# Facile access to labdane-type diterpenes: synthesis of coronarin C, zerumin B, labda-8(17), 13(14)-dien-15,16-olide and derivatives from (+)-manool

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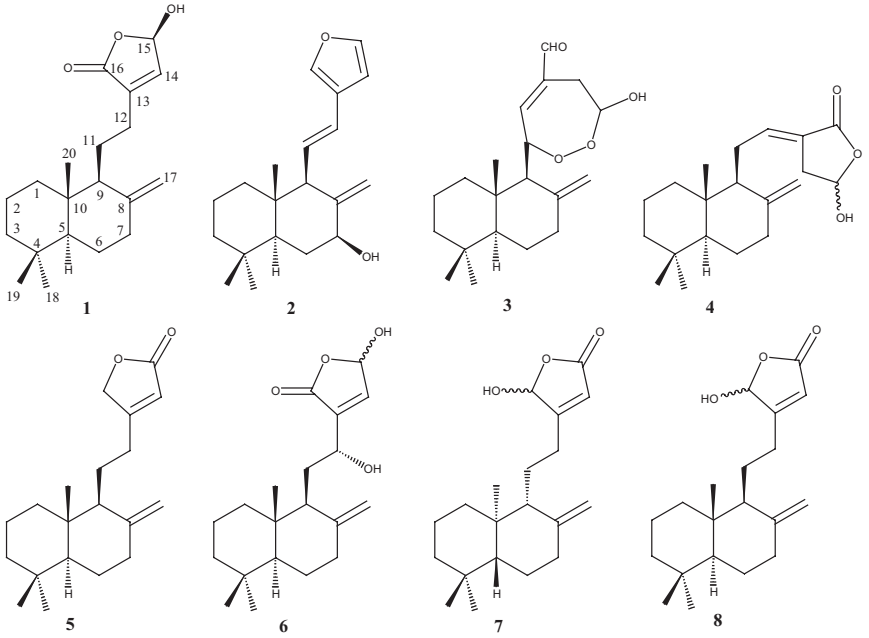
A practical method for the synthesis of optically active labdane-type diterpenes from (+)-manool **8**, is described. We prepared the natural labdane-type diterpene **5** *via* key intermediate peroxide **9** and coronarin C **1**, compound **8** and zerumin B **6** *via* a furan photosensitised oxygenation reactions.

**Keywords:** labdane-type diterpenes, coronarin C, zerumin B, *ent*-labdanes, diterpene

Labdane diterpenoids are among the most common types of diterpenes isolated from plants and sponge.[1] These compounds are interesting for their cytotoxic, antifungal, antiinflammatory, antiparasitic and analgesic properties.[2] However, as in the case of many other natural products, they can be isolated only in minute amounts limiting the study of their biological activities. *Hedychium coronarium* Koeng has been cultivated in Japan, China, India and Brazil. The rhizome of *H. coronarium*, has been used for the treatment of headache, sharp pain and rheumatism.[2] Several labdane-type diterpenes have been isolated from this herbal mediãne. In 1988, Itokawa *et al.*[3] isolated the labdane-type diterpene coronarin C **1** along with coronarin A **2**, B **3**,and D **4** from the rhizomes of *H. coronarium* cultivated in Brazil, showing cytotoxic activity against Chinese hamster V-79 cells. The absolute configuration at C-15 in coronarin C **3** was established to be "*R*" according to the exãton chirality rule, because the benzoate derivative of **3** exhibited a positive Cotton effect.[3] In 2002, Matsuda *et al.*[4] isolated the labdane-type diterpene labda-8(17), 13(14)-dien-15,16-olide **5** from the methanolic extract of the fresh rhizome of *H. coronarium* cultivated in Japan, which showed antiinflamatory activity. (+)-Zerumin B **6** is a bioactive diterpenoid isolated in 1996 by Xu *et al.*[5] from the Chinese mediãnal plant *Alpina zerumbet* and more recently Abas *et al.*[6] isolated this diterpenoid from the rhizomes *Curcuma mangga*, a popular vegetable used in Asian folk mediãne. In 1992, Zdero *et al.*[7] isolated the *ent*-labdane-type diterpene **7** from aerial parts of *Chrysocephalum ambiguum*. A negative Cotton effect and negative sign of optical rotation of that diterpene supported that belong to the *ent*-series. In 2003, Zani *et al.*[8a] isolated *ent*-labdane-type diterpenes from *Alomia myriadenia* showing cytotoxic and trypanoãdal activity. Recently the absolute configuration of some constituents of *Alomia myriadenia* has been changed as a result of their preparation from (+)-sclareolide.[8b]

To date, a number of semi-syntheses of these biologically active labdane-type diterpenoids have been reported employing (–)-sclareol and (+)-sclareolide as a starting material.[8b,9,10] In 1982, Nakano *et al.*[11] reported the synthesis of some labdane-type diterpenes such as lactone **5** from (+)-manool **9**, but with poor yield. Recently we have developed a new highly effiãent synthesis of optically active labdane-related natural products. The key reaction consists of the dehydration of commerãally available (+)-manool **9** and photooxidation of the resulting diene to give the peroxide **10**.[12] Continuing with our research in the synthesis of the labdane-type diterpenes, we have been interested in the development of synthetic routes to coronarin C **1**, natural diterpene **5** and

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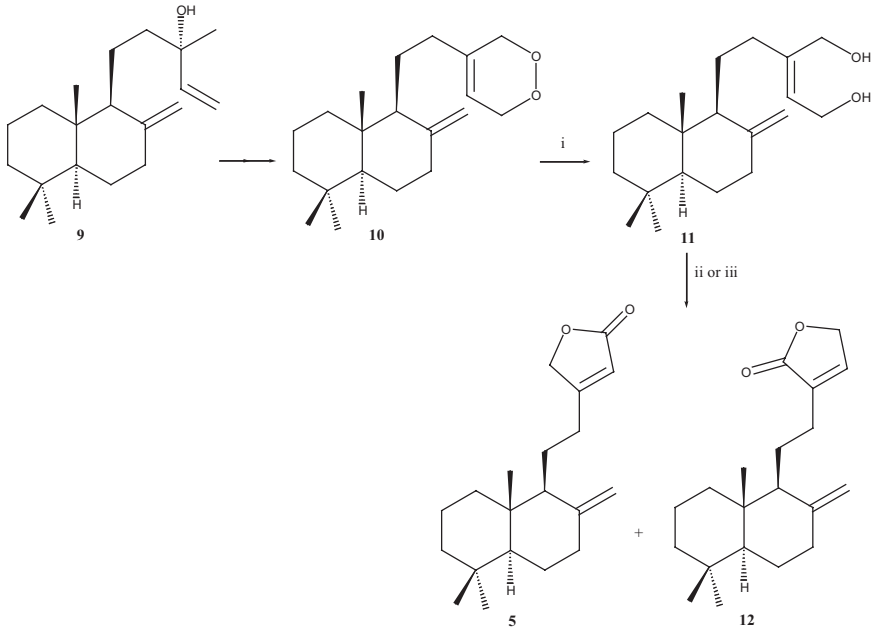
zerumin B **6**. In addition, to confirming the structure proposed for compound **7**, we report the synthesis of compound **8** having a normal configuration instead of natural *ent*-series proposed for **7**.

The first step of the synthetic sequence involves reduction of peroxide **9**, whose effiãent synthesis from (+)-manool **9** has been previously reported by the present authors.[12] Reduction of compound **10** with $LiAlH_4$ afforded the labda-8(17),13(*Z*)-diene-15,16-diol **11**.[12] In order to synthesise the title compound **5**, compound **11** was submitted to oxidative lactonisation. A satisfactory completion of the synthesis of lactone **5** required a selective oxidation of the C-15 hydroxymethyl group of the diol **11**. Oxidation with tetra-*n*-propylammonium perruthenate (TPAP)[13] yielded a mixture of lactones **5** and **12** as shown from the $^1$H NMR spectrum. Separation of this mixture over silica gel failed. It has been found that silver carbonate absorbed on celite (Fétizon's reagent)[14] is a neutral oxidising agent which selectively transforms primary diols to lactones. Oxidation of compound **11** with Fétizon's reagent[14] afforded the desired lactone **5** in good yield, whose physical and spectroscopic properties were identical with those reported,[3,11] only small amount of isomeric lactone **12** was isolated (Scheme 1).

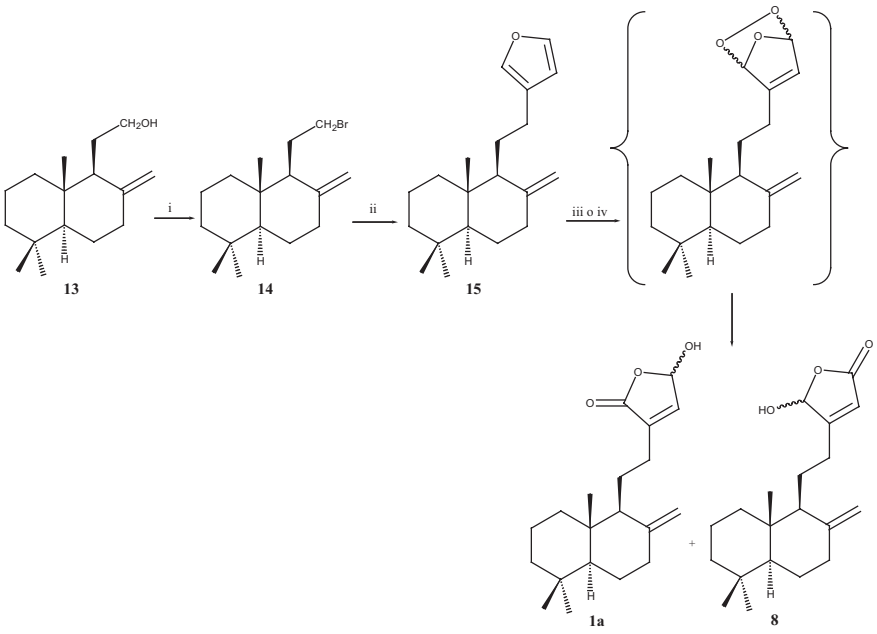
Compound **15** has been prepared previously by different methods.[12] In an attempt to increase the yield of the compound **15**, we first prepared the alcohol **13**.[12] Bromination of alcohol **13** with carbon tetrabromide and triphenylphosphine ($Ph_3P$) under neutral conditions gave the corresponding bromide **14**. The nucleophilic addition of the organolithium compound, derived from 3-bromofuran, to the bromide **14** afforded the desired compound **15** whose physical and spectroscopic properties were identical with those reported.[12] With compound **15** in hand, we continued the oxidation of furan ring to obtain the desired hydroxybutenolides. The photooxidation of 3-substituted furans is not regiospeãfic, yielding both the 2-alkyl-4-hydroxy- and the 3-alkyl-4-hydroxybutenolide regioisomers.[15] Irradiation of labdafuran **15** in THF (external 150 W halogen-tungsten lamps, Pyrex well) in the presence of oxygen and catalytic amount of Rose Bengal afforded a mixture of two regioisomeric hydroxybutenolides **1a** and **8**. Both lactones were separated by crystallisation from hexane in a 32 and 21% yield, respectively (Scheme 2). The formation of compounds **1a** and **8** was deduced by thermal decomposition of the unstable endoperoxide, which resulted from the [4 + 2] addition of singlet oxygen to labdafuran **15**.[15] The $^1$H NMR spectrum of **1a** was consistent with a α-alkyl-substituted-15-hydroxybutenolide, similar to natural coronarin C **1**.[3] Speãfiãally the presence of signals at 6.81 ppm, which must be assigned to proton H-14, placed at the β-position of an α,β-unsaturated butenolide, and the signal at 6.08 ppm assigned to H-15. The optical rotation of **1a** ($[\alpha]_D$ + 30, *c* 0,6; $CHCl_3$), was in accord with that of natural coronarin C **1** ($[\alpha]_D$ + 34.9, *c* 0.13, $CHCl_3$).[3] In the $^1$H NMR spectrum of regioisomeric hydroxybutenolide derivative **8** the most deshielded signal appeared at 5.95 ppm and was attributable to H-16. The signal at 5.83 ppm was assigned to H-14. The structure of α,β-alkyl-substituided-16-hydroxidebutenolide has been assigned to this compound and which had spectroscopic data identical with the natural *ent*-labdane **7** except that the optical rotation value and opposite sign was observed ($[\alpha]_D$ + 48, *c* 1.5, $CHCl_3$, lit.[7] $[\alpha]_D$ –100, *c* 0.43, $CHCl_3$). As none of the signals were doublets in the $^1$H NMR spectrum of compounds **1a** and **8**, while in the $^{13}$C NMR spectrum no additional signals were observed, only one of the two possible C-15 or C-16 epimers in compounds **1a** and **8** respectively was present. However, the configuration at C-15 or C-16 could not be determined. Probably, the difference between the optical rotation values can be due to that the compound **7**, isolated by Zdero *et al.*[7] is impure or is the other C-16 epimer compound.

In an attempt to increase the yield of the photooxidation reaction, we irradiated labdafuran **15** in $CHCl_3$ (external 150 W halogen–tungsten lamp) in the presence of oxygen, 2,6-lutidine and catalytic amount of *meso*-tetraphenylporphin afford to a mixture of two regioisomeric hydroxybutenolides **1a** and **8** (Scheme 2). The one which was formed in larger amounts (54%) was found to be hydroxybutenolide **8** and the other (5%) was found to be **1a**. The major formation of compound **8** was deduced by regiospeãfic removal of the hydrogen at C-15 on the intermediate endoperoxide, with a hindered base at low temperature in order to favour base-catalysed decomposition rather than thermal decomposition.[15]

To synthesise compound (+)-zerumin B **6**, we first prepared the easily separable C-12-(*R*) and (*S*) epimers furanolabdane



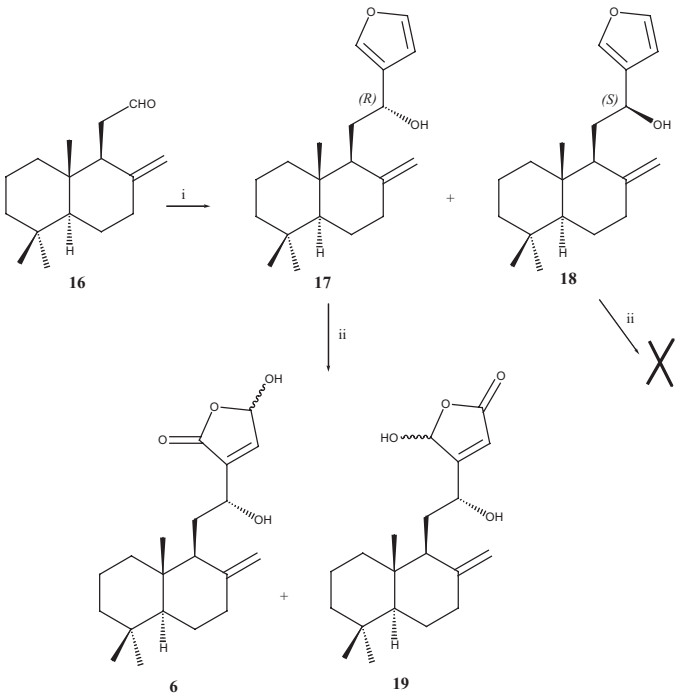

**Scheme 1** (i) $LiAlH_4$, THF, reflux (96%); (ii) TPAP, N-methylmorpholine N-oxide, $CH_2Cl_2$ (mixture of **5** and **12**); (iii) $Ag_2CO_3$–celite, benzene, r.t. (96% of **5**; 3% of **12**).




**Scheme 2** (i) $CBr_4$, $Ph_3P$, THF, r.t.; (ii) 3-bromofuran, *n*-BuLi, THF, –78°C; (iii) $O_2$, *hv*, Rose Bengal, THF, –0°C, 2 h (32% of **1a**; 21% of **8**); (iv) $O_2$, *hv*, *meso*-tetraphenylporphine, 2,6-lutidine, $CHCl_3$, –78°C, 2 h (5% of **1a**; 54% of **8**).

alcohols **17** and **18** from alcohol **13**.[12] The stereochemistry of furanolabdanes **17** and **18** was established by comparison with data reported.[16] Irradiation of labdafuran alcohol **17** in $CH_2Cl_2$ (external 150 W halogen–tungsten lamps, Pyrex well) in the presence of oxygen and catalytic amount of Rose Bengal afforded a mixture of two regioisomeric hydroxybutenolides **6** and **19**. Both lactones were separated by chromatography over silica gel gave a 39% and 54% yield, respectively (Scheme 2). The $^1$H NMR spectrum of **6** was consistent with a α-alkyl-substituted-15-hydroxybutenolide, similar to natural (+)-zerumin B.[5,6,10] The speãfic rotation of **6** ($[\alpha]_D$ + 38, *c* 1.0, acetone) was in close accord with that of natural zerumin B ($[\alpha]_D$ + 40, *c* 0.01, acetone).[6] In the $^1$H NMR spectrum of regioisomeric hydroxybutenolide derivative **19** the most deshielded signal appeared at 6.24 ppm attributable to H-16. The signal at 5.95 ppm was assigned to H-14, therefore the structure of α,β-alkyl-substituted-16-hydroxydebutenolide has been assigned to this compound. As in the previous case, none of the signals were doublets in the $^1$H NMR spectrum of compounds **6** and **19**, while in the $^{13}$C NMR spectrum no additional signals were observed, only one of the two possible C-15 or C-16 epimers in compounds **6** and **19** respectively was present. However, the configuration at C-15 or C-16 could not be determined.

In order to synthesise isomeric alcohol C-12-(*S*), we irradiated the furanolabdane alcohol **18** under the same conditions. However, this yielded a complex mixture of products.




**Scheme 3** (i) 3-bromofuran, *n*-BuLi, THF, –78°C; (ii) $O_2$, *hv*, Rose Bengal, THF, 0°C, 2 h.

## Experimental

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance-300 and Avance-500 spectrometers. IR spectra were recorded using a Nicolet Magna 560 FT–IR spectrometer. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-AX505WA mass spectrometer. The intensity of each peak in the mass spectrum relative to the base peak is reported in parentheses. Optical rotations were obtained for $CHCl_3$ solutions on a Perkin-Elmer 341 polarimeter, and their concentrations are expressed in g/100 ml. Manool resin was purchased from Westchem Industries, Ltd and purified to obtain (+)-Manool, $[\alpha]^{24}_D$ + 28 (*c* 1.5, $CHCl_3$). THF, ether, DME and benzene were freshly distilled from Na-benzophenone before use. All other solvents and reagents were obtained from commerãal suppliers and used without further purification. Merck silica gel (70–230 mesh ASTM) was used for column chromatography. TLC was performed on Analtech silica gel 60 $G_{254}$ and the spots were observed either by exposure to iodine or by UV light. All organic extracts were dried over $Na_2SO_4$ and evaporated under reduced pressure below 60°C.

*Reduction of peroxide* **10** *with lithium aluminium hydride:* To a suspension of $LiAlH_4$ (37.43 mg, 0.98 mmol) in dry THF (5 ml) was added dropwise peroxide **10** (0.250 g, 0.82 mmol) in THF (4 ml) at 0°C. This mixture was refluxed for 2 h. then water was added and the product was extracted with ether. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with 50% ether in hexane afforded diol **11** (0.241 g, 96%) as white crystals (hexane): m.p. 119–120°C; $[\alpha]_D$ + 40 (*c* 1.0, $CHCl_3$), lit.[12] $[\alpha]_D$ –42 (*c* 0.39, $CHCl_3$); IR(KBr) $\nu_{max}$ 3602, 3079, 1642, and 900 $cm^{-1}$; HRMS *m/z* 306.2558 ($M^+$, $C_{20}H_{34}O_2$ requires 306.2560); EIMS *m/z* 306 (5), 288 (20), 205 (75), 177 (65), 137 (100), 98 (86); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.65, 0.77, 0.84 (3H each, s, $CH_3$), 4.15 (1H, d, *J* = 12.9 Hz, H-16), 4.17 (1H, d, *J* = 12.9 Hz, H-16), 4.18 (2H, bd, H-15), 4.49 (1H, bs, H-17), 4.80 (1H, bt, H-17), and 5.57 (1H, bt, *J* = 6.9 Hz, H-14); $^{13}C$ NMR ($CDCl_3$, 75.45 MHz) δ 14.47 (C-20), 19.34 (C-11), 21.69 (C-19), 22.09 (C-2), 24.41 (C-6), 33.58 (C-4), 33.58 (C-18), 34.63 (C-12), 38.31 (C-7), 39.06 (C-1), 39.67 (C-10), 42.11 (C-3), 55.48 (C-5), 56.39 (C-9), 58.50 (C-16), 60.80 (C-15), 106.29 (C-17), 126.05 (C-14), 144.47 (C-13) and 148.56 (C-8);

*Oxidation of diol* **11** *with tetra-n-propylammonium perruthenate:* Diol **11** (0.110 g, 0.36 mmol) was dissolved in dichloromethane (3 ml) containing both 4Å molecular sieves (0.200 g) and N-methylmorpholine N-oxide (63.27 mg, 0.54 mmol). After stirring the mixture for 10 min, tetra-*n*-propylammonium perruthenate (6.3 mg, 0.018 mmol) was added and the reaction was followed by TLC until complete. After usual work-up, the crude product (0.105 g) was obtained. The NMR spectrum indicated that it consisted of a mixture of lactones **5** and **12**. Further purification over silica gel failed.

*Oxidation of diol* **11** *with silver carbonate-celite:* To a suspension of silver carbonate-celite (37.43 mg, 0.98 mmol) in dry benzene (3 ml) was added diol **11** (0.100 g, 0.32 mmol) in benzene (2 ml) at room temperature. The reaction mixture was filtered through silica gel and the filtrate was evaporated. The resulting crude product was chromatographed over silica gel. Elution with 50% ether in hexane afforded lactone **5** (95 mg, 96%), which after recrystallisation from hexane showed: m.p. 76–78°C; $[\alpha]^{24}_D$ + 39 (*c* 1.4, $CHCl_3$), lit.[4,11] $[\alpha]_D$ + 41 (*c* 1.2, $CHCl_3$); IR(KBr) $\nu_{max}$ 1775, 1740, 1640 and 1630 $cm^{-1}$; HRMS *m/z* 302.2258 ($M^+$, $C_{20}H_{30}O_2$ requires 302.2255); EIMS *m/z* 302 (10), 287 (15), 206 (34), 137 (71), 109 (100), 98 (92); $^1H$ NMR ($CDCl_3$, 300 MHz) 0.67, 0.78, 0.85 (3H each, s, $CH_3$), 4.42 (1H, br s, H-17), 4.66 (1H, dd, *J* = 17.3 and 1.7, H-16), 4.72 (1H, dd, *J* = 17.3 and 1.7, H-16), 4.84 (1H, br s, H-17), 5.81 (1H, t, *J* = 1.6, H-14); $^{13}C$ NMR ($CDCl_3$, 75.45 MHz) δ 14.36, 19.24, 21.20, 21.63, 24.32, 27.45, 33.51, 33.51, 38.14, 39.09, 39.70, 41.93, 55.42, 56.06, 73.08, 106.37, 115.07, 147.84, 171.06 and 174.17.

*Bromination of alcohol* **13***:* To a solution of alcohol **13** (0.2 g, 0.84 mmol) in THF (6 ml) was added $PPh_3$ (0.88 g, 3.36 mmol) and $CBr_4$ (0.83 g, 2.50 mmol) and the whole was stirred for 20 min at room temperature. The reaction mixture was diluted with brine and extracted with ether. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with hexane afforded bromide **14** (0.21 g, 83%) as a colourless oil; HRMS *m/z* 298.1299 ($M^+$, $C_{16}H_{27}Br$ requires 298.1296); $^1H$ NMR ($CDCl_3$, 300 MHz) 0.67, 0.78, 0.86 (3H each, s, $CH_3$), 2.38 (1H, ddd, *J* = 13, 4, 2), 3.25 (1H, ddd, *J* = 8.6, 8, 7, H-12), 3.51 (1H, ddd, *J* = 8.6, 8, 4, H-12), 4.45 (1H, br s, H-17), 4.82 (1H, br s, H-17); $^{13}C$ NMR ($CDCl_3$, 75.45 MHz) δ 14.81, 19.4, 21.8, 24.42, 28.06, 33.61, 33.61, 33.75, 38.22, 39.10, 39.64, 42.11, 55.33, 55.42, 106.20 and 147.71.

*Coupling of the bromide* **14** *with 3-furyllithium:* To a cooled solution of the 3-bromofuran (0.163 g, 0. mmol) in dry THF (3 ml) at –78°C, was added *n*-butyllithium (0.6 ml, 1.6M in hexane). The resulting brown solution was stirred for 10 min. at –78°C and then a solution of bromide **14** (0.121 g, 0.51 mmol) in THF (2 ml) was added dropwise. After this mixture had been stirred for 2 h at –78°C, excess $H_2O$ was added at room temperature with additional stirring for 30 min. The product was extracted with ether, dried and the solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with 5% diethyl ether in hexane afforded furanolabdane **15** (0.192 g, 93%) as a colourless oil; $[\alpha]_D$ + 23 (*c* 2.0, $CHCl_3$), lit.[12] $[\alpha]_D$ –22 (*c* 0.14, $CHCl_3$); IR (KBr) $\nu_{max}$ 3050, 1635, 1495, 870 $cm^{-1}$; HRMS *m/z* 286.2290 ($M^+$, $C_{20}H_{30}O$ requires 286.2299); EIMS *m/z* 286 (31), 271 (9), 191 (27), 137 (80), 95 (100), 67 (18); $^1H$ NMR ($CDCl_3$, 300 MHz) 0.67, 0.78, 0.85 (3H each, s, $CH_3$), 2.23 (1H, m, H-12), 2.39 (1H, m, H-7), 2.54 (1H, m, H-17), 4.55 (1H, bs, H-17), 4.84 (1H, bs, H-17), 6.25 (1H, bs, H-14), 7.18 (1H, bs, H-16), and 7.33 (1H, t, H-15); $^{13}C$ NMR ($CDCl_3$, 75.45 MHz) δ 14.47 (C-20), 19.36 (C-11), 21.70 (C-19), 23.59 (C-12), 24.05 (C-2), 24.42 (C-6), 33.55 (C-4), 33.55 (C-18), 38.30 (C-7), 38.98 (C-1), 39.56 (C- 10), 42.10 (C-3), 55.42 (C-5), 56.05 (C-9), 106.23 (C-17), 110.94 (C-14), 125.59 (C-13), 138.62 (C-16), 142.58 (C-15) and 148.51 (C-8).

*Photooxygenation of labdafuran* **15**

*Method A*: A solution of labdafuran **15** (0.105 g; 0.37 mmol) in THF (10 ml), containing Rose Bengal (1 mg), was irradiated at 0°C with an external 150 W halogen–tungsten lamp for 2 h during which time oxygen was bubbled through the reaction mixture. The solvent was evaporated under reduced pressure and the residue chromatographed over silica gel. Elution with 15% ethyl acetate in hexane afforded a mixture of compounds **1a** and **8**, as a colourless oil as evidenced by the NMR spectrum. Crystallisation from hexane gave pure compound **8** (25 mg, 21%): m.p. 89–91°C; $[\alpha]_D$ + 48 (*c* 0.7, $CHCl_3$), lit.[8] $[\alpha]_D$ –100 (*c* 0.43, $CHCl_3$); IR (KBr) $\nu_{max}$ 3364, 3015, 1645, 1762 $cm^{-1}$; HRMS *m/z* 318.1970 ($M^+$, $C_{20}H_{30}O_3$ requires 318.2193); EIMS *m/z* 318 (20), (23), 300 (15), 204 (19), 177 (25), 137 (100), 95 (37); $^1H$ NMR ($CDCl_3$, 300 MHz) 0.67, 0.78, 0.85 (3H each, s, $CH_3$), 1.31 (1H, m, H-6), 1.72 (1H, m, H-6), 1.93 (1H, m, H-7), 2.37 (1H, m, H-7), 4.45 (1H, bs, H-17), 4.84 (1H, bs, H-17), 5.83 (1H, s, H-14), 5.95 (1H, bs, H-16); $^{13}C$ NMR ($CDCl_3$, 75.45 MHz) δ 14.41 (C-20), 19.31 (C-11), 20.82 (C-2), 21.69 (C-19), 24.39 (C-6), 26.76 (C-12), 33.57 (C-4), 33.57 (C-18), 38.20 (C-7), 39.14 (C-10), 39.78 (C-1), 42.04 (C-3), 55.49 (C-5), 56.33 (C-9), 99.02 (C-16), 106.51 (C-17), 117.14 (C-14), 147.91 (C-8), 170.41 (C-13), 171.57 (C-15).

Chromatography of the mother-liquor of compound **1a** over silica gel with 15% ethlyl acetate in hexane afforded pure coronarin C **1a** (37.6 mg, 32%) as an oil; $[\alpha]_D$ + 30 (*c* 0,6; $CHCl_3$), lit.[3] $[\alpha]_D$ + 34.9 (*c* 0.13, $CHCl_3$); IR (KBr) $\nu_{max}$ 3426, 3015, 1643, 1763 $cm^{-1}$; HRMS *m/z* 318.2284 ($M^+$, $C_{20}H_{30}O_3$ requires 318.2193); EIMS *m/z* 318 (20), 303 (21), 177 (23), 137 (100), 95 (37); $^1H$ NMR ($CDCl_3$, 300 MHz) 0.65, 0.77, 0.84 (3H each, s, $CH_3$), 4.51 (1H, bs, H-17), 4.83 (1H, bs, H-17), 6.08 (1H, bs, H-15), 6.81 (1H, d, *J* = 1.5 Hz, H-14); $^{13}C$ NMR ($CDCl_3$, 75.45 MHz) δ 14.41 (C-20), 19.32 (C-2), 21.47 (C-12), 21.69 (C-19), 24.38 (C-6), 24.48 (C-11), 33.56 (C-4), 33.56 (C-18), 38.21 (C-7), 39.11 (C-1), 39.70 (C-10), 42.08 (C-3), 55.49 (C-5), 56.45 (C-9), 97.08 (C-15), 106.56 (C-17), 139.02 (C-13), 142.85 (C-14), 147.97 (C-8).

*Method B*: A solution of labdafuran **15** (0.1 g, 0.35 mmol) in $CH_2Cl_2$ (10 ml), containing *meso*-tetraphenylporphin (1 mg) and diisopropylamin (10 eq), was irradiated at –78°C with an external 150 W halogen–tungsten lamp for 2 h during which time oxygen was bubbled through the reaction mixture. The solution was warmed to 23°C, and saturated aqueous oxalic aãd (3 ml) was added. After 30 min of vigorous stirring, water (15 ml) and $CH_2Cl_2$–methanol (3 : 1, 50 ml) were added to the colourless mixture, and the aqueous portion was extracted with $CH_2Cl_2$–methanol (3 : 1, 2 × 50 ml). The solvent was evaporated under reduced pressure and the residue was chromatographed over silica gel. Crystallisation from hexane gave pure compound **8** (60.1 mg, 54%) as white crystals. Chromatography of the mother-liquor of compound **1a** over silica gel with 15% ethlyl acetate in hexane afforded pure compound **1a** (5 mg, 5%).

*Photooxygenation of labdafuran* **17**: A solution of labdafuran **17** (72 mg, 0.23 mmol) in THF (10 ml), containing Rose Bengal (1 mg), was irradiated at 0°C with an external 150 W halogen–tungsten lamp for 3 h during which time oxygen was bubbled through the reaction mixture. The solvent was evaporated under reduced pressure and the residue chromatographed over silica gel. Elution with 30% ethyl

acetate in hexane afforded zerumin B **6** (28 mg 39%) and compound **19** (39.2 mg 54%).

*Zerumin B* **6**: M.p. 172–174°C, lit.[6,10] 156–158°C; $[\alpha]_D$ + 38 (*c* 1.0, acetone), lit.[6,10] $[\alpha]_D$ + 40 (*c* 0.01 acetone); IR (KBr) $\nu_{max}$ 3372, 3083, 1745, 1689, 1644, 1250, 890 $cm^{-1}$; HRMS *m/z* 334.2126 ($M^+$, $C_{20}H_{30}O_4$ requires 334.2144); EIMS *m/z* 334 (2), 290 (5), 275 (11), 272 (2), 205 (7), 190 (100), 137 (62), 123 (28), 95 (39), 81 (47), and 69 (45); $^1$H NMR (acetone-$d_6$, 300 MHz) 0.65, 0.80, 0.86 (3H each, s, $CH_3$), 2.36 (1H, bs, *J* = 12 Hz), 4.46 (1H, bd, *J* = 10.6 Hz), 4.66 (1H, bs, H-17), 4.81 (1H, bs, H-17), 6.16 (1H, bs, H-15), 7.11 (1H, bs, H-14); $^{13}$C NMR (acetona-$d_6$, 75.45 MHz) δ 15.42 (C-20), 20.53 (C-2), 22.61 (C-19), 25.67 (C-6), 32.56 (C-11), 34.45 (C-18), 34.70 (C-4), 39.41 (C-7), 40.17 (C-10), 40.97 (C-1), 43.42 (C-3), 53.66 (C-5), 56.78 (C-9), 66.93 (C-12), 98.55 (C-15), 107.46 (C-17), 141.94 (C-13), 146.57 (C-14), 150.76 (C-8), and 171.65 (C-16).

*Hydroxybutenolide* **19**: $[\alpha]_D$ + (*c* 1.0, acetone), lit.[6,10] $[\alpha]_D$ + (*c* 0.01 acetone); IR (KBr) $\nu_{max}$ 3072, 1751, 1644, 891 $cm^{-1}$; HRMS *m/z* 334.2125 ($M^+$, $C_{20}H_{30}O_4$ requires 334.2144); EIMS *m/z* 334 (5), 290 (8), 275 (9), 205 (6), 190 (80), 137 (100), 123 (33), 95 (61), 81 (37), and 69 (53); $^1$H NMR (acetone-$d_6$, 300 MHz) 0.71, 0.81, 0.86 (3H each, s, $CH_3$), 2.33 (1H, bs), 4.60 (1H, bs), 4.71 (1H, bs, H-17), 4.81 (1H, bs, H-17), 5.95 (1H, bs, H-14), 6.24 (1H, bs, H-16); $^{13}$C NMR (acetona-$d_6$, 75.45 MHz) δ 15.32 (C-20), 20.49 (C-2), 22.57 (C-19), 25.68 (C-6), 32.23 (C-11), 34.39 (C-18), 34.65 (C-4), 39.37 (C-7), 40.09 (C-1), 41.07 (C-10), 43.31 (C-3), 53.72 (C-5), 56.60 (C-9), 57.72 (C-12), 99.48 (C-16), 107.65 (C-17), 118.31 (C-14), 131.30 (C-13), 150.53 (C-8), and 171.52 (C-15).

*Photooxygenation of labdafuran* **18**: A solution of labdafuran **18** (86 mg, 0.28 mmol) in THF (10 ml), containing Rose Bengal (1 mg), was irradiated at 0°C with an external 150 W halogen–tungsten lamp for 3 h during which time oxygen was bubbled through the reaction mixture. The NMR spectrum indicated that it consisted of a complex mixture.

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