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Methyl 3-bromomethyl-3-butenoate as an isopentane building block for the stereoselective preparation of (*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-carbaldehyde and (+)-faranal

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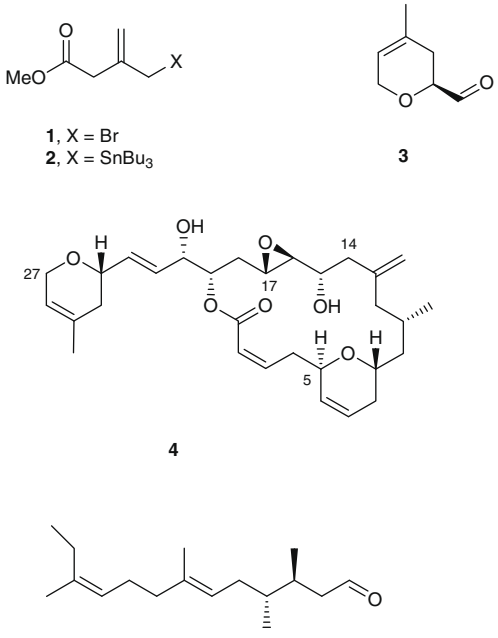
ABSTRACT

(*S*)-4-Methyl-3,6-dihydro-2*H*-pyran-2-carbaldehyde (**3**), the common intermediate in the syntheses of the C17–C27 subunit of laulimalide (**4**) and (+)-faranal (**5**), the trail pheromone of the pharaoh ant, *Monomorium pharaonis*, were obtained via transformation of methyl 3-bromomethyl-3-butenoate (**1**) into allylstannane **2** and subsequent allylation of (benzyloxy)acetaldehyde (**6**) in accordance with the Keck procedure as the key steps.

3-Methylbut-2-enoic acid and its derivatives are widely used as nucleophilic C_5 buildings blocks via the generation of a carbanionic centre by allylic deprotonation or metal–halogen exchange reactions.[1] The synthetic application of regioisomeric 3-methylbut-3-enoic acid derivatives has not been studied in detail, and to our knowledge, is limited to asymmetric allylation of aldehydes with ethyl 3-[(tributylstannyl)methyl]but-3-enoate[2] obtained in turn by ethoxycarbonylation of 1,3-bis-(tributylstannyl)-2-methylenepropane.[3] This allylating agent was successfully used for the preparation of δ-hydroxy-β-methylenealkanoic or (*E*)-δ-hydroxy-β-methyl-α,β-alkenoic esters after the displacement of the carbon–carbon double bond to a position conjugated to the carbonyl group.[2] Recently, we reported an effective preparation of a similar allyl stannane **2** by zinc-mediated stannylation of methyl 3-bromomethyl-3-butenoate (**1**).[4] Herein, compound **1** was exploited for the stereoselective preparation of (*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-carbaldehyde (**3**),[5] a common intermediate in several syntheses of the C17–C27 subunit of laulimalide (**4**),[5a–i,k,6] as well as in the synthesis of (+)-faranal, [(3*S*,4*R*,6*E*,10*Z*)-3,4,7,11-tetramethyl-6,10-tridecadienal] (**5**), the trail pheromone of the pharaoh ant, *Monomorium pharaonis*[7] (Scheme 1).

The previously reported syntheses of aldehyde **3** from the appropriate chiral precursors were based mainly on the formation



Scheme 1.

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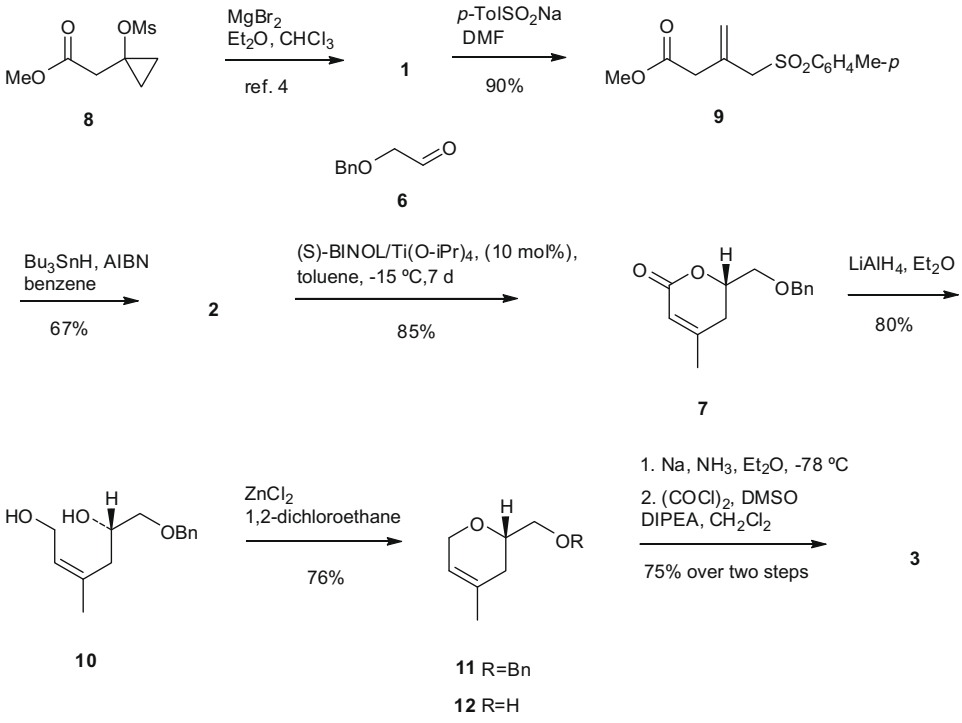
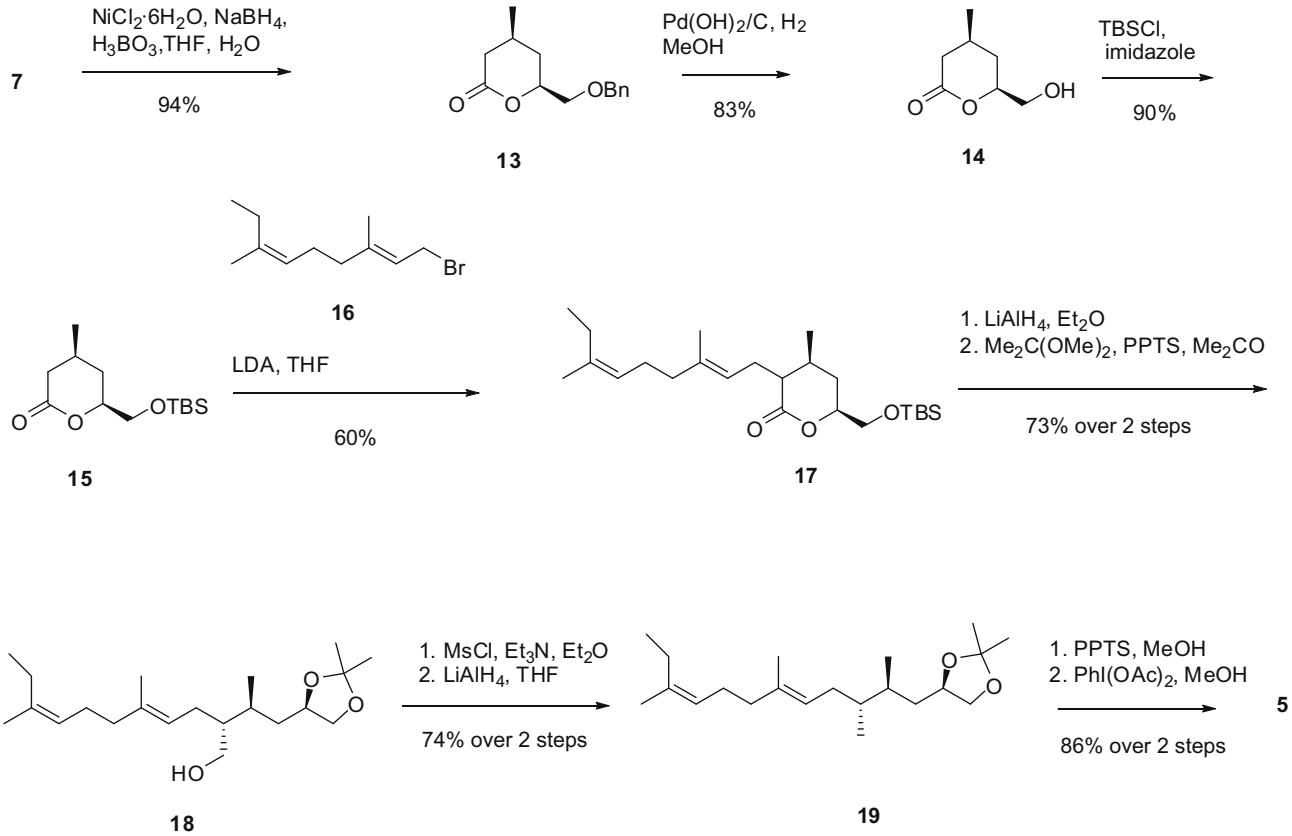


Scheme 2.



Scheme 3.

of a dihydropyran ring by a metathesis reaction.[5b–k] Its preparation via the enantioselective cycloaddition of α-functionalized aldehydes to isoprene[8] or 4-methoxyisoprene[9] in the presence of chiral Cr or Co complexes as catalysts was also reported. In this work, aldehyde **3** was obtained by transformation of ester **1** into functionalized allyl stannane **2** followed by the addition of the latter to (benzyloxy)acetaldehyde **6**[10] under Keck conditions[11] (Scheme 2). When the reaction was carried out in dichloromethane

in the presence of 10 mol % of (*S*)-BITIP catalyst, a complex mixture of products was formed and the conversion of aldehyde **6** was less than 50%. The allylation proceeded sufficiently faster and more smoothly when toluene was used as the solvent.[11] In this case, the reaction was accompanied by lactonization of the intermediate homoallylic alcohol and subsequent migration of the carbon–carbon double bond to a position conjugated to the carbonyl group to afford lactone **7**. For the preparation of allyl stannane **2**, allyl bromide **1**, obtained via the cationic cyclopropyl-allyl isomerization of the readily available cyclopropyl sulfonate **8**,[4,12] was converted on treatment with *p*-TolSO$_2$Na in *N*,*N*-dimethylformamide (DMF) into sulfone **9**. The latter was reacted with Bu_3SnH in the presence of AIBN[13,14] to give **2**. Reduction of lactone **7** with lithium aluminium hydride, followed by treatment of the product diol **10** with zinc dichloride in boiling 1,2-dichloroethane[15] led to dihydropyran **11**.[16] After debenzylation of **11** with sodium in liquid ammonia, chiral alcohol **12**[5a–c, g–k, 9a, 17] was obtained in 94% ee.[18,19] Finally, Swern oxidation gave aldehyde **3** in 23% overall yield based on allyl bromide **1**.

One of the most effective methods for the synthesis of (+)-faranal (**5**), the trail pheromone of the pharaoh ant, a foodstuff pest and a dangerous infection carrier in hospitals,[7d] was elaborated by Szántay and co-workers.[7a,b] The authors constructed the carbon skeleton of the molecule via diastereoselective allylation of (3*S*)-methyl valerolactone, which in turn was obtained by enzymatic reduction of methyl glutaconicoate.[7a,20] We found that lactone **7** could be successfully used to prepare (+)-faranal (**5**) by Szántay's modified procedure (Scheme 3). Diastereoselective reduction of the carbon–carbon double bond in lactone **7** with sodium borohydride in the presence of nickel chloride[21] followed by deprotection of the hydroxy group of unsaturated lactone **13** led to crystalline *cis*-lactone **14** in 78% yield over two steps.[22] The latter was recrystallized twice from a mixture of diethyl ether–ethyl acetate to give the product in greater than 99% ee.[19,23]

Silylation of the hydroxy group of **14** and subsequent treatment of a mixture of compound **15** and (*Z*)-homogeranyl bromide (**16**)[7a,b,24] with LDA in tetrahydrofuran initially for 2 h at −78 °C and then for 12 h at −30 °C[7a,7b,25] led to allylation product **17** which was isolated as a single diastereomer in 60% yield.[26] It is noteworthy that the TBS-protecting group in lactone **15** had an important influence on the alkylation process since lactone **13**, unlike **15**, under the same conditions, yielded a complex mixture of products. Reduction of alkylated lactone **17** with lithium aluminium hydride, followed by transformation of the product formed into acetonide derivative **18** and subsequent reductive elimination of the hydroxy group of the latter gave **19**. Hydrolysis of compound **19** and oxidative fragmentation of the formed vicinal diol with phenyliodine(III) diacetate in methanol led to (+)-faranal (**5**) in 28% yield based on lactone **15**.

In summary, methyl 3-bromomethyl-3-butenoate (**1**) was successfully used as a bifunctional isopentane building block in the synthesis of (*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-carbaldehyde (**3**) and (+)-faranal **5**. The Keck asymmetric condensation of (benzyloxy)acetaldehyde **6** and allyl stannane **2**, derived from allyl bromide **1** was the key step in both syntheses.

References and notes

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14. In comparison with the earlier reported one-step procedure,[4] the advantage of the described method in this two-step approach to the preparation of functionalized allyl stannane **2** from allyl bromide **1** via sulfone **9** is that equimolar quantities of the reagents are used and purification of the product by column chromatography is easier.
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16. *Experimental procedure*: A solution of 1.08 g (5 mmol) of diol **10** and 0.8 g (6 mmol) of anhyd $ZnCl_2$ in 30 ml of dichloroethane was refluxed for 1.5 h. After treatment with H_2O (30 ml) and extraction with CH_2Cl_2 (3 × 25 ml), the combined organic phase was washed with aq $NaHCO_3$ (40 ml) and dried over anhyd $MgSO_4$. Following evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent—petroleum ether/EtOAc), yielding 0.76 g (76%) of **11** as a colourless oil. $[\alpha]_D^{20}$ −75.7 (*c* 7.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.76–1.80 (m, 1H), 2.00–2.07 (m, 1H), 3.47 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.54 (dd, *J* = 10.2, 6.5 Hz, 1H), 3.73–3.79 (m, 1H), 4.17–4.21 (m, 2H), 4.57 (d, *J* = 12.3 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 5.42 (br s, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 32.1, 65.8, 72.9, 73.0, 73.5, 119.8, 127.6, 127.8 (2 × C), 128.3 (2 × C), 131.2, 138.2; IR (CCl_4) 1138, 1099 cm^{-1}; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.10; H, 8.28.
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22. *Experimental procedure*: 0.84 g of $NaBH_4$ (22 mmol) was added in small portions over 10 min each to a stirred emulsion of 2.32 g (10 mmol) of compound **7** in 50 ml THF–H_2O (1:1) at 0 °C, containing 2.60 g (11 mmol) of $NiCl_2 \cdot 6H_2O$ and 2.34 g (40 mmol) of H_3BO_3. After stirring for an additional 0.5 h, the reaction mixture was extracted with Et_2O (4 × 25 mL). The combined organic fraction was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent—petroleum ether/EtOAc) to give **13** (2.20 g, 94%) as a colourless oil. The latter was dissolved in 30 ml of absolute EtOH and stirred under H_2 in the presence of 0.05 g of 10% Pd/C for 2 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent—petroleum ether/EtOAc), yielding hydroxymethyl lactone **14** (1.34 g, 99% ee, 86%) as colourless crystals. Crystallization (twice) from Et_2O/EtOAc (10:1) gave 1.12 g (83%) of the product, with ee >99%.[23] Mp 80–81 °C; $[\alpha]_D^{20}$ +11.7 (*c* 0.6 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* 6.1 Hz, 3H), 1.32–1.42 (m, 1H), 1.58 (br s, 1H), 1.80–1.85 (m, 1H), 1.96–2.07 (m, 2H), 2.58–2.67 (m, 1H), 3.60 (ddd, *J* = 12.3, 6.1, 5.4 Hz, 1H), 3.75 (ddd, *J* = 12.3, 7.4, 2.6, 1H), 4.34–4.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.2, 32.2, 37.9, 64.5, 81.1, 171.5; IR (CCl_4) 3439,

1732, 1259, 1087 cm^{-1}; Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.37; H, 8.34.

23. The ee value of **14** was determined by Mosher's method.[19] The signals of the protons of the methoxy groups at δ 3.56 and δ 3.41 were used to determine the enantiomeric purity of **14**. Major isomer of (*R*)-(+)-MTPA ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.1, 3H), 1.23–1.32 (m, 1H), 1.83–1.89 (m, 1H), 1.99–2.10 (m, 2H), 2.66 (ddd, *J* = 17.1, 4.9, 2.1 Hz, 1H), 3.56 (s, 3H), 4.38 (dd, *J* = 11.8, 5.1 Hz, 1H), 4.41 (dd, *J* = 11.8, 3.6 Hz, 1H), 4.52–4.58 (m, 1H), 7.38–7.43 (m, 3H), 7.51–7.57 (m, 2H).
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26. *Compound* **17**. $[\alpha]_D^{20}$ −6.1 (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 0.94 (t, *J* = 7.7 Hz, 3H), 1.05 (d, *J* = 6.1 Hz, 3H), 1.37–1.46 (m, 1H), 1.63 (s, 3H), 1.65 (s, 3H), 1.85–1.93 (m, 2H), 1.97–2.08 (m, 6H), 2.13–2.19 (m, 1H), 2.41 (ddd, *J* = 15.1, 8.4, 4.6 Hz, 1H), 2.69 (dt, *J* = 15.1, 4.9 Hz, 1H), 3.64 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.73 (dd, *J* = 10.8, 4.1 Hz, 1H), 4.21–4.27 (m, 1H), 5.02 (t, *J* = 6.4 Hz, 1H), 5.06 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (2 × C), 12.8, 16.3, 18.3, 20.6, 22.8, 24.7, 26.1 (3 × C), 27.4, 29.6, 33.9, 40.1, 48.7, 65.3, 79.5, 120.2, 123.7, 137.2, 137.9, 173.3; IR (CCl_4) 1716, 1450, 1268, 1104, 1004 cm^{-1}; Anal. Calcd for $C_{24}H_{44}O_3Si$: C, 70.53; H, 10.85. Found: C, 70.59; H, 10.82.