

## Chemistry of xanthorrhizol: synthesis of several bisabolane sesquiterpenoids from xanthorrhizol

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**Abstract**—(–)-Xanthorrhizol (**1**) isolated from the rhizomes of *Curcuma xanthorrhiza* has been transformed to several bisabolane-type sesquiterpenoids, in a stereoselective manner. 10*R*- and 10*S*-10,11-dihydro-10,11-dihydroxyxanthorrhizols (**2**, **3**), (–)-curcuquinone (**4**), (–)-curcuhydroquinone (**5**), helibisabonol A (**7**) and allylic alcohol **8** have been prepared from xanthorrhizol in optically active forms. All the routes involved a Sharpless AD to introduce the stereogenic centre at C-10.  
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(–)-Xanthorrhizol (**1**), the major component of the essential oil of *Curcuma xanthorrhiza*, is a bisabolane-type sesquiterpenoid containing a stereogenic centre at the benzylic position. It was first isolated in 1970 and its absolute configuration was assigned as *R*.<sup>1</sup> With regards to its bioactivity, it has been shown that xanthorrhizol (**1**) exhibits antibacterial activity against *Streptococcus mutans* (MIC = 2 µg/mL).<sup>2</sup> Although nine syntheses have been reported for xanthorrhizol,<sup>1b,3</sup> the chemistry of **1** has not been explored fully. Aguilar et al. prepared several simple derivatives of xanthorrhizol, which displayed mild antifungal activity, but did not show cytotoxic activity towards certain human cell lines.<sup>4</sup> Thus, it is of interest to study the chemistry of **1** in order to exploit the readily availability of xanthorrhizol as a precursor for the preparation other useful compounds.

We noted that xanthorrhizol (**1**) is a potential chiral starting material for the synthesis of bisabolane-type sesquiterpenoids. Compound **1** can be converted to several naturally occurring sesquiterpenoids, namely (10*R*/10*S*)-10,11-dihydro-10,11-dihydroxyxanthorrhizols (**2**, **3**), (–)-curcuquinone (**4**), (–)-curcuhydroquinone (**5**) and helibisabonol A (**7**). Compounds **2** and **3** were

isolated as minor constituents from the Mexican medicinal plant, *Iostephane heterophylla*, using bioguided fractionation.<sup>5</sup> Curcuquinone (**4**) and curcuhydroquinone (**5**) were isolated from the Caribbean gorgonian *Pseudopterogorgia rigida* and show antibacterial properties against *Staphylococcus aureus* and *Vibrio anguillarum*.<sup>6</sup> Helibisabonol A (**7**), is an allelochemical isolated by Macías and co-workers from the CH<sub>2</sub>Cl<sub>2</sub> extracts of dried sunflower leaves (*Helianthus annuus* L. cv. Peredovick).<sup>7</sup> The allylic alcohol derivative of xanthorrhizol, 2-methyl-5-(4*S*-hydroxy-1*R*,5-dimethylhex-5-enyl)-phenol (**8**) is a bisabolane-type sesquiterpenoid found in the Mexican medicinal plant, *I. heterophylla*<sup>8</sup> and recently has been isolated from the resins of the African plant, *Commiphora kua*. Manguro et al. reported that allylic alcohol **8** inhibited the growth of the plant pathogenic fungus *Cladosporium cucumerinum*.<sup>9</sup>

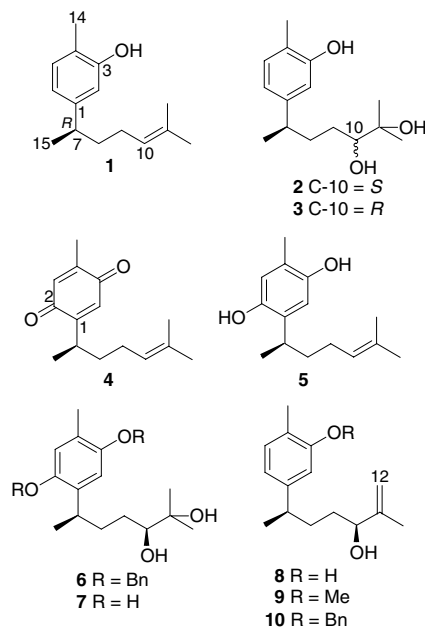
To date, no enantioselective synthesis has been reported for triols **2** and **3**, helibisabonol A (**7**) and allylic alcohol **8**. There are literature reports on the synthesis of curcuquinone (**2**) and curcuhydroquinone (**3**) in racemic form<sup>10</sup> and only a few reports on the optically active forms.<sup>3i,11</sup> In this paper, we report the stereoselective syntheses of compounds **2–7**, (7*R*,10*R*)-helibisabonol A (**21**), methyl **9** and benzyl **10** ethers and the naturally occurring allylic alcohol **8**, starting from naturally occurring xanthorrhizol (**1**).

Hydrodistillation of the chopped fresh rhizomes of *C. xanthorrhiza* yielded the essential oil in 1.14% yield. The essential oil was subjected to vacuum liquid chromatography to give xanthorrhizol in 20% yield. It

**Keywords:** Xanthorrhizol; (10*R*/10*S*)-10,11-Dihydro-10,11-dihydroxyxanthorrhizols; (–)-Curcuquinone; (–)-Curcuhydroquinone; Helibisabonol A; Sharpless AD.

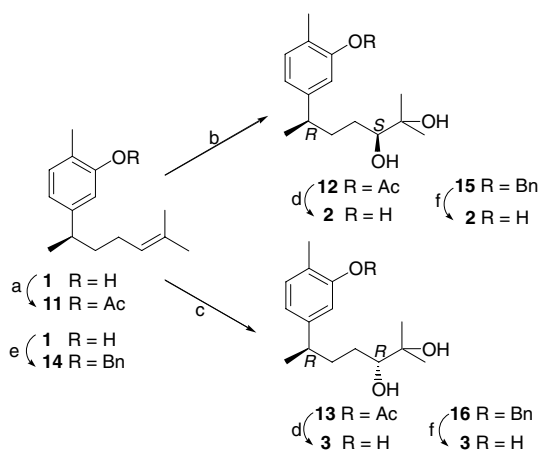
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proved difficult to isolate **1** in high purity, but this posed no problem because the subsequent reaction steps facilitated isolation.

The synthetic route to triols **2** and **3** is illustrated in Scheme 1. First, xanthorrhizol (**1**) was protected as its acetate (**11**). The acetate group served as a protecting group and at the same time facilitated compound purification. Thus, pure **11** was easily obtained after column chromatography albeit starting with approximately 70% pure xanthorrhizol. Acetate **11** was subjected to an asymmetric dihydroxylation (AD) reaction employing AD-mix- $\alpha$ <sup>12</sup> in the presence of methanesulfonamide in aqueous *tert*-butanol at 0 °C to give diol **12** in 62% yield. The diastereomeric excess of **12** was >98% as determined by <sup>1</sup>H NMR analysis of its (*S*)-MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid] ester



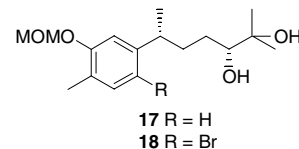
**Scheme 1.** Reagents and conditions: (a) Ac<sub>2</sub>O, py, rt, 72%; (b) AD-mix- $\alpha$ , MeSO<sub>2</sub>NH<sub>2</sub>, *t*-BuOH/H<sub>2</sub>O (1:1), 0 °C, 62% (**12**), 53% (**15**); (c) AD-mix- $\beta$ , MeSO<sub>2</sub>NH<sub>2</sub>, *t*-BuOH/H<sub>2</sub>O (1:1), 0 °C, 65% (**13**), 29% (**16**); (d) satd NaHCO<sub>3</sub>, MeOH/H<sub>2</sub>O (2:1), rt, 68% (**2**), 71% (**3**); (e) benzyl bromide, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux, 51%; (f) H<sub>2</sub>, Pd/C, MeOH, rt, 96% (**2**), 95% (**3**).

derivative. The absolute configuration of the newly formed stereogenic centre was deduced to be *S* by the modified Mosher method.<sup>13</sup> Diol **12** was treated with aqueous sodium bicarbonate to give triol **2**. The overall yield of **2** was 30%. The diastereomer of **2**, (*7R,10R*)-**3** was obtained in 33% overall yield, following the same sequence of reactions except using AD-mix- $\beta$  instead.

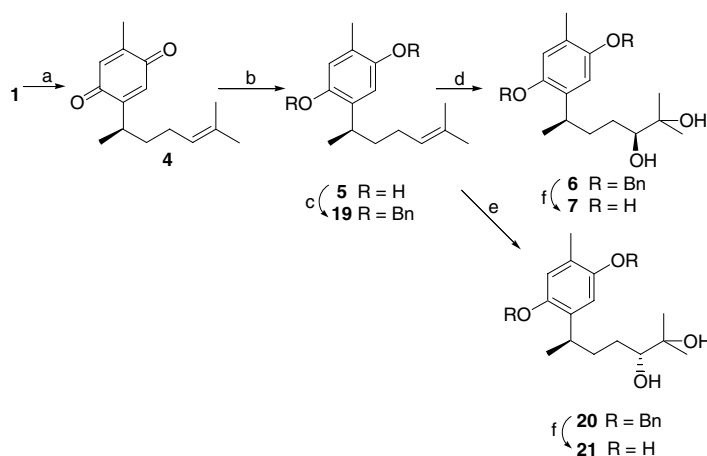
Triols **2** and **3**, have also been synthesised by employing a benzyl group as a protecting group. The approach is similar to the acetate. Xanthorrhizol (**1**) was converted into benzyloxy derivative **14** without much difficulty. Treatment of **14** with AD-mix- $\alpha$  under the same conditions as above gave diol **15** in 53% yield. On the other hand, when benzyloxy derivative **14** was subjected to an AD reaction with AD-mix- $\beta$ , compound **16** was obtained in 29% yield. Catalytic hydrogenolysis (Pd/C) of both diols **15** and **16** gave triols **2** and **3** in 96% and 95% yields, respectively. The overall yield was 26% for **15** and 14% for **16**.

The spectroscopic and physical properties of synthetic **2** and **3**<sup>14</sup> were similar with those of the natural products except for the optical rotation of **3**. The optical rotation of synthetic (*7R,10R*)-(**3**) was +3.33 (*c* 0.30, MeOH), while naturally occurring **3** (obtained from  $\beta$ -cellulase hydrolysis of xanthorrhizol glycoside) had the opposite sign and was much larger, [ $\alpha$ ]<sub>D</sub> −57 (*c* 0.30, MeOH).<sup>5</sup>

Another differences between synthetic **2** and **3** and natural **2** and **3** were the coupling constants of 10-H. The coupling constants reported in the literature [ $\delta$  3.37 (dd, *J* 12.6, 2.7 Hz) for natural **2**, and  $\delta$  3.30 (dd, *J* 13.9, 4.8 Hz)] for natural **3** were larger than those of the synthetic products [ $\delta$  3.37 (br d, *J* 10.2 Hz) for synthetic **2** and  $\delta$  3.30 (dd, *J* 9.9, 2.1 Hz) for synthetic **3**]. However, it is interesting to note that the coupling constants of the oxymethine proton of closely related compounds **17** and **18** were *J* 10.0, 2.0 Hz and *J* 9.6, 2.8 Hz, respectively,<sup>15</sup> which are closer to our values. Based on these comparisons, the *J* values for the oxymethine groups of synthetic triols **2** and **3** are in agreement with the reported values of compounds **17** and **18**.<sup>15</sup>



The synthetic route to helibisabonol A (**7**) is summarised in Scheme 2. Treatment of xanthorrhizol with Fremy's salt (potassium nitrosulfonate) under buffered conditions (pH 6.45) gave curcuquinone (**4**) {[ $\alpha$ ]<sub>D</sub> −4.58 (*c* 2.62, CHCl<sub>3</sub>); lit.<sup>6</sup> [ $\alpha$ ]<sub>D</sub> −1.3 (*c* 2.62, CHCl<sub>3</sub>)}, which was subsequently reduced to curcuhydroquinone (**5**) {[ $\alpha$ ]<sub>D</sub> −48.3 (*c* 0.89, CHCl<sub>3</sub>); lit.<sup>11b</sup> [ $\alpha$ ]<sub>D</sub> −48.0 (*c* 2.78, CHCl<sub>3</sub>)} by sodium dithionite. Curcuhydroquinone (**5**) was isolated as white crystals, with a mp of 93–96 °C, whereas it had been isolated and synthesised previously as a colourless oil (on one occasion from *Pseudoptero-gorgia acerosa* as white crystals, with a mp of 86–87 °C).<sup>16</sup> The spectroscopic properties of **4** and **5**

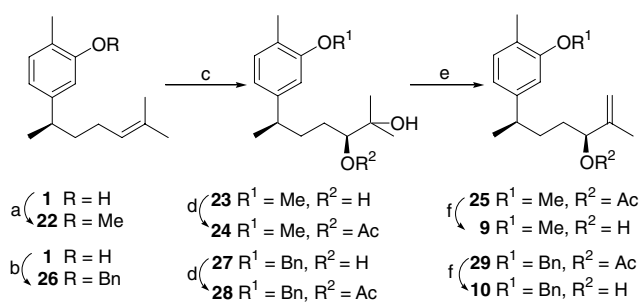


**Scheme 2.** Reagents and conditions: (a)  $(\text{K}_2\text{S}_2\text{O}_8)_2\text{NO}^-$  (Fremy's salt), MeOH,  $\text{Na}_2\text{HPO}_4\text{--Na}_2\text{HPO}_4$ , pH 6, rt, 56%; (b)  $\text{Na}_2\text{S}_2\text{O}_4$ , THF/ $\text{H}_2\text{O}$  (3:2), rt, 90%; (c) benzyl bromide,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 36%; (d) AD-mix- $\alpha$ ,  $\text{MeSO}_2\text{NH}_2$ , *t*-BuOH/ $\text{H}_2\text{O}$  (1:1), 0 °C, 92%; (e) AD-mix- $\beta$ ,  $\text{MeSO}_2\text{NH}_2$ , *t*-BuOH/ $\text{H}_2\text{O}$  (1:1), 0 °C, 40%; (f)  $\text{H}_2$ , Pd/C, MeOH, rt, 84% (7), 92% (21).

were in good agreement with the literature data. Sequential protection of **5** as its dibenzyloxy ether and asymmetric dihydroxylation of the protected hydroquinone (**19**) with AD-mix- $\alpha$  gave dibenzyloxy helibisabonol A (**6**) in 92% yield from compound (**5**). The diastereomeric excess was >98% [(*S*)-MTPA ester] and the absolute configuration at C-10 in **6** was determined to be *S* based on the modified Mosher's method.<sup>13</sup>

The remaining synthetic task was the deprotection of the benzyl groups to form helibisabonol A. Cleavage of the benzyl groups by hydrogenolysis with  $\text{H}_2$  in the presence of Pd/C as catalyst afforded helibisabonol A (**7**)<sup>17</sup> in 24% overall yield. The diastereomer of (**7**), (*7R,10R*) helibisabonol A **21**, white crystals, mp 64–67 °C, was obtained following the same sequence of reactions, except AD-mix- $\beta$  was used instead.<sup>17</sup>

Besides the preparation of natural products, we attempted to convert xanthorrhizol to an unnatural derivative, allylic alcohol **9**. Compound **9** is the methyl ether of the naturally occurring allylic alcohol **8**. The synthetic route to allylic alcohol **9** is illustrated in Scheme 3. Xanthorrhizol was first converted to *O*-methyl-xanthorrhizol (**22**) by treatment with MeI and  $\text{K}_2\text{CO}_3$  in refluxing acetone. The protected compound **22** was subjected to Sharpless AD employing AD-mix- $\alpha$  to give methoxydiol **23** in 91% isolated yield with an ee >98%. The absolute configuration at C-10 in **23** was assigned as *S* based on the modified Mosher's method.<sup>13</sup> Methoxydiol **23** was acetylated with acetic anhydride–pyridine to give monoacetate **24** in a quantitative yield. Dehydration of **24** was affected by treatment with methanesulfonyl chloride, triethylamine and *N,N*-dimethylaminopyridine (DMAP) to afford allylic acetate **25**. Completion of the reaction sequence was carried out by hydrolysis of allylic acetate **25** with  $\text{K}_2\text{CO}_3$  in methanol to furnish allylic alcohol **9** in 91% yield [ $[\alpha]_D^{25} -16.6$  (*c* 1.34,  $\text{CHCl}_3$ )].<sup>18</sup> This synthesis afforded allylic alcohol **9** in 25% overall yield, in five steps. In addition, xanthorrhizol (**1**) was also protected as benzyloxy derivative **26**. Compound **26** was converted to an unnatural derivative,



**Scheme 3.** Reagents and conditions: (a) MeI,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 8 h, 65%; (b) benzyl bromide,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 4 h, 51%; (c) AD-mix- $\alpha$ ,  $\text{MeSO}_2\text{NH}_2$ , *t*-BuOH/ $\text{H}_2\text{O}$  (1:1), 0 °C, 91% (**23**), 53% (**27**); (d)  $\text{Ac}_2\text{O}$ , py, rt, 24 h, 99% (**24**), 60% (**28**); (e)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , 0 °C → rt, 3.75 h, 47% (**25**), 36% (**29**); (f)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 91% (**9**), 93% (**10**).

allylic alcohol **10**, by implementing a similar sequence of reactions as above.

In conclusion, we have demonstrated that naturally occurring (–)-xanthorrhizol (**1**) can be used as a precursor for the synthesis of several other bisabolane-type sesquiterpenoids, including the first enantioselective syntheses of triols **2** and **3**, facile and short syntheses of (–)-curcuquinone (**4**), (–)-curcuhydroquinone (**5**), helibisabonol A (**7**) and the epimer of helibisabonol A (**21**), as well as syntheses of the unnatural allylic alcohols **9** and **10**.

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## References and notes

- (a) Rimpler, H.; Hänsel, R.; Kochendoerfer, L. *Z. Naturforsch.* **1970**, *25*, 995–998; (b) John, T. K.; Rao, K. *Indian J. Chem.* **1985**, *24B*, 35–37.
- Hwang, J.-K.; Shim, J.-S.; Baek, N.-I.; Pyun, Y.-R. *Planta Med.* **2000**, *66*, 196–197.
- (a) Mane, R. B.; Rao, G. S. K. *Indian J. Chem.* **1974**, *12B*, 938–939; (b) ApSimon, J. In *The Total Synthesis of Natural Products*; John Wiley & Sons: USA, 1983; Vol. 5, pp 42–43; (c) Garcia, G. E.; Mendoza, V.; Guzman, B. A. *J. Nat. Prod.* **1987**, *50*, 1055–1058; (d) Krause, W.; Bohlmann, F. *Tetrahedron Lett.* **1987**, *28*, 2575–2578; (e) Rane, R. K.; Desai, U. V.; Mane, R. B. *Indian J. Chem.* **1987**, *26B*, 572–573; (f) Nagumo, S.; Irie, S.; Hayashi, K.; Akita, H. *Heterocycles* **1996**, *43*, 1175–1178; (g) Meyers, A. I.; Stoianova, D. *J. Org. Chem.* **1997**, *62*, 5219–5221; (h) Sato, K.; Bando, T.; Shindo, M.; Shishido, K. *Heterocycles* **1999**, *50*, 11–15; (i) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758–3764.
- Aguilar, M. I.; Delgado, G.; Villarreal, M. L. *Rev. Soc. Quim. Mex.* **2001**, *45*, 56–59.
- Aguilar, M. I.; Delgado, G.; Hernández, L.; Villarreal, M. L. *Nat. Prod. Lett.* **2001**, *15*, 93–101.
- McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661–1664.
- Macías, F. A.; Torres, A.; Galindo, J. L. G.; Varela, R. M.; Álvarez, J. A.; Molinillo, J. M. G. *Phytochemistry* **2002**, *61*, 687–692.
- Aguilar, M. I.; Delgado, G.; Bye, R.; Linares, E. *Phytochemistry* **1993**, *33*, 1161–1163.
- Manguero, L. O. A.; Ugi, I.; Lemmen, P. *Chem. Pharm. Bull.* **2003**, *51*, 479–482.
- (a) Sánchez, I. H.; Lemini, C.; Joseph-Nathan, P. *J. Org. Chem.* **1981**, *46*, 4666–4667; (b) Ono, M.; Yamamoto, Y.; Todoroki, R.; Akita, A. *Heterocycles* **1994**, *37*, 181–185; (c) Ono, M.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553–558; (d) Kad, G. L.; Khurana, A.; Singh, V.; Singh, J. *J. Chem. Res. (S)* **1999**, 164–165; (e) Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *69*, 2461–2468.
- (a) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807–1808; (b) Yoshimura, T.; Kisyuku, H.; Kamei, T.; Takabatake, K.; Shindo, M.; Shishido, K. *Arkivoc* **2003**, *8*, 247–255.
- Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
- Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
- Analytical data for (7*R*,10*S*)-10,11-dihydro-10,11-dihydroxyxanthorrhizol (**2**):  $R_f = 0.29$  (PE/Et<sub>2</sub>O, 1/9);  $[\alpha]_D -64.7$  (*c* 0.51, MeOH); IR (neat) 3361, 1619, 1589, 1260 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 (3 H, s, H-12), 1.15 (3H, s, H-13), 1.18 (1H, m, H-9'), 1.23 (3H, d, *J* 6.9 Hz, H-15), 1.40 (1H, m, H-9), 1.60 (1H, m, H-8'), 1.86 (1H, m, H-8), 2.21 (3H, s, H-14), 2.64 (1H, sext, *J* 6.9 Hz, H-7), 3.37 (1H, br d, *J* 10.2 Hz, H-10), 5.06 (1H, s, OH), 6.62 (1H, d, *J* 1.8 Hz, H-2), 6.66 (1H, dd, *J* 7.8, 1.8 Hz, H-6), 7.02 (1H, d, *J* 7.8 Hz, H-5); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  15.4 (C-14), 23.0 (C-12), 23.2 (C-15), 26.5 (C-13), 29.6 (C-9), 35.0 (C-8), 39.3 (C-7), 73.3 (C-11), 78.6 (C-10), 113.3 (C-2), 119.4 (C-6), 121.3 (C-4), 130.9 (C-5), 146.4 (C-1), 153.9 (C-3); EIMS *m/z* 252 (29) [M<sup>+</sup>, C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>], 234 (2), 216 (7), 194 (53), 175 (64), 161 (24), 148 (89), 135 (100), 121 (21), 109 (27), 91 (21), 77 (11), 67 (6), 59 (95).  
For (7*R*,10*R*)-10,11-dihydro-10,11-dihydroxyxanthorrhizol (**3**):  $R_f = 0.29$  (PE/Et<sub>2</sub>O, 1/9);  $[\alpha]_D +3.33$  (*c* 0.30, MeOH); IR (neat) 3382, 1619, 1589, 1256 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.11 (3H, s, H-12), 1.14 (3H, s, H-13), 1.22 (3H, d, *J* 6.9 Hz, H-15), 1.34 (2H, m, H-9 and H-9'), 1.58 (1H, m, H-8'), 1.85 (1H, m, H-8), 2.21 (3H, s, H-14), 2.61 (1H, sext, *J* 6.9 Hz, H-7), 3.30 (1H, dd, *J* 9.9, 2.1 Hz, H-10), 6.62 (1H, d, *J* 1.8 Hz, H-2), 6.67 (1H, dd, *J* 7.8, 1.8 Hz, H-6), 7.02 (1H, d, *J* 7.8 Hz, H-5); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  15.3 (C-14), 23.1 (C-15), 23.4 (C-12), 26.5 (C-13), 29.9 (C-9), 35.5 (C-8), 39.7 (C-7), 73.1 (C-11), 78.8 (C-10), 113.4 (C-2), 119.1 (C-6), 121.1 (C-4), 130.9 (C-5), 146.9 (C-1), 153.8 (C-3); EIMS *m/z* 252 (11) [M<sup>+</sup>, C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>], 234 (2) [M–H<sub>2</sub>O]<sup>+</sup>, 216 (3), 194 (17), 175 (36), 161 (15), 148 (47), 135 (100), 121 (31), 109 (17), 91 (52), 77 (28).
- Kishuku, H.; Yoshimura, T.; Kakehashi, T.; Shindo, M.; Shishido, K. *Heterocycles* **2003**, *61*, 125–131.
- Miller, S. L.; Tinto, W. F.; Mclean, S.; Reynolds, W. F.; Yu, M. *J. Nat. Prod.* **1995**, *58*, 1116–1119.
- Analytical data for helibisabolon A (**7**): colourless oil;  $R_f = 0.16$  (PE/Et<sub>2</sub>O = 1/4);  $[\alpha]_D -31.5$  (*c* 0.30, MeOH); IR (neat) 3416, 1652, 1452, 1202 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, C<sub>3</sub>D<sub>6</sub>O)  $\delta$  0.97 (3H, s, H-12), 1.15 (3H, s, H-13), 1.18 (3H, d, *J* 6.9 Hz, H-15), 1.36–1.49 (2H, m, H-9), 1.60 (1H, m, H-8), 1.79 (1H, m, H-8'), 2.09 (3H, s, H-14), 3.15 (1H, sext, *J* 6.9 Hz, H-7), 3.72 (1H, dd, *J* 4.8, 8.1 Hz, H-10), 6.58 (1H, s, H-3), 6.62 (1H, s, H-6); <sup>13</sup>C NMR (75 MHz, C<sub>3</sub>D<sub>6</sub>O)  $\delta$  14.8 (C-14), 20.8 (C-15), 22.4 (C-12), 25.5 (C-13), 27.5 (C-9), 31.6 (C-7), 34.3 (C-8), 79.6 (C-11), 83.0 (C-10), 113.1 (C-6), 117.4 (C-3), 121.8 (C-4), 131.2 (C-1), 147.4 (C-5), 148.4 (C-2).  
For 7*R*,10*R*-**(21)**: white crystals; mp: 64–67 °C;  $R_f = 0.16$  (PE/Et<sub>2</sub>O = 1/4); IR (neat) 3514, 1638, 1533, 1425, 1251 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, C<sub>3</sub>D<sub>6</sub>O)  $\delta$  0.98 (3H, s, H-12), 1.16 (3H, d, *J* 6.9 Hz, H-15), 1.19 (3H, s, H-13), 1.36–1.48 (2H, m, H-9), 1.62–1.79 (2H, m, H-8), 2.09 (3H, s, H-14), 3.10 (1H, sext, *J* 6.9 Hz, H-7), 3.66 (1H, dd, *J* 3.9, 8.7 Hz, H-10), 6.58 (1H, s, H-3), 6.62 (1H, s, H-6); <sup>13</sup>C NMR (75 MHz, C<sub>3</sub>D<sub>6</sub>O)  $\delta$  15.0 (C-14), 20.7 (C-15), 22.4 (C-12), 25.5 (C-13), 27.4 (C-8), 34.6 (C-9), 32.1 (C-7), 79.7 (C-11), 83.5 (C-10), 113.0 (C-6), 117.3 (C-3), 121.6 (C-4), 131.1 (C-1), 147.1 (C-5), 148.3 (C-2).
- Analytical data for allylic alcohol (**9**): colourless oil;  $R_f = 0.24$  (PE/Et<sub>2</sub>O, 8/2);  $[\alpha]_D -16.6$  (*c* 1.34, CHCl<sub>3</sub>); IR (neat) 3382, 2936, 2868, 1612, 1583, 1500, 1457, 1414, 1255, 1135, 1043, 900, 853, 815 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.25 (3H, d, *J* 6.9 Hz, H-15), 1.39–1.64 (4H, m, H-8, H-9), 1.66 (3H, t, *J* 1.2 Hz, H-13), 2.18 (3H, s, H-14), 2.66 (1H, sext, *J* 6.9 Hz, H-7), 3.83 (3H, s, –OMe), 4.03 (1H, m, H-10), 4.82 (1H, m, H-12b), 4.91 (1H, m, H-12a), 6.64 (1H, d, *J* 1.5 Hz, H-2), 6.68 (1H, dd, *J* 7.5, 1.5 Hz, H-6), 7.04 (1H, dd, *J* 7.5, 0.6 Hz, H-5); EIMS *m/z* 248 (37) [M<sup>+</sup>, C<sub>16</sub>H<sub>24</sub>O<sub>2</sub>], 230 (2) [M–H<sub>2</sub>O]<sup>+</sup>, 205 (4), 189 (5), 175 (4), 162 (100), 149 (100), 135 (47), 123 (41), 117 (19), 105 (16), 91 (51), 84 (6), 77 (20), 71 (26); HREIMS calcd for C<sub>16</sub>H<sub>24</sub>O<sub>2</sub> 248.1776, found 248.1773.  
For allylic alcohol (**10**): colourless oil;  $R_f = 0.55$  (PE/Et<sub>2</sub>O, 2/3); IR (neat) 3403, 3066, 3030, 2926, 2865, 1649, 1610, 1582, 1510, 1453, 1419, 1378, 1308, 1254, 1161, 1132, 1025, 899, 850, 815 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.26 (3H, d, *J* 6.9 Hz, H-15), 1.42 (2H, m, H-9), 1.58 (2H, m, H-8), 1.68 (3H, s, H-13), 2.28 (3H, s, H-14), 2.69 (1H, sext, *J* 6.9 Hz, H-7), 4.03 (1H, t, *J* 6 Hz, H-10), 4.84 (1H, m, H-12b), 4.93 (1H, m, H-12a), 5.12 (2H, s, OCH<sub>2</sub>Ph), 6.73 (1H, d, *J* 1.5, H-2), 6.75 (1H, dd, *J* 1.5, 7.8 Hz, H-6), 7.09 (1H, dd, *J* 0.6, 7.8 Hz, H-5), 7.32–7.39 (5H, m, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  16.0 (C-14), 17.5 (C-13), 22.4 (C-15), 33.0 (C-9), 33.9 (C-8), 30.9 (C-7), 70.3 (OCH<sub>2</sub>Ph), 75.7 (C-10), 110.8 (C-8), 112.2 (C-12), 119.3 (C-6), 124.7 (C-4), 126.8–128.4 (C-2'–C-6'), 130.5 (C-5), 137.7 (C-1'), 146.4 (C-1), 148.8 (C-11), 157.0 (C-3); HRMS calcd for C<sub>22</sub>H<sub>28</sub>O<sub>2</sub> 324.2180, found 324.2182.