Stereoselective total synthesis of (±)-fragranol by $TiCl_4$ promoted [2+2] cycloaddition of allyl-*tert*-butyldiphenylsilane and methyl methacrylate†

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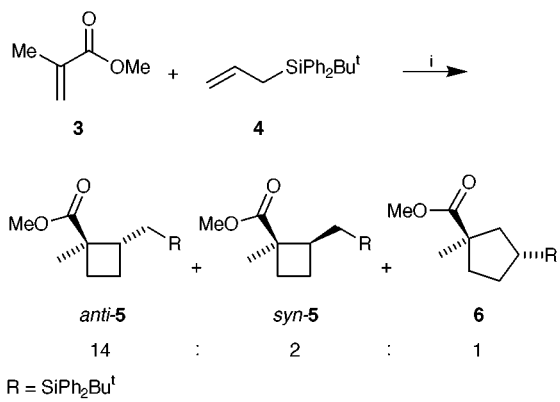
A stereoselective total synthesis of the monoterpenoid alcohol (±)-fragranol has been accomplished utilizing a $TiCl_4$ promoted [2 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane and methyl methacrylate as the key step.

1 **2**

The monoterpenoid alcohol fragranol **1** was isolated in 1973 by Bohlmann and co-workers from the roots of *Artemisia fragrans* Willd.[2] The diastereoisomeric grandisol **2** is a sex pheromone of the male cotton boll weevil *Anthonomus grandis* Boheman and other beetles.[3] Because of their structural features and biological activity both compounds represent important targets for novel procedures directed towards the total synthesis of four-membered ring natural products.[4] Over the past years we developed a novel synthetic methodology for the stereoselective construction of cyclobutanes by $TiCl_4$ promoted [2 + 2] cycloaddition of allylsilanes and acrylic esters.[5] We now report the stereoselective total synthesis of fragranol **1** which is the first application of this strategy to the total synthesis of a natural product.[6]

The $TiCl_4$ promoted [2 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane **4** and methyl methacrylate **3** afforded the two diastereoisomeric silylmethylcyclobutanes *anti*-**5** and *syn*-**5** along with the silylcyclopentane **6** in a total yield of 84% and a ratio of 14 : 2 : 1 (Scheme 1).‡ The structural and stereochemical assignments were based on comparison of the ^{13}C NMR data with those of our previous studies.[5a] After chromatography the major isomer *anti*-**5** was crystallized in pure form out of this mixture and structurally confirmed by X-ray crystallography (Fig. 1).§



Scheme 1 *Reagents and conditions*: i, $TiCl_4$, CH_2Cl_2, 40 °C, 4 d (84%, ratio *anti*-**5** : *syn*-**5** : **6** = 14 : 2 : 1), then crystallization from this mixture afforded selectively *anti*-**5** (67%).

† See ref. 1.

For the projected total synthesis the silyl group had to be converted into a hydroxy group. We have recently shown that by modifaction of the Fleming–Tamao oxidation[7] sterically hindered silyl groups, like triphenylsilyl, diisopropylphenylsilyl and *tert*-butyldiphenylsilyl, can be transformed to hydroxy groups.[8] Using these conditions the *tert*-butyldiphenylsilyl derivative *anti*-**5** was first converted to the *tert*-butyldifluorosilyl derivative **7** and then to the alcohol **8** (Scheme 2). The next task was to transform the hydroxymethyl group into the isopropenyl group present in the natural product. For the oxidation of the hydroxy to the formyl group we required reaction conditions which avoided an epimerization at the stereogenic center. Swern oxidation[9] and oxidation with the Dess–Martin periodinane reagent[10] provided good yields, however to a large extent with epimerization. Treatment of **8** with tetrapropylammonium perruthenate (TPAP)[11] provided a yield of 94% for the aldehydes *anti*-**9** and *syn*-**9** which were obtained in a ratio of 13 : 1.

Chemoselective addition of methyltitanium triisopropoxide[12] at the formyl group at −10 °C afforded the alcohol **10** as a 1 : 1 mixture of two diastereoisomers (Scheme 3). A further oxidation with TPAP[11] provided in 94% yield the methyl ketone **11** without epimerization at the chiral center. Wittig reaction using methylenetriphenylphosphorane gave the isopropenyl derivative **12** which was reduced to the alcohol **13** by $LiAlH_4$. Finally, a homologation of the primary alcohol was required. For this purpose the alcohol **13** was transformed to the aldehyde **14** by Swern oxidation.[9] Wittig reaction using methoxymethyltriphenylphosphonium bromide/sodium amide[13] followed by hydrolysis of the resulting enol ether afforded the homologated

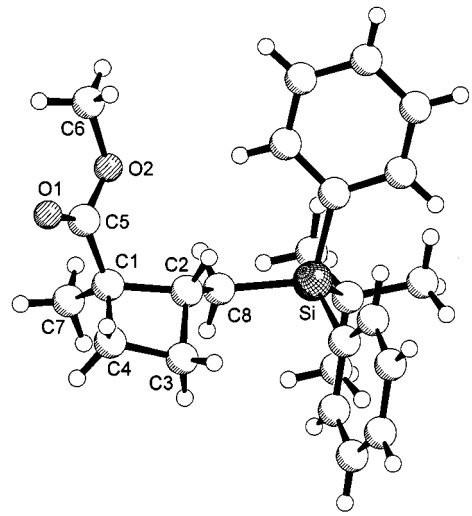
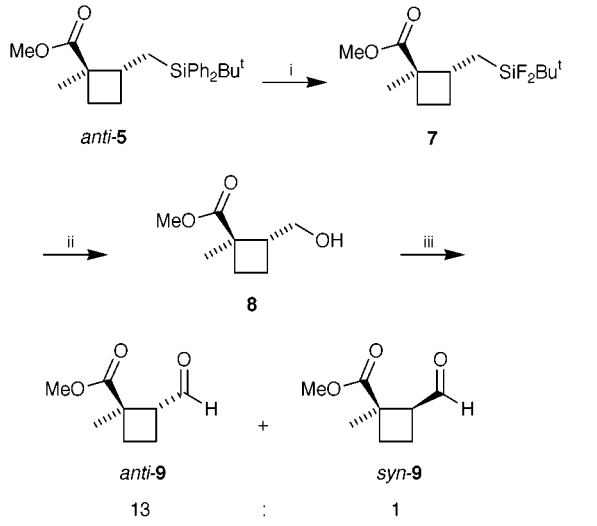
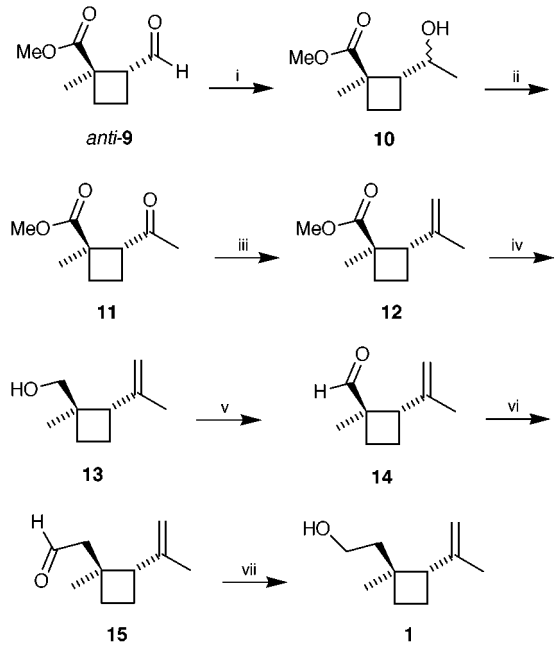


Fig. 1 Molecular structure of *anti*-**5** in the crystal. Selected bond lengths (Å): C(1)–C(2) 1.570(3), C(2)–C(3) 1.538(3), C(3)–C(4) 1.532(3), C(1)–C(4) 1.541(4), C(1)–C(5) 1.507(4), C(1)–C(7) 1.516(4), C(2)–C(8) 1.525(3), C(8)–Si 1.883(2).



Scheme 2 *Reagents and conditions*: i, BF_3·2 HOAc, CH_2Cl_2, 40 °C, 4 h (87%); ii, H_2O_2, KF, $NaHCO_3$, THF–MeOH (1:1), 25 °C, 24 h (51%); iii, TPAP (cat.), NMO, powdered 4 Å molecular sieves, CH_2Cl_2, 0 to 25 °C, 2 h (94%, ratio *anti*-**9**:*syn*-**9** = 13:1).



Scheme 3 *Reagents and conditions*: i, $MeTi(OP^ir)_3$, CH_2Cl_2, −10 to 25 °C, 14 h (70%); ii, TPAP (cat.), NMO, powdered 4 Å molecular sieves, CH_2Cl_2, 0 to 25 °C, 2 h (94%); iii, $Ph_3P{=}CH_2$, THF, 0 to 25 °C, 2 h (65%); iv, $LiAlH_4$, THF, 0 to 25 °C, 12 h (99%); v, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 20 min (84%); vi, $MeOCH_2Ph_3P^+Br^-$, $NaNH_2$, Et_2O, −20 to 25 °C, 12 h, then TFA–H_2O (4:1), Et_2O, 25 °C, 12 h (78%); vii, $LiAlH_4$, Et_2O, 0 °C, 10 min (93%).

aldehyde **15** which on reduction with $LiAlH_4$ provided (±)-fragranol **1**. The spectral data of our synthetic fragranol (IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS)¶ were in full agreement with those reported for the natural product.[2,6]

The present synthesis *via* the [2 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane **4** afforded fragranol in 11 steps and 7% overall yield based on methyl methacrylate **3**. It has been demonstrated for the first time that the Lewis acid promoted cycloaddition of allyl-*tert*-butyldiphenylsilane followed by our modified Fleming–Tamao oxidation represents a powerful new tool in natural product synthesis.

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Notes and references

‡ *Synthesis* of *anti*-**5**: A solution of methyl methacrylate **3** (3.37 g, 33.7 mmol, 3.6 ml) in dry CH_2Cl_2 (30 ml) was added to a stirred solution of $TiCl_4$ (6.92 g, 36.5 mmol, 4 ml) in dry CH_2Cl_2 (50 ml) under argon at room temperature. After addition of a solution of allyl-*tert*-butyldiphenylsilane **4** (13.6 g, 48.5 mmol) in dry CH_2Cl_2 (30 ml) the reaction mixture was heated at reflux for 4 days. The mixture was hydrolyzed by addition of aq. NH_4Cl, the organic layer was separated, the aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (hexane–Et_2O 20:1) of the residue on silica gel afforded a mixture of *anti*-**5**, *syn*-**5** and **6** (10.8 g, 84%, ratio 14:2:1). Crystallization out of this oil over a period of 14 days provided the cyclobutane *anti*-**5** (8.6 g, 67%) as colorless crystals, mp 65 °C; δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9 H), 1.12–1.27 (m, 3 H), 1.33 (s, 3 H), 1.44 (m, 2 H), 2.10 (dt, *J* 9.0, 10.8, 1 H), 2.70 (dddd, *J* = 12.4, 10.3, 8.4, 2.1, 1 H), 3.67 (s, 3 H), 7.31–7.41 (m, 6 H), 7.63 (m, 4 H); δ_C (100 MHz, $CDCl_3$)11.43 (CH_2), 16.99 (CH_3), 18.11 (C), 25.29 (CH_2), 27.83 (3 CH_3), 28.62 (CH_2), 37.47 (CH), 46.75 (C), 51.44 (CH_3), 127.37 (2 CH), 127.52 (2 CH), 128.96 (CH), 129.00 (CH), 134.26 (C), 135.26 (C), 135.95 (2 CH), 136.04 (2 CH), 177.94 (C=O) (calc. for $C_{24}H_{32}O_2Si$: C, 75.74; H, 8.47; found: C, 75.65; H, 8.35%).

§ *Crystal data* for *anti*-**5**: $C_{24}H_{32}O_2Si$, *M* = 380.59, orthorhombic, space group $P2_12_12_1$, *a* = 7.900(3), *b* = 14.751(5), *c* = 18.956(6) Å, *U* = 2209.0(13) Å^3, *Z* = 4, D_c = 1.144 g cm^{-3}, μ = 0.121 mm^{-1}, *T* = 200(2) K, Mo-Kα (λ = 0.71073 Å), 10267 reflections collected, 4228 unique (R_{int} = 0.0912), 249 parameters; STOE IPDS area detector. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on F^2 (SHELXL-97). R_1 [$I > 2\sigma(I)$] = 0.0523, wR_2 = 0.1392, absolute structure (Flack parameter): χ = −0.10(14). CCDC 182/1352. See http://www.rsc.org/suppdata/cc/1999/1737/ for crystallographic data in .cif format.

¶ *Spectral data* for **1**: ν_{max} (film)/cm^{-1} 3352 (br), 3080, 2960, 2931, 2870, 1646, 1455, 1378, 1283, 1182, 1161, 1054, 886; δ_H (500 MHz, $CDCl_3$) 0.92 (s, 3 H), 1.41 (m, 1 H), 1.64 (s, 3 H), 1.67 (br s, 1 H), 1.72–1.84 (m, 4 H), 1.97 (m, 1 H), 2.56 (m, 1 H), 3.67 (m, 2 H), 4.61 (s, 1 H), 4.82 (q, *J* 1.5, 1 H); δ_C (125 MHz, $CDCl_3$): 19.46 (CH_3), 19.73 (CH_2), 23.02 (CH_3), 30.23 (CH_2), 40.93 (C), 46.64 (CH_2), 50.52 (CH), 59.79 (CH_2), 109.77 (CH_2), 145.58 (C); *m*/*z* (35 °C): 154 (M^+, 0.2), 139 (2), 136 (1), 123 (2), 121 (6), 109 (43), 107 (11), 69 (17), 68 (100), 67 (41) (calc. for $C_{10}H_{18}O$: 154.1358, found: 154.1349).

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