Synthesis of (−)-malyngolide using reactions of alkylidenecarbenes

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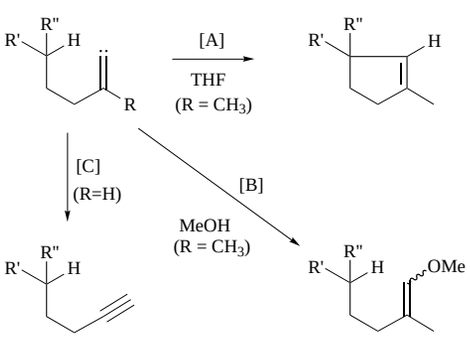
An alkylidenecarbene has been generated by the reaction of dimethyl (diazomethyl)phosphonate (DAMP), Bu^{t}OK and methyl ketone 6, which itself has been derived from D-mannitol in high yield. The carbene undergoes an intramolecular 1,5 C–H insertion reaction to give the chiral cyclopentane derivative 3 in good yield. It has been found that the same conversion can be conveniently carried out on a large scale with lithiotrimethylsilyldiazomethane. The double bond of 3 has been cleaved to give the keto aldehyde 2, which has been subjected to a double C_1 elongation reaction *via* alkylidenecarbenes using DAMP and K_2CO_3. The resulting alkyne has been alkylated to give an intermediate 11 which has the carbon skeleton of malyngolide. Deprotection of 11, followed by elaboration of the functional groups completes the chiral synthesis of (−)-malyngolide 1.

Introduction

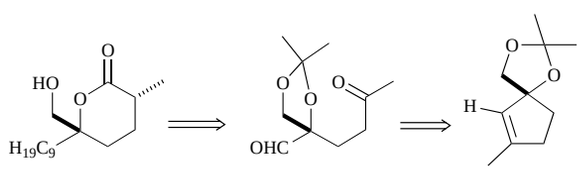
The interest in carbenes and carbenoids as useful intermediates for organic synthesis has grown a great deal.[1] In particular, extensive studies of rhodium carbenoids provided many useful synthetic tools, and these reactions were used as key steps in the syntheses of natural products. Free alkylidenecarbenes are also increasingly interesting to organic chemists as various new methods for their generation have been recently developed.[2,3] The representative reactions of alkylidenecarbenes[2e] are shown in Scheme 1. Intramolecular C–H insertion leads to cyclopentene formation (reaction [A]); intermolecular O–H insertion with an alcohol gives an enol ether (reaction [B]); and the Fritsh–Buttenberg–Wiechell rearrangement (1,2-hydride shift) produces a terminal alkyne (reaction [C]). Here, we report the details of the novel chiral synthesis of (−)-malyngolide **1** using all three of these reactions.[3c] Malyngolide, (−)-**1** is an antibiotic, isolated from a blue-green alga *Lyngbya majuscula* Gomont.[4]



Scheme 1

Results and discussion

The major stereochemical problem with the synthesis of **1** is how to construct the chiral quaternary center (protected tertiary alcohol), since 2-*epi*-**1** is convertible to (−)-**1** with base.[5] Examining the structure of (−)-**1**, the keto aldehyde **2** obtainable by scission of the double bond of **3** was a suitable synthetic intermediate (Scheme 2). If the C_9-alkyl chain and lactone carbonyl group were introduced, respectively, from the aldehyde and the ketone site of **2**, the whole carbon skeleton and all functionalities for **1** would be complete. Therefore, the first stage of the synthesis was effective preparation of the cyclopentane **3**, using intramolecular C–H insertion of an alkylidenecarbene.



1 **2** **3**

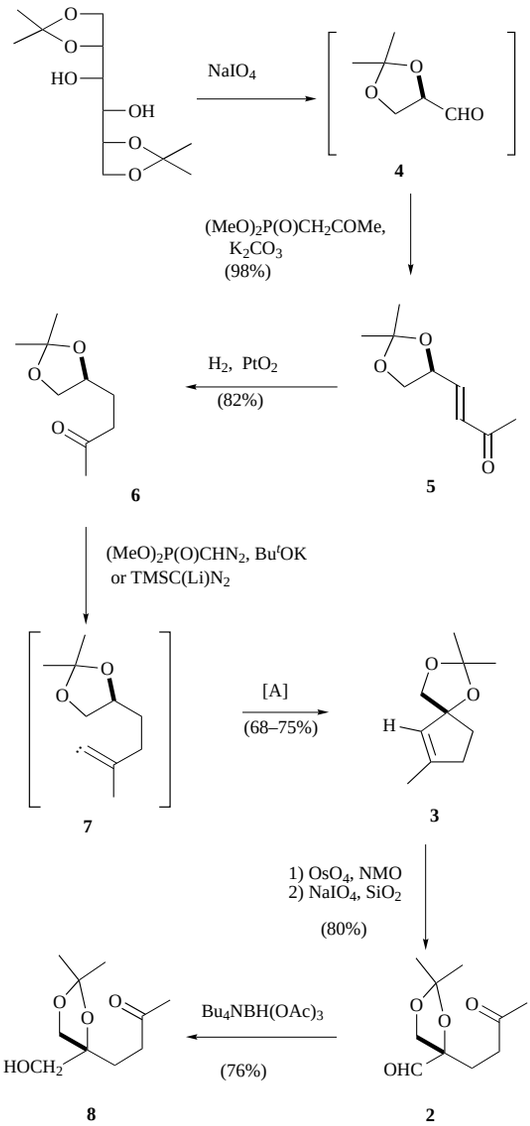
Scheme 2

Modifying Takano's procedure for (*S*)-ethyl 4,5-*O*-isopropylidene-4,5-dihydroxypent-2-enoate,[6] chiral glyceraldehyde **4** was treated with dimethyl 2-oxopropylphosphonate at 0 °C for 1 h to give the α,β-unsaturated ketone **5**, accompanied by a small amount of *cis* isomer (Scheme 3). In this reaction, control of the temperature was important to prevent Michael addition of the solvent to the product. Ketone **5** was hydrogenated over Pd/C or PtO_2 to give the saturated ketone **6**. Treatment of **6** with excess methyl diazomethylphosphonate (DAMP)[7] and Bu^{t}OK at −78 °C for 5 h generated the alkylidenecarbene **7**, which furnished the cyclized product **3** *via* 1,5-intramolecular C–H insertion.

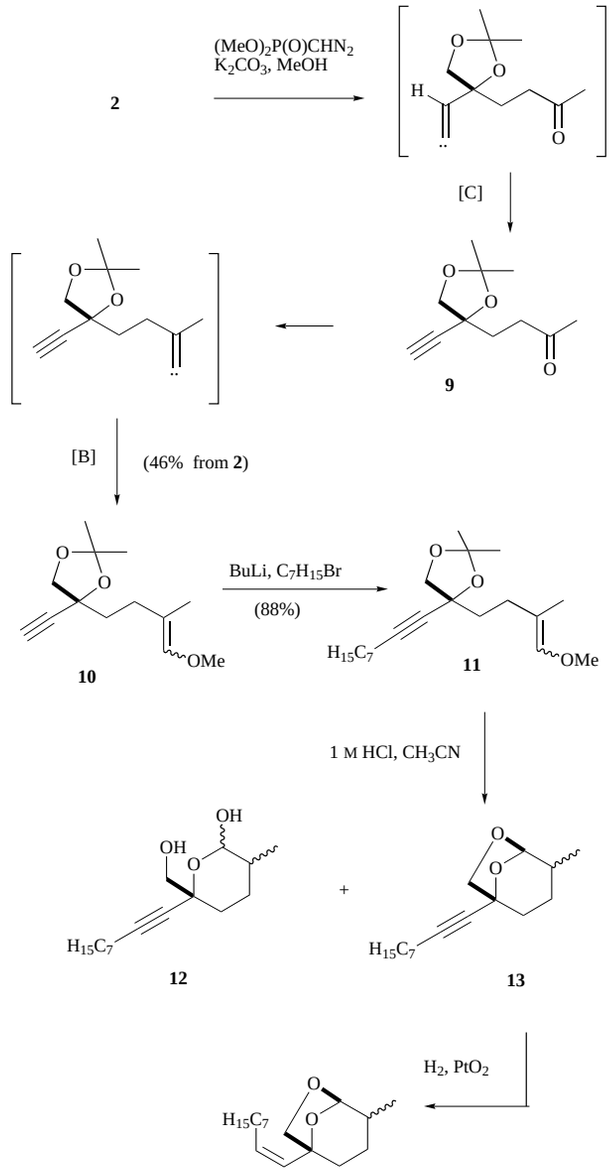
The reaction proceeded cleanly in a reasonable yield, however, some shortcomings were found when it was conducted on a large scale. Because of the instability and low nucleophilicity of the corresponding anion of DAMP, the reaction must be carried out at low temperature (−78 °C) over a long period (5–10 h) using an excess (two- to three-fold) of reagent and Bu^{t}OK. In addition, the preparation of DAMP on a large scale was troublesome and the safety of the reagent is not well known.

By analogy with the Wittig–Horner reaction and the Peterson reaction, we attempted to use a safe and commercially available reagent, trimethylsilyldiazomethane[8] instead of DAMP. At the outset of the work, there had been two reports regarding the reactions of lithiotrimethylsilyldiazomethane ($TMSCLiN_2$) and aldehydes or ketones.[9] One was epoxy silane formation from aldehydes[10] and another was phenylacetylene formation from benzophenone.[11] In the latter case, implementation of the generation of free alkylidenecarbene appeared encouraging to us.

Fortunately, we found that similar results to those with DAMP were obtained by mixing only 1.5 equivalents of



Scheme 3



Scheme 4

$TMSCLiN_2$ and ketones at −78 °C and just warming the reaction mixture to 0 °C.[2l] Ketone **6** was an especially good substrate for the reaction. Thus, the multi-gram scale preparation of cyclopentene **3** became routinely possible.

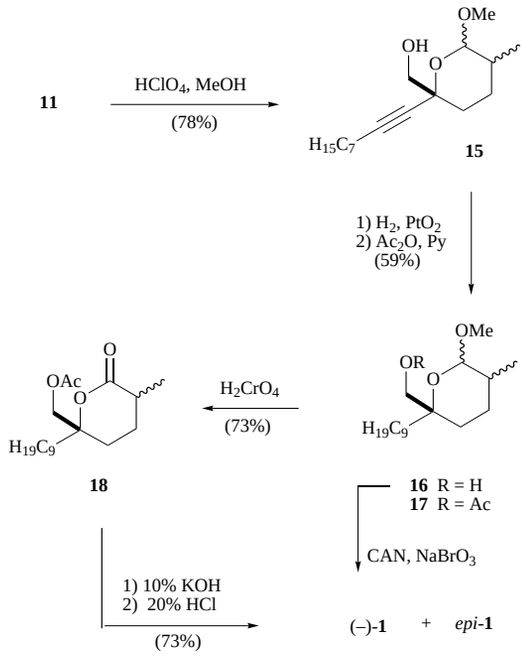
After dihydroxylation of the double bond of **3**, silica gel-assisted glycol fission[12] gave the keto aldehyde **2** in good yield. Direct cleavage of the double bond of **3** by ozonolysis or Johnson–Lemieux's conditions resulted in a lower yield of **2**. Selective reduction of the aldehyde group of **2** with tetrabutylammonium triacetoxyborohydride gave the keto alcohol **8**. The optical purity of **8** was determined to be 97% ee by NMR measurement of both the (*S*)- and (*R*)-MTPA esters of **8**. Partial racemization probably occurred during the conversion of **4** to **5** under the basic conditions.

The keto aldehyde **2** was treated with DAMP in methanol with base (Scheme 4). Reaction of the aldehyde and the reagent proceeded rapidly, providing the alkyne **9** *via* rearrangement of the terminal alkylidene carbene. Without the isolation of **9**, the keto group of **9** slowly reacted with the reagent at room temperature. The carbene intermediate underwent O–H insertion with the solvent to give the enol ether **10**. When the reaction was carried out at room temp. for 20 h with 5 equiv. of DAMP and K_2CO_3 as base, the double C_1 elongation reaction occurred to produce **10** as a diastereomeric mixture in 46% yield, accompanied with 15% yield of the ketone **9**. Use of Bu^{t}OK as base resulted in a poor yield of **10**, due to decomposition of the products. Since ketone **9** could be converted to **10** in 75% yield by Wittig reaction with methoxymethylenetriphenylphosphorane in DMSO, the total yield of **10** from **2** was calculated at 54%.

Deprotonation of the alkyne **10** followed by alkylation with 1-bromoheptane in the presence of HMPA gave the compound **11** that includes all carbons of the target molecule. Hydrolysis of both the acetonide and enol ether with hydrochloric acid furnished the hemiacetal **12** and the cyclic acetal **13** as a mixture of stereoisomers. Upon standing, **12** readily cylized to **13**. Hydrogenation of **13** partially occurred to give exclusively olefin **14** using PtO_2 as a catalyst under atmospheric pressure. Oxidation of acetal **13** or hemiacetal **12** to the lactone alcohol was unsuccessful with various reagents.

Acidic methanolysis of **11** gave the acetal **15** in good yield (Scheme 5). In contrast to the bicyclic compound **13**, catalytic hydrogenation of **15** to the saturated compound **16** was possible under atmospheric pressure. Oxidation of **16** with ceric ammonium nitrate (CAN) and $NaBrO_3$ in wet CH_3CN[13] gave the final product (−)-**1** and its epimer, however, the yield (5–6%) was unsatisfactory.

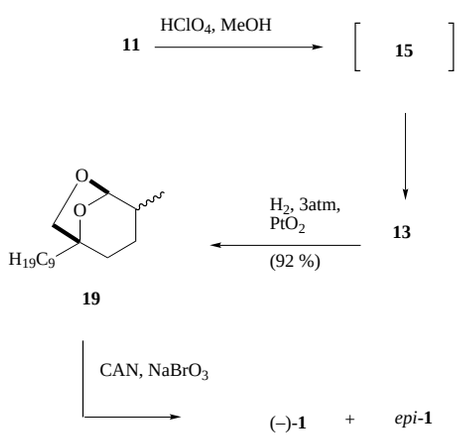
Thus, we decided to protect the primary alcohol. Acetylation of **16**, to give **17**, followed by Jones' oxidation gave the lactone acetate **18**, which was hydrolyzed with aqueous NaOH. Acidic



Scheme 5

work-up with 6 M HCl induced re-lactonization giving a 1:1 ratio of (−)-malyngolide **1** and its epimer in good yield. The spectral and physical properties of the synthetic malyngolide were identical with those reported in the literature.[4] As the epimer is known to be convertible to **1**,[5] our synthesis of (−)-**1** was accomplished at this point. The total yield from mannitol diacetonide was 2% in 13 steps.

During this preparation of **1** on a larger scale for the full characterization of synthetic intermediates, the acidic methanolysis of **11** almost exclusively yielded the cyclized product **13**, due to a trivial difference in reaction conditions (Scheme 6).



Scheme 6

As the attempt to convert **13** into **15** failed, we again tried to use **13** as the precursor of **1**. Fortunately, **13** could be hydrogenated to saturated compound **19** in good yield under higher pressure (3 kg cm^{-3}) than before. Opening of the cyclic acetal **19** was unsuccessful, however, the formation of (−)-**1** and its epimer was detected when the direct oxidation of **19** was conducted with CAN and $NaBrO_3$ in wet CH_3CN. A long reaction time increased the decomposition of products and starting material and did not improve the yield. Finally, the best yield based on recovered starting material was obtained by interrupting the reaction after 1 h reflux (about 20% conversion). By repeating the reaction four times under those conditions, a 45% yield of **1** and its epimer was obtained from **19**. As a result, the formal overall yield (3%) and the number of steps for **1** (10 steps) were both slightly improved.

Experimental

Melting points were measured on a Yanaco MP-J3 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1720 FT-IR spectrometer. Optical rotations were measured in 0.2 or 0.5 dm cells on a Horiba SEPA-200 polarimeter at ambient temperature and are given in 10^{-1} deg cm^2 g^{-1}. Nuclear magnetic resonance spectra (NMR) were recorded on either a JEOL JNM-GSX400 or a Bruker ARX-400 spectrometer. *J* Values are given in Hz. Mass spectra (MS) and exact mass determinations were obtained with a JEOL JMS-DX303HF or JMX-700 mass spectrometer. Elemental analyses were performed with a Perkin-Elmer PE-2400 analyzer. THF and Et_2O were distilled from sodium benzophenone ketyl under nitrogen. CH_2Cl_2 and MeOH were distilled over calcium hydride under nitrogen. Analytical TLC was performed on 1.5 × 5 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm) manufactured by E. Merck. Column chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM).

(4*S*)-2,2-Dimethyl-4-[(*E*)-3-oxobut-1-enyl]-1,3-dioxolane 5

Takano's method was modified.[6] To a suspension of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (7.0 g, 26.7 mmol) in 5% aq. $NaHCO_3$ (126 ml), was added a solution of $NaIO_4$ (6.95 g, 32.2 mmol) in distilled water (35 ml) at 0 °C. After stirring for 3 h at 0 °C, dimethyl (2-oxopropyl)phosphonate and 6 M aq. K_2CO_3 were added to the mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, and extracted with CH_2Cl_2. The organic layer was washed with water and dried over anhydrous K_2CO_3. The solvent was evaporated and the residue was purified by column chromatography on silica gel (5:1→4:1 hexane–EtOAc) to give **5** (8.54 g, 94%) as an oil; $[\alpha]_D^{20}$ +42.5 (*c* 1.53, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1686 (C=O), 1636 (C=C); $\delta_H(CDCl_3)$ 1.42 (3H, s), 1.46 (3H, s), 2.29 (3H, s, $COCH_3$), 3.69 (1H, dd, *J* 7.2, 8.2, CH_2O), 4.20 (1H, dd, *J* 6.6, 8.2, CH_2O), 4.68 (1H, dddd, *J* 0.1, 5.8, 6.6, 7.2, CHO), 6.32 (1H, dd, *J* 0.1, 16.0, C=CHCO), 6.70 (1H, dd, *J* 5.8, 16.0, =C*H*CH); $\delta_C(CDCl_3)$ 25.6, 26.4, 27.4, 68.8, 75.1, 110.2, 131.1, 143.2, 198.0; *m*/*z* 155 (90%, $M^+ - Me$), 113 (65), 82 (45), 72 (36), 43 (100) (Found: C, 63.34; H, 8.15. Calc. for $C_9H_{14}O_3$: C, 63.51; H, 8.29%).

(4*S*)-2,2-Dimethyl-4-(3-oxobutyl)-1,3-dioxolane 6

Platinum(IV) oxide (86 mg) in EtOAc (80 ml) was treated with hydrogen for 30 min under atmospheric pressure. After the addition of a solution of **5** (6.465 g, 38.0 mmol) in EtOAc (50 ml), the mixture was stirred for 4 h. The catalyst was removed by filtration and the filtrate was evaporated. Column chromatography on silica gel (5:1→3:1 hexane–EtOAc) gave **6** (5.36 g, 82%) as an oil; $[\alpha]_D^{21}$ −35.4 (*c* 1.06, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (C=O); $\delta_H(CDCl_3)$ 1.34 (3H, s), 1.40 (3H, s), 1.71–1.80 (1H, m), 1.84–1.92 (1H, m), 2.17 (3H, s, $COCH_3$), 2.51–2.67 (2H, m, $COCH_2$), 3.53 (1H, dd, *J* 7.7, 7.0, CH_2O), 4.04 (1H, dd, *J* 7.7, 6.2, CH_2O), 4.07–4.15 (1H, m, CHO); $\delta_C(CDCl_3)$ 25.6, 26.9, 27.4, 29.9, 39.6, 69.2, 75.0, 108.9, 208.1; *m*/*z* 157 (100%, $M^+ - Me$), 115 (28), 97 (41), 71 (36), 55 (13), 41 (15) (Found: C, 63.02; H, 9.19. Calc. for $C_9H_{16}O_3$: C, 62.77; H, 9.36%).

(5*R*)-2,2,7-Trimethyl-1,3-dioxaspiro[4.4]non-6-ene 3

To a solution of trimethylsilyldiazomethane (2.0 M in hexane, 23.8 ml, 47.6 mmol) in THF (105 ml), was added *n*-butyllithium in hexane (1.4 M, 30.1 ml, 42 mmol) at −78 °C under nitrogen. After stirring for 1 h, a solution of **6** in THF (35 ml) was added and the stirring was continued for 1 h. The mixture was warmed to 0 °C and stirred for an additional 0.5 h. The reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with pentane. The organic layer was dried over anhydrous Na_2SO_4 and carefully evaporated at 50 °C. Evaporation under highly reduced pressure or a long evaporation time induced the loss of the volatile **3**, and significantly lowered the

yield. The crude product was chromatographed on silica gel (6:1 hexane–EtOAc) to give **3** (3.53 g, 73%); $[\alpha]_D^{21}$ +13.1 (*c* 1.33, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1658 (C=C), 1051; $\delta_H(CDCl_3)$ 1.39 (3H, s), 1.40 (3H, s), 1.77 (3H, br s, $=CCH_3$), 2.04–2.23 (3H, m), 2.39–2.47 (1H, m), 3.58 (2H, s, CH_2O), 5.31–5.33 (1H, m, C=CH); $\delta_C(CDCl_3)$ 16.9, 26.82, 26.85, 35.0, 37.0, 73.2, 93.2, 108.7, 127.0, 146.2; *m*/*z* 168 (0.2%, M^+), 153 (4), 110 (41), 97 (33), 93 (40), 81 (46), 72 (33), 58 (16), 53 (31), 43 (100).

(5*S*)-6,7-Dihydroxy-2,2,7-trimethyl-1,3-dioxaspiro[4.4]nonane

To a solution of **3** (710 mg, 4.22 mmol) in THF–water (3:1, 21 ml), was added osmium tetroxide (0.079 M in water, 1.1 ml, 0.084 mmol) and then *N*-methylmorpholine *N*-oxide (50% in water, 4.5 ml, 29.5 mmol) was added. After stirring for 41 h at room temp., the mixture was evaporated and the aqueous residue was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (3:1→1:1 hexane EtOAc) to give the diol (584 mg, 68%) as a diastereomeric mixture; mp 45–49 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3453 (OH); $\delta_H(CDCl_3)$ 1.33 (3H, s), 1.38 (3H, s), 1.42 (3H, s, $HOCCH_3$), 1.76–1.88 (3H, m), 1.97–2.05 (1H, m), 3.72 (1H, d, *J* 9.0, OCH_2), 3.75 (1H, s, HOC*H*), 4.32 (1H, d, *J* 9.0); $\delta_C(CDCl_3)$ 26.2, 26.3, 26.8, 32.8, 34.5, 69.8, 76.6, 82.4, 88.8, 108.2 (Found: C, 59.28; H, 9.17. Calc. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97%).

(4*S*)-4-Formyl-2,2-dimethyl-4-(3-oxobutyl)-1,3-dioxolane 2

A solution of the diol (722 mg, 3.55 mmol) in CH_2Cl_2 (9 ml) was added to a stirring mixture of silica gel (230–400 mesh, 6.8 g) and a solution of sodium periodate (1.112 g) in water (8 ml) and CH_2Cl_2 (50 ml). The mixture was stirred overnight, filtered and evaporated to give the essentially pure keto aldehyde **2** (664 mg, 93%), which was used in the next reaction without purification; $\nu_{max}(CHCl_3)/cm^{-1}$ 1734 (MeC=O), 1718 (HC=O); $\delta_H(CDCl_3)$ 1.435 (3H, s), 1.436 (3H, s), 1.89–1.97 (1H, m), 2.06–2.13 (1H, m), 2.16 (3H, s, $COCH_3$), 2.43–2.62 (2H, m, $COCH_2$), 3.78 (1H, d, *J* 9.2, CH_2O), 4.19 (1H, d, *J* 9.2, CH_2O), 9.64 (1H, s, CHO); $\delta_C(CDCl_3)$ 26.2, 26.4, 27.1, 29.8, 37.3, 69.7, 86.4, 111.4, 202.4, 207.2.

(4*R*)-4-Ethynyl-4-(3-oxobutyl)-2,2-dimethyl-1,3-dioxolane 9 and (4*R*)-4-ethynyl-4-(4-methoxy-3-methylbut-3-enyl)-2,2-dimethyl-1,3-dioxolane 10

To a solution of dimethyl (diazomethyl)phosphonate (10.25 g, 68.3 mmol) and keto aldehyde **2** (2.65 g, 13.2 mmol) in MeOH, was slowly added anhydrous K_2CO_3 at room temperature. After stirring for 20 h, the reaction was quenched with the addition of saturated aqueous NH_4Cl. MeOH was evaporated and the aqueous residue was extracted with CH_2Cl_2. The organic layer was evaporated, and the crude product was purified by column chromatography on silica gel (10:1→5:1 hexane–EtOAc) giving the ketone **9** (0.39 g, 15%) and the enol ether **10** (1.38 g, 46%) as a diastereomeric mixture.

9: $[\alpha]_D^{21}$ +8.6 (*c* 1.04, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3306 (HC≡C), 2117 (C≡C), 1715 (C=O); $\delta_H(CDCl_3)$ 1.39 (3H, s), 1.49 (3H, s), 2.00 (2H, t, *J* 7.5, $OCCH_2$), 2.19 (1H, s, C≡CH), 2.50 3H, s, $COCH_3$), 2.73 (2H, dd, *J* 7.5, 14.2, $COCH_2$), 3.86 (1H, d, *J* 8.4, CH_2O), 4.18 (1H, d, *J* 8.4, CH_2O); $\delta_C(CDCl_3)$ 25.8, 26.8, 30.0, 33.5, 39.0, 73.1, 74.9, 76.0, 84.4, 111.1, 207.7; *m*/*z* 181 (6%, $M^+ - Me$), 138 (2), 67 (2), 58 (3), 53 (3), 51 (3), 43 (100), 39 (15) (Found: C, 67.01; H, 8.38. Calc. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%).

10: $[\alpha]_D^{21}$ +4.3 (*c* 1.05, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3307 (HC≡C), 2126 (C≡C), 1688 (C=C); $\delta_H(CDCl_3)$ 1.40 (2.1H, s), 1.41 (0.9H, s), 1.51 (3H, s), 1.60 (3H, s, $=CCH_3$), 1.71–1.90 (2H, m), 2.00–2.28 (2H, m), 2.495 (0.3H, s, C≡CH), 2.501 (0.7H, s, C≡CH), 3.52 (0.9H, s, OCH_3), 3.55 (2.1H, s, OCH_3), 3.83 (0.7H, d, *J* 8.4, CH_2O), 3.88 (0.3H, d, *J* 8.4, CH_2O), 4.16 (1H, d, *J* 8.4, CH_2O), 5.75 (0.3H, s, C=CH), 5.82 (0.7H, s, C=CH); $\delta_C(CDCl_3)$ 12.85, 17.21, 24.12, 25.98, 26.03, 26.85, 26.89, 28.99, 37.38, 38.58, 59.23, 72.66, 72.84, 74.39, 74.66, 76.90, 84.92, 85.08, 110.73, 112.90, 113.05, 142.05, 142.15; *m*/*z* 224 (4%, M^+), 166 (17), 153 (10), 137 (12), 91 (12), 77 (12), 45 (15), 43 (100) (HRMS Found: 224.1452. Calc. for $C_{13}H_{20}O_3$: 224.1411).

(4*R*)-4-(Non-1-ynyl)-5-(4-methoxy-3-methylbut-3-enyl)-2,2-dimethyl-1,3-dioxolane 11

To a solution of alkyne **10** (166 mg, 0.74 mmol) in THF (2.5 ml), was added butyllithium in hexane (0.74 ml, 1.18 mmol) at −78 °C under nitrogen. After 10 min, hexamethylphosphorus triamide was added and the solution was stirred for 30 min at −78 °C. After the addition of 1-bromoheptane, the mixture was warmed to room temp., stirred for 3.5 h, and quenched with saturated aqueous NH_4Cl. It was extracted with hexane, and the organic layer was dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography on silica gel (30:1 hexane–EtOAc) yielded **11** (210 mg, 88%) as an oil; $[\alpha]_D^{21}$ −1.41 (*c* 1.80, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2241 (C≡C), 1687 (C=C); $\delta_H(CDCl_3)$ 0.88 (3H, t, *J* 6.4, CH_3CH_2), 1.27 (10H, br s, $CH_2 \times 5$), 1.39 (3H, s, $OCCH_3$), 1.50 (3H, s, $OCCH_3$), 1.54 [0.9H, d, *J* 1.4, $C(CH_3)=C$], 1.59 [2.1H, d, *J* 1.3, $C(CH_3)=C$], 1.65–1.85 (3H, m, $CH_2CH_2C=CH$), 1.99–2.15 (1H, m, CH_2-$CH_2C=CH$), 2.21 (2H, t, *J* 7.0, $CH_2C\equiv C$), 3.51 (0.9H, s, OCH_3), 3.54 (2.1H, s, OCH_3), 3.80 (0.7H, d, *J* 8.1, CH_2O), 3.86 (0.3H, d, *J* 8.1, CH_2O), 4.07 (1H, d, *J* 8.1, CH_2O), 5.74 (0.3H, br s, C=CH), 5.81 (0.7H, br s, C=CH); $\delta_C(CDCl_3)$ 12.9, 14.0, 17.2, 18.7, 22.6, 24.3, 26.0, 26.1, 27.00, 27.04, 28.6, 28.8, 29.2, 31.7, 38.0, 39.2, 59.2, 74.6, 74.9, 76.7, 77.2, 77.4, 81.0, 81.2, 85.4, 85.6, 110.1, 110.2, 113.3, 113.5, 141.8, 141.9; *m*/*z* 322 (0.2%, M^+), 232 (5), 205 (4), 173 (3), 161 (4), 133 (8), 119 (8), 115 (8), 105 (10), 85 (16), 55 (17), 43 (100) (Found: C, 74.72; H, 10.81. Calc. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63%).

4-Methyl-1-(non-1-ynyl)-6,8-dioxabicyclo[3.2.1]octane 13

$HClO_4$ (6.6 ml) was added to a solution of acetonide **11** (1.707 g) in MeOH (100 ml) at room temp. After stirring for 0.5 h at room temp., saturated aqueous $NaHCO_3$ was added. MeOH was evaporated and the residue was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica gel (15:1 hexane–EtOAc) gave the cyclized product **13** (464 mg, 35%) as an oil; $[\alpha]_D^{21}$ −53.1 (*c* 1.75, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2250 (C≡C); $\delta_H(CDCl_3)$ 0.85 (3H, t, *J* 6.8, CH_3CH_2), 0.85 (0.9H, d, *J* 6.9, $CHCH_3$), 1.01 (2.1H, d, *J* 7.2, $CHCH_3$), 1.27–1.37 (10H, m), 1.40–1.54 (1H, m), 1.60–1.66 (1H, m), 1.72–1.79 (1H, m), 1.97–2.07 (1H, m), 2.12–2.17 (1H, m), 2.210 (0.6H, t, *J* 7.1, $CH_2C\equiv C$), 2.212 (1.4H, t, *J* 7.2, $CH_2C\equiv C$), 3.69 (0.7H, dd, *J* 6.8, 1.8, CH_2O), 3.72 (0.3H, dd, *J* 6.8, 1.8, CH_2O), 3.97 (0.3H, d, *J* 6.8, CH_2O), 4.03 (0.7H, d, *J* 6.8, CH_2O), 5.26 (0.3H, br s, OCHO), 5.31 (0.7H, br s, OCHO); $\delta_C(CDCl_3)$ 14.1, 15.1, 16.6, 18.7, 22.5, 22.6, 25.0, 28.4, 28.7, 28.8, 31.6, 31.7, 32.9, 34.9, 35.1, 71.9, 73.0, 74.7, 77.6, 87.0, 106.48, 106.53 (Found: C, 76.97; H, 10.61. Calc. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%).

4-Methyl-1-nonyl-6,8-dioxabicyclo[3.2.1]octane 19

The alkyne **13** (464 mg) in ethanol (10 ml) was hydrogenated in the presence of platinum oxide (50.8 mg) under 3 kg cm^{-2} pressure. After filtration and evaporation, the residue was chromatographed on silica gel (20:1 hexane–EtOAc) to give the saturated compound **19** (436 mg, 92% yield); major isomer: $[\alpha]_D^{21}$ −56.3 (*c* 0.40, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1102 (C–O–C); $\delta_H(CDCl_3)$ 0.85 (3H, d, *J* 6.7, $CHCH_3$), 0.87 (3H, t, *J* 6.6, CH_2CH_3), 1.26 (12H, br s), 1.33–1.46 (2H, m), 1.53–1.83 (7H, m), 3.41 (1H, dd, *J* 6.8, 1.6, CH_2O), 3.80 (1H, d, *J* 6.8, CH_2O), 5.18 (1H, s, OCHO); $\delta_C(CDCl_3)$ 14.1, 16.7, 22.6, 24.2, 25.3, 29.3, 29.5, 30.1, 31.8, 32.2, 35.4, 36.6, 72.3, 80.8, 106.1 (Found: C, 75.66; H, 11.62. Calc. for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%).

(−)-Malyngolide 1 and 2-*epi*-malyngolide

The cyclic acetal **19** (367 mg) in CH_3CN–water (7:3, 7.2 ml)

was treated with ceric ammonium nitrate (158 mg) and $NaBrO_3$ (608 mg) at 60 °C for 45 min. After evaporation of the solvent, the residue was extracted with aq. $NaHCO_3$ and CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography on silica gel (10:1 hexane–EtOAc) gave the starting material (296 mg, 81%), malyngolide **1** (11 mg, 5.4%) and its 2-epimer (6 mg, 4.1%).

1: $[a]_D^{22}$ −12.5 (*c* 1.08, $CHCl_3$) {lit.,[4] $[a]_D$ −13 (*c* 2, $CHCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3596, 3424 (OH), 1718 (C=O); $\delta_H(CDCl_3)$ 0.88 (3H, t, *J* 7.0, CH_2CH_3), 1.26 (14H, br s, CH_2 × 7), 1.30 (3H, d, *J* 7.0, $CHCH_3$), 1.54–1.81 (4H, m, O=CCHC$H_2$$CH_2$ and CCH_2), 1.91–2.02 (2H, m, O=CCHCH_2CH_2), 2.42 (2H, m, OH and C*H*-CH_3), 3.49 (1H, d, *J* 11.9, CH_2OH), 3.66 (1H, d, *J* 11.9, CH_2OH); *m*/*z* 239 (13%), 211 (8), 155 (10), 143 (9), 115 (4), 95 (9), 71 (12), 55 (76), 43 (100) (Found: C, 71.15; H, 10.92. Calc. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18%).

epi-**1**: $[a]_D^{22}$ +19.4 (*c* 1.42, $CHCl_3$) {lit.,[5] $[a]_D^{25}$ +19.1 (*c* 1.13, $CHCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3595, 3418 (OH), 1719 (C=O); $\delta_H(CDCl_3)$ 0.88 (3H, t, *J* 7.0, CH_2CH_3), 1.26 (14H, br s, CH_2 × 7), 1.29 (3H, d, *J* 7.0, $CHCH_3$), 1.7 (4H, m, O=CCHC$H_2$$CH_2$ and CCH_2), 1.95 (3H, m, OH and O=CCHCH_2CH_2), 2.45 (1H, m, C*H*CH_3), 3.61 (2H, s, CH_2OH); *m*/*z* 239 (44%), 211 (30), 155 (17), 143 (15), 115 (5), 95 (11), 71 (29), 55 (100).

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