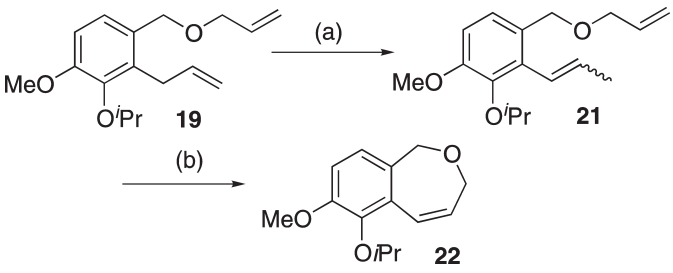


Scheme 1

Reagents and conditions: (**a**) LiAlH$_4$, THF, 0°C, N$_2$, 12 h, 86%; (**b**) allyl bromide, NaH, THF, reflux, N$_2$, 20 h, 77%; (**c**) **16** (5 mol %), toluene, 60°C, N$_2$, 2 h, 52%.

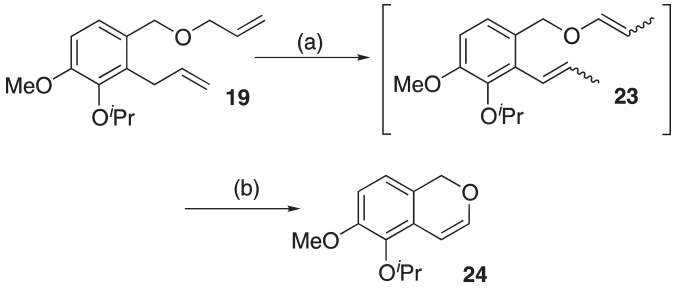
Gratifyingly, when compound **21** was subjected to metathesis it afforded 1,3-dihydro-6-isopropoxy-7-methoxy-2-benzoxepine **22** in an acceptable yield (64%) along with some unreacted starting material **21** (28%). Confirmation of the structure of **22** was once again supplied by NMR spectroscopy. The proposed position of the alkene, conjugated to the aromatic ring, was supported by the ^{13}C NMR spectrum as the only methylene signals occurred at δ 72.8 and 73.0, indicating that both were adjacent to the ring oxygen atom. Finally, the HRMS for compound **22** (calculated for $C_{14}H_{18}O_3$: 234.1256, found: 234.1256) confirmed that a metathetic cyclization had occurred on substrate **21**. A point to note is that this example represents the first use of metathesis to form the 2-benzoxepine skeleton.

Finally we also decided to synthesize the oxygen-containing



Scheme 2

Reagents and conditions: (**a**) KOBu^t, DMF, r.t., N$_2$, 16 h, quantitative; (**b**) **16** (5 mol %), toluene, 80°C, N$_2$, 2 h, 64% and recovered **21** 28%.



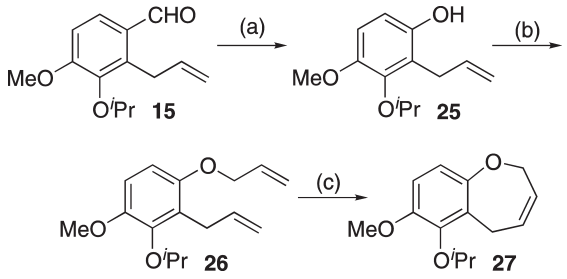
Scheme 3

Reagents and conditions: (**a**) **17** (0.5 mol %), toluene, 60°C, N_2, 2 h, 52%; (**b**) **16** (5 mol %), toluene, 60°C, N_2, 2 h, 83% over two steps.

heterocycle **24** by way of a bis-isomerization-RCM strategy.[12a] When compound **19** was reacted with catalyst **17** (0.5 mol %) the formation of compound **23** was monitored by TLC and ^{1}H NMR spectroscopy on crude aliquots of the reaction mixture. When the isomerization process was considered complete, Grubb's second-generation catalyst **16** was added to **23** and the 1*H*-isochromene **24** was isolated in a good yield of 83% over two steps after chromatographic purification. In the ^{1}H NMR spectrum of **24** the two alkene peaks were evident as doublets (J = 5.8 Hz) at δ 6.10 and 6.58 and the methylene peak was present as a singlet at δ 4.95. The HRMS spectrum confirmed that a cyclization had taken place to afford 1*H*-isochromene **24** (calculated for $C_{13}H_{16}O_3$: 220.1099, found: 220.1098). Once again, this methodology, involving a bis-isomerization followed by a metathesis reaction, is novel in its application to the synthesis of the 1*H*-isochromene skeleton.[12a]

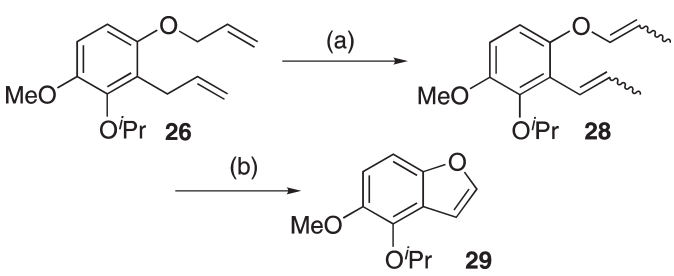
Next we decided to modify substrate **15** by performing a Bayer-Villiger oxidation and subsequent hydrolysis to form phenol **25**; in effect removing a methylene fragment from substrate **18** previously used in our study. Reaction of **15** with acidic H_2O_2 resulted in a good yield of **25** after purification by chromatography.[18] The intermediate ester is assumed to have undergone hydrolysis during the purification step. This compound was then subjected to our standard allylation conditions (allyl bromide, potassium carbonate, acetone, reflux) to afford the bis-allyl system **26**. Once again this substrate readily gave the 7-membered unsaturated 2,5-dihydro-1-benzoxepine system **27** in excellent yield under our standard metathesis conditions. The HRMS molecular ion for this compound, 234.1266, compared well the calculated value for $C_{14}H_{18}O_3$: 234.1256 and the NMR spectra corresponded to the data published for similar 2,5-dihydro-1-benzoxepines in the literature.[18,19]

This same bis-allyl **26** substrate was also exposed to the isomerization catalyst **17** which led to the facile isomerization of both alkenes to the more thermodynamically stable compound



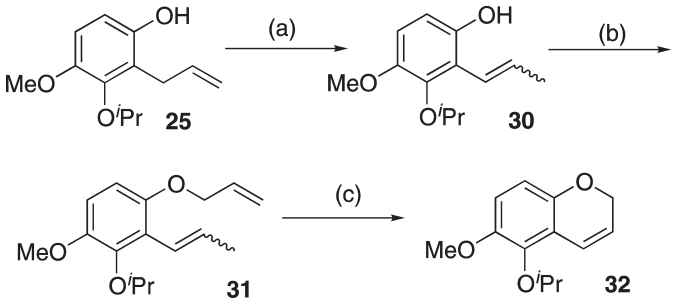
Scheme 4

Reagents and conditions: (**a**) H_2O_2, H_2SO_4, MeOH, 0°C → r.t., N_2, 2 h, 93%; (**b**) allyl bromide, K_2CO_3, acetone, reflux, N_2, 2 h, then r.t., 48 h, 97%; (**c**) **16** (5 mol %), toluene, 60°C, N_2, 13 h, 80%.



Scheme 5

Reagents and conditions: (**a**) **17** (0.5 mol %), toluene, 65°C, N_2, 14 h, 99%; (**b**) **16** (5 mol %), toluene, 60°C, N_2, 14 h, 55%.



Scheme 6

Reagents and conditions: (**a**) **17** (5 mol %), toluene, 65°C, N_2, 23 h, 93%; (**b**) allyl bromide, K_2CO_3, acetone, reflux, Ar, 20 h, 75%; (**c**) **16** (5 mol %), toluene, 60°C, N_2, 2 h, 76%.

28 as a mixture of *E*- and *Z*-alkenes. Treatment of this substrate with Grubb's II catalyst **16** afforded the substituted benzofuran **29** in an analogous manner to previous work published by us.[12f] Of interest is that this compound has been synthesized before albeit using different methodology to insert the vinyloxy group[20] and the spectral data generated for compound **29** compared well with that published in the literature.

Finally we wished to extend our methodology to synthesize the corresponding 2*H*-chromene from the precursor **25**, in a similar manner to what we have published before for chromene systems.[12g] Firstly we attempted a selective isomerization on bis-allyl compound **26** but were unable to find the conditions to successfully achieve this reaction. We were thus forced to change our strategy and fortunately the isomerization of **25** occurred without mishap resulting in the formation of the desired styrene **30** in good yield. A standard O-allylation reaction[21] then readily afforded **31** which underwent a RCM reaction to afford 6-methoxy-5-isopropoxy-2*H*-chromene **32** in a moderate yield.[22] The HRMS molecular ion for compound **32**, 220.1101, compared well with the calculated value for $C_{13}H_{16}O_3$: 220.1099, confirming that the metathesis reaction had successfully generated the 2*H*-chromene skeleton.

3. Conclusion

In this paper we have demonstrated the advantage of the strategic application of metathesis and isomerization methodologies to synthesize oxygen-containing benzo-fused compounds: 1*H*-2-benzoxocine **20**, 2-benzoxepine **22**, 1*H*-isochromene **24**, 1-benzoxepine **27**, 1-benzofuran **29** and 2*H*-chromene **32**. All were synthesized from a common precursor, the benzaldehyde **15**, underlining the strength of this methodology. We are presently using this synthetic approach towards the syntheses of various naturally-occurring compounds and their analogues.

4. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-200, Bruker 300 or Bruker DRX 400 spectrometer at the frequency indicated. All ^{13}C signals in the aromatic/alkene region have been assigned as quaternary (C) or non-quaternary (CH). Infrared spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Macherey-Nagel kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography. All solvents used for reactions and chromatography were distilled prior to use. In certain cases solvents were degassed by bubbling argon gas through the solvent for 15 min.

(2-Allyl-3-isopropoxy-4-methoxyphenyl)methanol 18. 2-Allyl-3-isopropoxy-4-methoxybenzaldehyde **15** (1.01 g, 4.32 mmol) was dissolved in dry THF (30 cm^3). The solution was cooled to 0°C before $LiAlH_4$ (0.32 g, 8.5 mmol) was added slowly. The resulting mixture was then heated to 40°C and stirred under a N_2 atmosphere for 12 h. After that, the reaction mixture was quenched with an aqueous hydrochloric acid solution (5%, 100 cm^3). The aqueous layer was then extracted with Et_2O (2 × 30 cm^3) followed by dry CH_2Cl_2 (2 × 30 cm^3). The organic layer was then combined and dried ($MgSO_4$). The residue was then purified by silica gel column chromatography (20–30% EtOAc-hexane) to afford the desired benzyl alcohol **18** as a clear oil (0.868 g, 86%). ν_{max} (film)/cm^{-1} (NaCl plate) 3447 br, 2975, 1637, 1601, 1579, 1488, 1466, 1437, 1407, 1382, 1369 and 1345; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) 1.27 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 2.06 (1H, s, OH), 3.55–3.57 (2H, m, ArCH_2CHCH$_2$), 3.82 (3H, s, OCH_3), 4.51 [1H, sept, J = 6.2Hz, CH(CH$_3$)$_2$], 4.60 (2H, s, ArCH_2OH), 4.91–5.02 (2H, m, CH$_2$CHCH_2), 5.93–6.04 (1H, m, CH$_2$CHCH$_2$), 6.77 (1H, d, J = 8.4Hz, 5-H) and 7.05 (1H, d, J = 8.4Hz, 6-H); ^{13}C NMR (75 MHz; $CDCl_3$) 22.6 [CH(CH$_3$)$_2$], 30.6 (ArCH$_2$CHCH$_2$), 55.6 (OCH$_3$), 63.3 (ArCH$_2$OH), 74.5 [CH(CH$_3$)$_2$], 110.1 (CH), 115.0 (CH), 123.9 (CH), 132.3 (CH), 137.7 (C), 137.8 (C), 145.1 (C) and 152.5 (C); MS *m/z* 236 (M$^+$, 100%), 209 (24), 194 (71), 193 (61), 177 (58), 163 (38) and 161 (64); HRMS calculated for $C_{14}H_{20}O_3$: 236.1412, found: 236.1412.

2-Allyl-1-[(allyloxy)methyl]-3-isopropoxy-4-methoxybenzene 19. (2-Allyl-3-isopropoxy-4-methoxyphenyl)methanol **18** (0.25 g, 1.06 mmol) and allyl bromide (0.11 cm^3, 1.3 mmol) were dissolved in dry THF (20 cm^3). NaH (60% in oil, 0.076 g, 3.2 mmol) was then added to the clear solution. The reaction mixture was heated under reflux for 20 h under a N_2 atmosphere while stirring. Workup was done by adding H_2O (50 cm^3) and subsequent extraction of the organic material with Et_2O (3 × 30 cm^3). The organic layer was combined, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was then purified by silica gel column chromatography (20% EtOAc-hexane) to afford the desired product **19** as a clear oil (0.225 g, 77%). ν_{max} (film)/cm^{-1} (NaCl plate) 1638, 1601, 1580, 1489, 1466, 1437 and 1381; ^{1}H NMR (300 MHz, $CDCl_3$, assignments with same superscript may be interchanged) 1.27 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.52–3.54 (2H, m, ArCH_2CHCH$_2$), 3.82 (3H, s, OCH_3), 3.99–4.01 (2H, m, OCH_2CHCH$_2$), 4.44 (2H, s, ArCH$_2$O), 4.50 [1H, sept, J = 6.2Hz, CH(CH$_3$)$_2$], 4.89–4.98 (2H, m, CH$_2$CHCH_2),[a] 5.17–5.32 (2H, m, OCH$_2$CHCH_2),[a] 5.85–6.02 (2H, m, ArCH$_2$CH=CH$_2$ and OCH$_2$CH=CH$_2$), 6.75 (1H, d, J = 8.4Hz, 5-H) and 7.04 (1H, d, J = 8.4Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$, assignments with same superscript may be interchanged) 22.6 [CH(CH$_3$)$_2$], 30.6 (ArCH$_2$CHCH$_2$), 55.6 (OCH$_3$), 70.1 (ArCH$_2$O),[b] 71.1 (OCH$_2$CH=CH$_2$),[b] 74.5 [CH(CH$_3$)$_2$], 109.8 (CH), 114.8 (CH), 117.0 (CH), 124.4 (CH), 129.6 (C), 132.9 (C), 135.0 (CH), 136.9 (CH), 145.1 (C) and 152.6 (C); MS *m/z* 276 (M$^+$, 92%), 193 (15), 178 (52), 177 (85), 176 (100), 161 (59) and 145 (32); HRMS calculated for $C_{17}H_{24}O_3$: 276.1725, found: 276.1726.

7-Isopropoxy-8-methoxy-3,6-dihydro-1*H*-2-benzoxocine 20. To a solution of 2-allyl-1-[(allyloxy)methyl]-3-isopropoxy-4-methoxybenzene **19** (0.20 g, 0.72 mmol) in toluene (60 cm^3), was added Grubb's catalyst **16** (5 mol %, 0.031 g, 0.04 mmol) and the reaction mixture was stirred at 60°C for 2 h The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography (2–10% EtOAc-hexane) to give the desired cyclized product **20** as a clear oil (0.092 g, 52%). ν_{max} (film)/cm^{-1} (NaCl plate) 1269, 1381, 1436, 1488, 1574 and 1598; ^{1}H NMR (300 MHz, $CDCl_3$, assignments with same superscript may be interchanged) 1.21 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.67 (2H, d, J = 7.2 Hz, 6-H), 3.75 (3H, s, OCH$_3$), 4.08 (2H, d, J = 4.9 Hz, 3-H), 4.35 [1H, sept, J = 6.2 Hz, CH(CH$_3$)$_2$], 4.73 (2H, s, 1-H), 5.54–5.61 (1H, m, 4-H),[a] 5.82–5.91 (1H, m, 5-H),[a] 6.64 (1H, d, J = 8.3 Hz, 9-H) and 6.75 (1H, d, J = 8.3 Hz, 10-H); ^{13}C NMR (75 MHz; $CDCl_3$, assignments with same superscript may be interchanged) 22.6 [CH(CH$_3$)$_2$], 25.9 (6-C), 55.7 (OCH$_3$), 66.3 (3-C),[a] 72.2 (1-C),[a] 74.8 [CH(CH$_3$)$_2$], 109.5 (CH), 123.7 (CH), 127.9 (CH), 130.1 (C), 131.7 (CH), 133.6 (C), 144.3 (C) and 152.8 (C); MS *m/z* 248 (M$^+$, 100%), 206 (29), 177 (20), 175 (16), 161 (18), 143 (17) and 117 (12); HRMS calculated for $C_{15}H_{20}O_3$: 248.1412, found: 248.1413.

1-[(Allyloxy)methyl]-3-isopropoxy-4-methoxy-2-(1-propenyl) benzene 21. 2-Allyl-1-[(allyloxy)methyl]-3-isopropoxy-4-methoxybenzene **19** (0.10 g, 0.39 mmol) was dissolved in distilled DMF (15 cm^3). KOBu^t (0.044 g, 0.36 mmol) was added slowly to the clear solution at r.t. The mixture was then stirred under a N_2 atmosphere at r.t. for 16 h The reaction mixture was then quenched with aqueous HCl (5%, 50 cm^3), followed by extraction of the aqueous layer with CH_2Cl_2 (3 × 30 cm^3). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was then purified by silica gel column chromatography (10–20% EtOAc-hexane) to afford the desired product **21** as a clear oil (0.099 g, quantitative, *E:Z* 5:1). ν_{max} (film)/cm^{-1} (NaCl plate) 1597, 1573, 1484, 1425 and 1381; ^{1}H NMR (300 MHz; $CDCl_3$, only *E*-isomer listed) 1.24 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 1.90 (3H, dd, J = 6.6 and 1.6 Hz, CHCHCH_3), 3.81 (3H, s, OCH$_3$), 4.01–4.04 (2H, m, OCH_2CHCH$_2$), 4.32 [1H, sept, J = 6.2 Hz, CH(CH$_3$)$_2$], 4.43 (2H, s, ArCH$_2$O), 5.16–5.33 (2H, m, CH$_2$CHCH_2), 5.90–6.01 (1H, m, CHCHCH$_3$), 6.03–6.17 (1H, m, CH$_2$CHCH$_2$), 6.48 (1H, dd, J = 16.0 and 1.6 Hz, CHCHCH$_3$), 6.76 (1H, d, J = 8.4 Hz, 5-H) and 7.08 (1H, d, J = 8.4 Hz, 6-H); ^{13}C NMR (75 MHz; $CDCl_3$, only *E*-isomer listed, assignments with same superscript may be interchanged) 19.2 (CH$_3$), 22.5 [CH(CH$_3$)$_2$], 55.7 (OCH$_3$), 70.5 (ArCH$_2$O)[a], 71.0 (OCH$_2$CHCH$_2$)[a], 75.1 [CH(CH$_3$)$_2$], 110.0 (CH), 116.9 (CH), 123.6 (C), 124.9 (CH), 125.0 (CH), 128.5 (C), 131.6 (CH), 135.0 (CH), 144.9 (C) and 152.7 (C); MS *m/z* 276 (M$^+$, 87%), 193 (100), 178 (38), 175 (63) and 161 (55); HRMS calculated for $C_{17}H_{24}O_3$: 276.1725, found: 276.1725.

6-Isopropoxy-7-methoxy-1,3-dihydro-2-benzoxepine 22. To 1-[(allyloxy)methyl]-3-isopropoxy-4-methoxy-2-(1-propenyl) benzene **21** (0.12 g, 0.43 mmol) in toluene (12 cm^3) was added to Grubb's catalyst **16** (5 mol %, 0.018 g, 0.02 mmol) and the reaction mixture was stirred at 60°C for 2 h and then heated for another 2 h at 80°C. After removal of the solvent, the residue was purified by silica gel chromatography (5–10% EtOAc-hexane) to give the desired cyclized product **22** as a pale yellow oil (0.065 g, 64%), starting material was also recovered (0.033 g, 28%). ν_{max} (film)/cm^{-1} (NaCl plate) 1598, 1578, 1487, 1434, 1402, 1380 and

1342; ^{1}H NMR (300 MHz; $CDCl_3$) 1.29 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.82 (3H, s, OCH_3), 4.39 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 4.53–4.54 (2H, m, 3-H), 4.55 (2H, s, 1-H), 5.83–5.90 (1H, m, 4-H), 6.72 (1H, d, J = 8.2 Hz, 8-H), 6.83 (1H, d, J = 8.2 Hz, 9-H) and 6.90–6.96 (1H, m, 5-H); ^{13}C NMR (75 MHz; $CDCl_3$, assignments with same superscript may be interchanged) 22.5 [CH(CH_3)$_2$], 55.8 (OCH_3), 72.8 (3-C)[a], 73.0 (1-C)[a], 75.7 [CH(CH_3)$_2$], 110.3 (CH), 122.3 (CH), 123.1 (CH), 123.5 (C), 132.2 (CH), 132.9 (C), 145.3 (C) and 152.7 (C); MS *m/z* 234 (M^+, 81%), 192 (62), 177 (100) and 164 (38); HRMS calculated for $C_{14}H_{18}O_3$: 234.1256, found: 234.1256.

5-Isopropoxy-6-methoxy-1*H*-isochromene 24. To a degassed solution of 2-allyl-1-[(allyloxy)methyl]-3-isopropoxy-4-methoxybenzene **19** (0.10 g, 0.36 mmol) in toluene (20 cm^3) was added RuClH(CO)(PPh_3)$_3$ (1.5 mol %, 0.005 g, 0.005 mmol). The mixture was heated at 60°C for 2 h under a N_2 atmosphere. Afterwards Grubb's catalyst **16** (5 mol %, 0.015 g, 0.018 mmol) was added and the mixture was stirred for another 2 h at 60°C. After cooling the mixture, the toluene was evaporated under reduced pressure. The organic extract was then subjected to column chromatography (5–20% EtOAc-hexane) to afford the desired cyclized product **24** as a clear oil (0.066 g, 83%). ν_{max}(film)/cm^{-1} (NaCl plate) 1623, 1483, 1438 and 1382; ^{1}H NMR (300 MHz, $CDCl_3$, assignments with same superscript may be interchanged) 1.28 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.81 (3H, s, OCH_3), 4.39 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 4.95 (2H, s, 1-H), 6.10 (1H, d, J = 5.8 Hz, 4-H),[a] 6.58 (1H, d, J = 5.8 Hz, 3-H),[a] 6.67 (2H, br s, 7-H and 8-H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.5 [CH(CH_3)$_2$], 55.8 (OCH_3), 67.7 (1-C), 75.2 [CH(CH_3)$_2$], 101.0 (CH), 109.0 (CH), 119.0 (CH), 121.5 (C), 125.2 (C), 140.4 (C), 145.9 (CH) and 152.8 (C); MS *m/z* 220 (M^+, 78%), 194 (54), 178 (83), 166 (86), 151 (91) and 150 (100); HRMS calculated for $C_{13}H_{16}O_3$: 220.1099, found: 220.1098.

2-Allyl-3-isopropoxy-4-methoxyphenol 25. 35% H_2O_2 (1.8 cm^3) was added dropwise to a cooled (ice bath) solution of 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **15** (2.0 g, 8.5 mmol) in MeOH (22 cm^3).[18] To this solution was immediately added concentrated H_2SO_4 (3 drops) and the reaction mixture was allowed to warm to r.t. The reaction mixture was stirred at this temperature until TLC confirmed that the aldehyde had been consumed (1.5–2 h). The MeOH was removed under reduced pressure and water (15 cm^3) was then added to the resultant residue. The aqueous layer was extracted with EtOAc (3 × 10 cm^3), subsequently followed by washing of the organic phase with brine solution (2 × 5 cm^3) and drying ($MgSO_4$). The solvent was removed under vacuum and the resultant residue was then purified by silica gel chromatography (10–15% EtOAc-hexane) to give the desired product **25** as a pale yellow semi-solid (1.75 g, 93%). ν_{max} (film)/cm^{-1} (NaCl plate) 3354 br, 1501, 1459 and 1254; ^{1}H NMR (300 MHz; $CDCl_3$) 1.29 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.52 (2H, br d, J = 6.0 Hz, CH_2CHCH$_2$), 3.78 (3H, s, OCH_3), 4.48 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 4.85 (1H, br s, OH, D_2O exchangeable), 5.13–5.19 (2H, m, CH_2CHCH_2), 5.92–6.05 (1H, m, CH_2CHCH_2), 6.53 (1H, d, J = 8.8 Hz, 5-H) and 6.70 (1H, d, J = 8.8 Hz, 6-H); ^{13}C NMR (75 MHz; $CDCl_3$) 22.6 [CH(CH_3)$_2$], 29.0 (CH_2CHCH$_2$), 56.3 (OCH_3), 74.8 [CH(CH_3)$_2$], 110.2 (CH), 111.5 (CH), 116.2 (CH), 120.4 (C), 136.3 (CH), 145.5 (C), 147.3 (C) and 149.2 (C); MS *m/z* 222 (M^+, 52%), 180 (80), 165 (100), 137 (43) and 119 (16); HRMS calculated for $C_{13}H_{18}O_3$: 222.1256, found: 222.1268.

2-Allyl-1-(allyloxy)-3-isopropoxy-4-methoxybenzene 26. Allyl bromide (0.22 cm^3, 2.5 mmol) and K_2CO_3 (0.35 g, 2.5 mmol) were added to 2-allyl-3-isopropoxy-4-methoxyphenol **25** (0.28 g, 1.3 mmol) dissolved in acetone (10 cm^3) and the reaction slurry was then stirred at reflux for 2 h and then at r.t. for 48 h After cooling, the excess K_2CO_3 was removed by filtration and the solvent was removed under reduced pressure. The resultant brown residue was then purified using silica gel column chromatography (10–20% EtOAc-hexane) to afford compound **26** as a pale yellow oil (0.32 g, 97%). ν_{max} (film)/cm^{-1} (NaCl plate) 1558; ^{1}H NMR (300 MHz; $CDCl_3$) 1.19 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.39 (2H, br d, J = 6.2 Hz, ArCH_2CHCH$_2$), 3.70 (3H, s, OCH_3), 4.39 (2H, br d, J = 5.0 Hz, ArOCH_2CHCH$_2$), 4.45 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 4.84–4.96 (2H, m, CH_2CHCH_2), 5.16 [1H, dd, J = 10.6 and 1.5 Hz, CH_2CHC(H)H], 5.30–5.36 [1H, m, CH_2CHC(H)H], 5.85–6.01 (2H, m, 2 × CH_2CHCH_2), 6.45 (1H, d, J = 8.8 Hz, 5-H) and 6.60 (1H, d, J = 8.8 Hz, 6-H); ^{13}C NMR (75 MHz; $CDCl_3$) 22.6 [CH(CH_3)$_2$], 28.9 (ArCH$_2$CHCH$_2$), 56.1 (OCH_3), 69.4 (ArOCH$_2$CHCH$_2$), 74.6 [CH(CH_3)$_2$], 106.4 (CH), 110.0 (CH), 114.4 (CH), 116.6 (CH), 124.0 (C), 133.8 (CH), 136.9 (CH), 145.8 (C), 147.5 (C) and 151.4 (C); MS *m/z* 262 (M^+, 53%), 220 (28), 179 (100), 147 (68), 73 (30) and 41 (24); HRMS calculated for $C_{16}H_{22}O_3$: 262.1569, found: 262.1589.

6-Isopropoxy-7-methoxy-2,5-dihydro-1-benzoxepine 27. 2-Allyl-1-(allyloxy)-3-isopropoxy-4-methoxybenzene **26** (0.10 g, 0.38 mmol) was dissolved in toluene (10 cm^3) and Grubb's catalyst **16** (5 mol%, 0.016 g, 0.019 mmol) was added. The reaction mixture was then stirred at 60°C for 13 h After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (5–20% EtOAc-hexane) to give the desired cyclized product **27** as a pale yellow oil (0.070 g, 80%). ν_{max} (film)/cm^{-1} (NaCl plate) 1672, 1569, 1481, 1377 and 1262; ^{1}H NMR (300 MHz; $CDCl_3$) 1.26 [6H, d, J = 6.1 Hz, CH(CH_3)$_2$], 3.53–3.56 (2H, m, 5-H), 3.84 (3H, s, OCH_3), 4.33 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 4.51–4.55 (2H, m, 2-H), 5.40 (1H, br d, J = 11.4 Hz, 4-H), 5.78–5.84 (1H, m, 3-H), 6.67 (1H, d, J = 8.7 Hz, 5-H) and 6.77 (1H, d, J = 8.7 Hz, 6-H); ^{13}C NMR (75 MHz; $CDCl_3$) 22.5 [CH(CH_3)$_2$], 29.7 (5-C), 56.0 (OCH_3), 71.9 (2-C), 75.2 [CH(CH_3)$_2$], 109.9 (CH), 115.7 (CH), 125.7 (CH), 127.7 (CH), 132.0 (C), 143.7 (C), 149.9 (C) and 152.9 (C); MS *m/z* 234 (M^+, 37%), 206 (11), 192 (17), 177 (100) and 131 (15); HRMS calculated for $C_{14}H_{18}O_3$: 234.1256, found: 234.1266.

2-Isopropoxy-1-methoxy-3-(1-propenyl)-4-(1-propenyloxy) benzene 28. 2-Allyl-1-allyloxy-3-isopropoxy-4-methoxybenzene **26** (0.084 g, 0.36 mmol) and [RuClH(CO)(PPh_3)$_3$] **17** (0.015 g, 0.016 mmol, 5 mol %) were dissolved in distilled, degassed toluene (5 cm^3). The reaction was heated at 65°C for 14 h and completion of the reaction was confirmed by NMR spectroscopy of a crude sample. The reaction mixture was evaporated to dryness and the resulting residue was purified by silica gel chromatography (10–15% EtOAc-hexane) and evaporated under reduce pressure to afford the product **28** (0.083 g, 99%) as a mixture of *E,Z* isomers. ν_{max} (film)/cm^{-1} (NaCl plate) 1550 and 1475; ^{1}H NMR (300 MHz; $CDCl_3$) 1.26 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 1.72 (3H, dd, J = 6.2 and 1.4 Hz, CHCHCH_3), 1.91 (3H, d, J = 5.1 Hz, CHCHCH_3), 3.79 (3H, s, OCH_3), 4.41 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 4.75–4.80 (1H, m, CHCHCH$_3$), 6.23–6.27 (1H, m, CHCHCH$_3$) and 6.54–6.68 (4H, m, 5-H, 6-H and 2 × CHCHCH$_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 9.4 (CHCHCH$_3$), 20.0 (CHCHCH$_3$), 22.5 [CH(CH_3)$_2$], 56.2 (OCH_3), 75.3 [CH(CH_3)$_2$], 105.6 (CH), 110.2 (CH), 110.7 (CH), 122.1 (CH), 123.5 (CH), 131.6 (CH), 142.4 (CH), 145.5 (C), 149.0 (C) and 149.9 (C); MS *m/z* 262 (M^+, 53%), 220 (16), 205 (27), 191 (100), 177 (18) and 164 (19); HRMS calculated for $C_{16}H_{22}O_3$: 262.1569, found: 262.1583.

4-Isopropoxy-5-methoxy-1-benzofuran 29. 2-Isopropoxy-1-methoxy-3-(1-propenyl)-4-(1-propenyloxy)benzene **28** (0.061 g, 0.23 mmol) was dissolved in degassed toluene (5 cm^3) and

Grubb's catalyst **16** (5 mol%, 0.0010 g, 0.0012 mmol) was added. The reaction mixture was then stirred at 60°C for 3 h After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (5–20% EtOAc-hexane) to give the desired product **29** as a pale yellow oil (0.026 g, 55%). The spectra obtained for compound **29** compared well with that already published in the literature.[20]

3-Isopropoxy-4-methoxy-2-(1-propenyl)phenol 30. 2-Allyl-3-isopropoxy-4-methoxyphenol **25** (1.0 g, 4.5 mmol) and [RuClH(CO)(PPh_3)$_3$] **17** (0.22 g, 0.22 mmol, 5 mol %) were dissolved in distilled, degassed toluene (21 cm^3). The reaction was heated at 65°C for 23 h and the completion of the reaction was confirmed by NMR spectroscopy of a crude sample. The reaction mixture was evaporated to dryness and the resulting residue was purified by silica gel chromatography (5–20% EtOAc-hexane) and evaporated under reduce pressure to afford the product **30** (0.94 g, 93%, *E*:*Z* 3:1). ν_{max} (film)/cm^{-1} (NaCl plate) 3300 (br), 1550, 1477 and 1377; ^{1}H NMR (300 MHz; $CDCl_3$, only *E*-isomer listed) 1.25 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 1.93 (3H, d, J = 6.2 Hz, CHCHCH_3), 3.77 (3H, s, OCH_3), 4.43 [1H, sept, J = 6.2 Hz, CH(CH_3)$_2$], 5.30 (1H, br s, OH), 6.16–6.23 (1H, m, CHCHCH$_3$) and 6.46–6.79 (3H, m, 2 × ArH and CHCHCH$_3$); ^{13}C NMR (75 MHz; $CDCl_3$, only *E*-isomer listed) 19.2 (CHCHCH_3), 22.5 [CH(CH_3)$_2$], 56.5 (OCH_3), 75.2 [CH(CH$_3$)$_2$], 109.6 (CH), 112.1 (CH), 120.4 (C), 124.0 (CH), 131.0 (CH), 145.3 (C), 146.8 (C) and 147.6 (C); MS *m*/*z* 222 (M^+, 61%), 180 (100), 165 (93), 137 (53) and 87 (70); HRMS calculated for $C_{13}H_{18}O_3$: 222.1256, found: 222.1242.

1-(Allyloxy)-3-isopropoxy-4-methoxy-2-(1-propenyl)benzene 31. Allyl bromide (0.33 cm^3, 0.45 g, 3.8 mmol) and K_2CO_3 (0.51 g, 3.8 mmol) were added to 3-isopropoxy-4-methoxy-2-(1-propenyl)phenol 30 (0.42 g, 1.8 mmol) dissolved in acetone (10 cm^3) and the reaction slurry was then stirred at reflux, under an Ar atmosphere, for 20 h After cooling, the base was removed by filtration through a pad of celite and the solvent was removed under reduced pressure. The resultant brown residue was then purified using silica gel column chromatography (10% EtOAc-hexane) to afford compound **31** as a pale yellow oil (0.37 g, 75%, *E*:*Z* 7:3). ν_{max} (film)/cm^{-1} (NaCl plate) 1650, 1479 and 1378; ^{1}H NMR (300 MHz; $CDCl_3$, only *E*-isomer listed) 1.20–1.27 [6H, m, CH(CH_3)$_2$], 1.90 (3H, d, J = 5.6 Hz, CHCHCH_3), 3.78 (3H, s, OCH_3), 4.38–4.49 [3H, m, CH(CH$_3$)$_2$ and OCH_2CHCH$_2$], 5.24–5.28 (1H, m, CH$_2$CHC(*H*)H), 5.37–5.43 (1H, m, CH$_2$CHC(H)*H*), 5.83–6.31 (2H, m, CH$_2$CHCH$_2$ and CHCHCH$_3$) and 6.53–6.68 (3H, m, 2 × ArH and CHCHCH$_3$); ^{13}C NMR (75 MHz; $CDCl_3$, *Z*-isomer listed in brackets) (19.8), 19.9 (CHCHCH_3), 22.5 [CH(CH_3)$_2$], (56.1), 56.3 (OCH_3), (69.7), 69.9 (OCH_2), (75.1), 75.2 [CH(CH$_3$)$_2$], (107.1), 107.3 (CH), 110.3, (110.6) (CH), (116.9), 117.0 (CH), 122.4, (122.8) (CH), 129.1 (C), 131.1, (131.3) (CH), 133.8, (133.9) (CH), 145.7 (C), 147.9 (C), (150.6) and 151.1 (C); MS *m*/*z* 262 (M^+, 66%), 220 (21), 205 (30), 191 (100), 179 (20), 177 (23), 164 (23) and 147 (89); HRMS calculated for $C_{16}H_{22}O_3$: 262.1569, found: 262.1570.

5-isopropoxy-6-methoxy-2*H*-chromene 32. 1-(Allyloxy)-3-isopropoxy-4-methoxy-2-(1-propenyl)benzene **31** (0.31 g, 1.2 mmol) was dissolved in toluene (30 cm^3) and Grubb's catalyst **16** (5 mol %, 0.0050 g, 0.059 mmol) was added. The reaction mixture was then stirred at 60°C for 2 h After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (5% EtOAc-hexane) to give the desired product **32** as a pale yellow oil (0.198 g, 76%). ν_{max} (film)/cm^{-1} (NaCl plate) 1649, 1482 and 1379; ^{1}H NMR (300 MHz; $CDCl_3$) 1.27 [6H, d, J = 6.2 Hz, CH(CH_3)$_2$], 3.77 (3H, s, OCH_3), 4.44 [1H, sept, J = 6.2 Hz, CH(CH$_3$)$_2$], 4.68 (2H, dd, J = 3.6 and 1.8 Hz, 2-H), 5.79 (1H, dt, J = 9.9 and 3.6 Hz, 3-H), 6.49 (1H, d, J = 8.8 Hz, 7-H), 6.66 (1H, d, J = 8.8 Hz, 8-H) and 6.77 (1H, br d, J = 9.9 Hz, 4-H); ^{13}C NMR (75 MHz; $CDCl_3$) 22.5 [CH(CH_3)$_2$], 56.4 (OCH_3), 64.9 (2-C), 75.4 [CH(CH$_3$)$_2$], 109.9 (CH), 112.6 (CH), 118.0 (C), 120.5 (CH), 121.7 (CH), 142.9 (C), 147.4 (C) and 148.2 (C); MS *m*/*z* 220 (M^+, 21%), 205 (30), 191(100), 179 (20), 164 (23) and 147 (89); HRMS calculated for $C_{13}H_{16}O_3$: 220.1099, found: 220.1101.

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References and Notes

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