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Enantioselective synthesis of 1(*R*)-hydroxypolygodial

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This work is dedicated to the memory of Professor G. Sodano

Abstract—Enantioselective preparation of 1(*R*)-hydroxypolygodial (**5**) has been achieved starting from α-ionone through a synthetic strategy involving a Corey–Bakshi–Shibata oxazaborolidine-mediated reduction and a stereoselective Diels–Alder reaction as key steps.

Polygodial (**1**) belongs to a group of terpenoid unsaturated 1,4-dialdehydes, isolated from terrestrial and marine sources,[1] which are known to show a pungent sensation in the human tongue. Recently, a vanilloid activity has been reported for some of them.[2] Some years ago, some researchers suggested that biological activities of these compounds are linked to the dialdehyde moiety and to reactivity towards nucleophiles.[3] The observation that some bulkier molecules, for example, isocopalendial (**2**) and scalaradial (**3**), were not hot tasting, suggested that the size of the molecule was also important.[4] However, the hot taste reported for compound **4**,[5] a deacetoxy derivative of the tasteless sesterterpenoid scalaradial, pointed out the influence of an oxygenated function, such as the acetoxy group, on the bioactivity of these compounds (Fig. 1). This stimulated a research program directed to vanilloid active compounds containing the unsaturated 1,4-dialdehyde moiety and hydroxy or acetoxy groups in their skeleton and we chose 1(*R*)-hydroxypolygodial (**5**) as first target of our investigation.

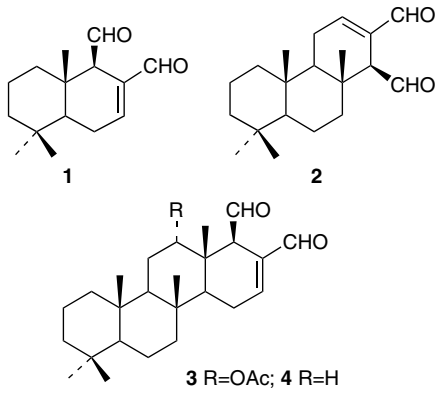
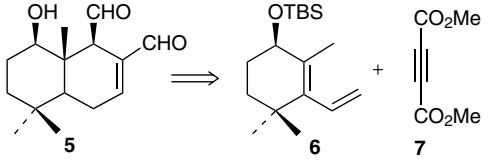


Figure 1.

Preparation of hydroxylated drimane compounds involving a microbial hydroxylation was not considered as this leads to a mixture of mono and diol derivatives containing the hydroxyl function in several positions of the drimane skeleton except at C-1.[6] We planned a synthetic scheme based on a Diels–Alder reaction starting from dimethylacetylenedicarboxylate (**7**) and the hydroxydiene derivative **6** whose preparation involves a stereocontrolled Corey–Bakshi–Shibata reduction (Scheme 1).[7]



Scheme 1. Retrosynthetic analysis.

Keywords: Total synthesis; Diels–Alder reaction; Terpenoids; Polygodial; Vanilloid activity.
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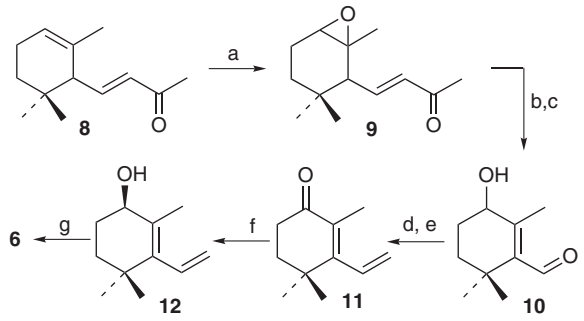


Scheme 2. Preparation of hydroxydiene **6**. Reagents and conditions: (a) MCPBA, CH_2Cl_2, −78 °C → 0 °C, 12 h; (b) O_3, CH_2Cl_2, −78 °C, 4 h then Me_2S, CH_2Cl_2, −78 °C → rt, 12 h; (c) pyrrolidine, Et_2O, rt, 12 h, 76% (three steps); (d) $MeP^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C → rt, 4 h; (e) PDC, CH_2Cl_2, rt, 1 h, 79% (two steps); (f) (*S*)-MeCBS reagent, BH_3·THF (syringe pump addition: 1.2 mmol/h), THF, 35 °C, 88%, 93% ee; (g) TBSCl, imidazole, CH_2Cl_2, rt, 12 h, 96%.

The first step of the synthesis (Scheme 2) consists of preparation of epoxide **9** from α-ionone (**8**).[8] Ozonolysis of **9**, followed by reductive work-up, afforded an epoxy-aldehyde which proved to be quite sensible to purification conditions; therefore, the following eliminative ring opening of the epoxide was performed on the crude extract obtained after ozonolysis leading to compound **10** (76% yield from **8**). The synthesis of ketone **11** was completed by Wittig reaction of aldehyde **10** with $CH_2{=}PPh_3$, followed by PDC oxidation (79%, two-step yield). (*R*)-2,4,4-Trimethyl-3-vinyl-2-cyclohexene-1-ol (**12**) was prepared by enantioselective reduction of dienone **11** with (*S*)-Me-Corey–Bakshi–Shibata [(*S*)-MeCBS] oxazaborolidine–borane reagent, giving dienol **12** (88% yield and 93% enantiomeric excess)[9] which was then converted into silyl derivative **6** (96%).

The Diels–Alder reaction of **6** with dimethylacetylenedicarboxylate (**7**) proceeded quite slowly (neat, 110 °C, 48 h) affording compound **13**[10] as a major product (40%) together with small amounts of its diastereomer **14** (5%) and triene **15** (8.5%) (Fig. 2). The reaction was stopped after 48 h, although unreacted diene **6** was still present, because longer reaction time favoured the increase of triene **15**.

The stereoselectivity observed can be rationalized by an approach of the dienophile to the diene *anti* to the allylic substituent. Ley's reductive isomerization procedure for **13** (H_2, Pd–C and HCl)[11] proved to be unsuitable for our substrate, causing partial loosing of the protecting group (Scheme 3). Furthermore, deprotection of **17** proved to be very difficult probably due to the bad

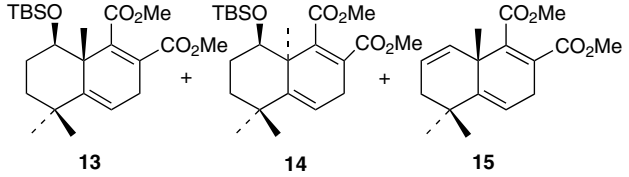
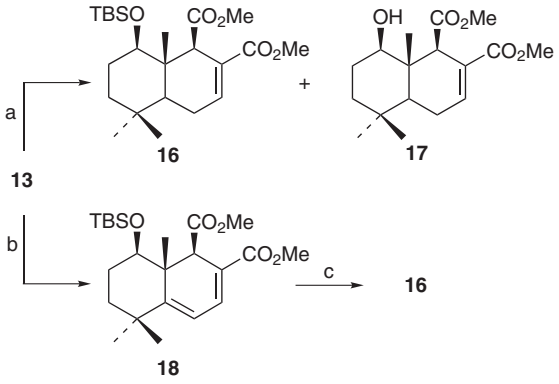


Figure 2.



Scheme 3. Preparation of **16**. Reagents and conditions: (a) H_2, Pd–C, HCl and MeOH, 12 h, **16** (27%), **17** (49%); (b) DBU, THF, 40 °C, 4 h, 90%; (c) H_2, Pd–C and MeOH, 5 h, 72%.

accessibility to the hydroxyl function. Therefore, we decided to move to the methodology of Lallemand and co-workers involving two steps: a base catalyzed isomerization followed by hydrogenation.[12]

DBU catalyzed isomerization[13] afforded mainly the conjugated diene **18** (90% yield), which was subjected to hydrogenation (H_2, Pd–C and MeOH) affording compound **16**[14] (72% yield). The stereochemistry of **16** was established via ^{1}H NMR NOE measurements (Fig. 3). Irradiation of H-1 (δ 3.74 ppm) led to enhancements of the signals due to H-5 (δ 1.17 ppm) and H-9 (δ 3.21 ppm).

These experiments indicated that H-1, H-5 and H-9 were in *cis*-relationship. Reduction of the ester functionalities produced diol **19**, which was then oxidized using Swern conditions ($C_2O_2Cl_2$, DMSO and NEt_3) to give dialdehyde **20** (87%).

Finally, 1(*R*)-hydroxypolygodial (**5**)[15] was produced by deprotection of the TBS ether using TBAF (74%) (Scheme 4).

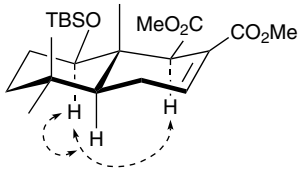
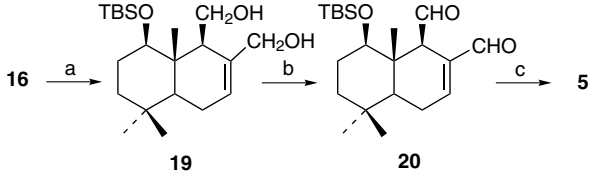


Figure 3.



Scheme 4. Synthesis of target **5**. Reagents and conditions: (a) DIBALH, THF, toluene, −78 °C → rt, 12 h, 94%; (b) Swern, 1 h, 87%; (c) TBAF, THF, rt, 2 h, 74%.

In conclusion, we have completed the synthesis of 1(*R*)-hydroxypolygodial (**5**), starting from α-ionone in 13 steps and 8% overall yield. An investigation on the vanilloid activity of **5** is now in progress and the results will be given in due course. This synthetic scheme offers the possibility of preparing other correlated naturally occurring dialdehydes, such as those isolated from *Drimys brasiliensis*.[16]

Acknowledgements

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9. The enantiomeric excess was determined by HPLC analysis (Chiralcel OD, 1% 2-propanol in hexane, 1 mL/min, t_R (*R*): 10.37 min, t_R (*S*): 9.21 min).
10. *Physical data of compound* **13**: $[\alpha]_D^{25}$ −50.7 (*c* 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (3H, s, CH_3Si–), 0.09 (3H, s, CH_3Si–), 0.89 (9H, s, $(CH_3)_3CSi$–), 1.08 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.34 (1H, m, H-3), 1.47 (1H, ddd, *J* = 4.5, 4.5, 13.6 Hz, H′-3), 1.73–1.79 (2H, m, H-2 and H′-2), 2.78 (1H, dd, *J* = 2.1, 22.4 Hz, H-7), 3.04 (1H, dd, *J* = 5.8, 22.4 Hz, H′-7), 3.69 (3H, s, $–CO_2CH_3$), 3.78 (3H, s, $–CO_2CH_3$), 4.17 (1H, dd, *J* = 5.8, 8.4 Hz, H-1), 5.70 (1H, dd, *J* = 2.1, 5.8 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −3.0 (q), −2.6 (q), 18.9 (s), 21.7 (q), 26.4 (×3) (q), 26.8 (t), 28.5 (t), 31.3 (q), 32.2 (q), 35.4 (s), 36.1 (t), 46.3 (s), 51.9 (q), 52.5 (q), 74.1 (d), 119.0 (d), 126.6 (s), 148.0 (s), 148.8 (s), 166.4 (s), 169.2 (s). EIMS: *m*/*z* 422, 365, 333, 305, 291, 259, 231, 199.
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14. *Physical data of compound* **16**: $[\alpha]_D^{25}$ −39.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.04 (3H, s, CH_3 Si–), 0.09 (3H, s, CH_3Si–), 0.85 (3H, s, CH_3), 0.90 (9H, s, $(CH_3)_3CSi$–), 0.91 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.17 (1H, dd, *J* = 6.0, 10.6 Hz, H-5), 1.26 (1H, m, H-3), 1.43 (1H, ddd, *J* = 3.3, 3.3, 13.6 Hz, H′-3), 1.58 (1H, dddd, *J* = 3.0, 11.2, 13.4, 13.6 Hz, H-2), 1.71 (1H, dddd, *J* = 3.3, 4.2, 4.2, 13.4 Hz, H′-2), 2.15–2.28 (2H, m, H-6 and H′-6), 3.21 (1H, m, H-9), 3.61 (3H, s, $–CO_2CH_3$), 3.66 (3H, s, $–CO_2CH_3$), 3.74 (1H, dd, *J* = 4.2, 11.2 Hz, H-1), 7.02 (1H, m, H-7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −2.9 (q), −2.3 (q), 9.2 (q), 18.9 (s), 21.8 (q), 24.5 (t), 26.6 (×3) (q), 28.5 (t), 32.5 (s), 32.6 (q), 39.4 (t), 43.4 (s), 48.1 (d), 51.6 (q), 51.7 (q), 56.6 (d), 80.6 (d), 129.6 (s), 140.3 (d), 167.3 (s), 173.3 (s). EIMS: *m*/*z* 424, 367, 335, 205, 171, 157, 145, 131.
15. *Physical data of 1(R)-hydroxypolygodial* (**5**): $[\alpha]_D^{31}$ −175.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.24 (1H, ddd, *J* = 4.0, 13.5, 13.5 Hz, H-3), 1.44 (1H, ddd, *J* = 3.2, 3.2, 13.5 Hz, H′-3), 1.54 (1H, dd, *J* = 5.1, 11.5 Hz, H-5), 1.57–1.72 (2H, m, H-2 and H′-2), 2.24 (1H, br dd, *J* = 11.5, 20.4 Hz, H-6), 2.51 (1H, ddd, *J* = 5.1, 5.1, 20.4 Hz, H′-6), 3.63 (1H, dd, *J* = 4.4, 10.9 Hz, H-1), 3.71 (1H, br s, H-9), 7.04 (1H, m, H-7), 9.39 (1H, s, OHCC-8), 9.93 (1H, d, *J* = 1.2 Hz, OHCC-9). ^{13} C NMR ($CDCl_3$, 100 MHz): δ 15.1 (q), 21.9 (q), 25.5 (t), 27.7 (t), 32.2 (q), 32.4 (s), 39.5 (t), 43.0 (d), 44.0 (s), 54.5 (d), 75.6 (d), 137.9 (s), 152.5 (d), 192.6 (d), 202.8 (d). ESMS: *m*/*z* 249 $[M-H]^-$.
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