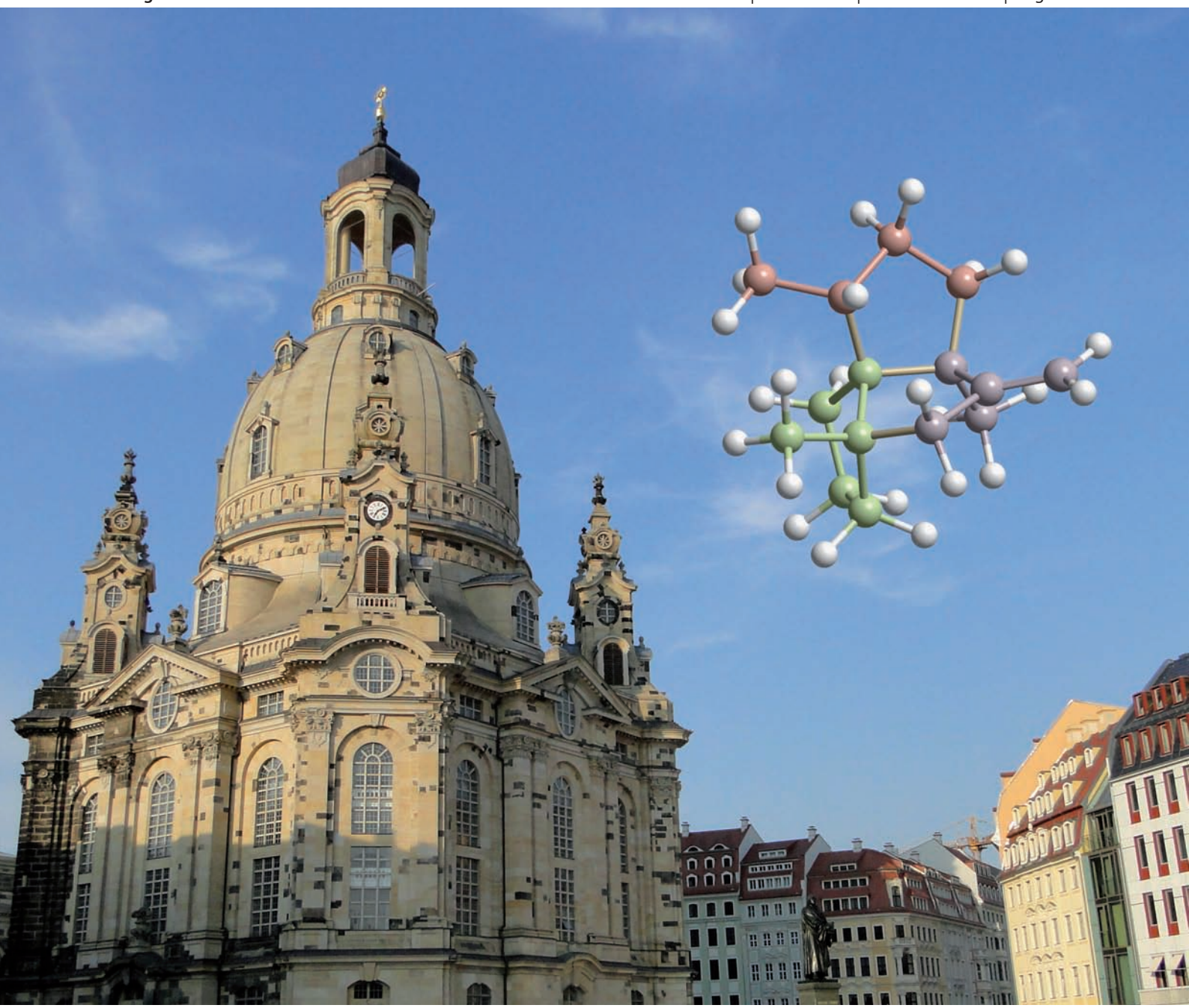
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 8 | Number 20 | 21 October 2010 | Pages 4485–4776



ISSN 1477-0520

RSC Publishing

Organosilicon-mediated total synthesis of the triquinane sesquiterpenes (±)-β-isocomene and (±)-isocomene†‡

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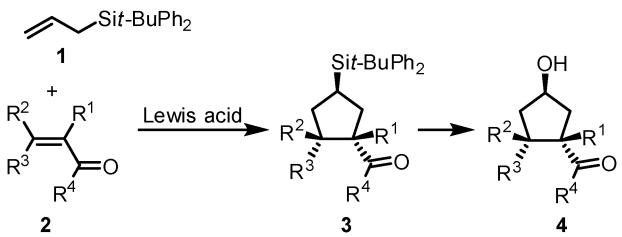
Received 27th April 2010, Accepted 5th July 2010
DOI: 10.1039/c0ob00051e

We describe an efficient total synthesis of the sesquiterpenes (±)-β-isocomene and (±)-isocomene using a Lewis acid-promoted [3 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane as the key-step.

Introduction

In 1990, we showed that silylated cyclopentanes are obtained as by-products of the well-known Hosomi–Sakurai reaction.[1] These silylcyclopentanes derive from a [1,2]-migration of the silyl group (sila-Wagner–Meerwein rearrangement). By using allylsilanes with bulky substituents at the silicon atom, the silylcyclopentanes become the major products. This formal [3 + 2] cycloaddition of allylsilanes has found many applications in organic synthesis.[2] Thus, the Lewis acid-promoted reaction of allyl-*tert*-butyldiphenylsilane (**1**) with enones (**2**) affords silylcyclopentanes (**3**) (Scheme 1).[1c–g] Generally, silyl and acyl substituents are on opposite faces of the cyclopentane ring. Moreover, we have demonstrated that the Lewis acid-promoted [2 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane (**1**) with α,β-unsaturated esters provides silylmethylcyclobutanes.[3]



Scheme 1 [3 + 2] Cycloaddition of the allylsilane **1** and enones **2**.

For further functionalisation, we have developed a modified protocol for the classical Fleming–Tamao oxidation which is utilised for the transformation of silyl derivatives with sterically highly hindered carbon–silicon bonds into the corresponding carbinols, *e.g.* conversion of **3** to **4**.[4,5]

In the present paper, we wish to report the application of the Lewis acid-promoted [3 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane (**1**) to the total synthesis of the sesquiterpenes (±)-isocomene [(±)-**5**] and (±)-β-isocomene [(±)-**6**] (Fig. 1). (–)-Isocomene (**5**) was isolated first in 1977 by Zalkow *et al.* from the hexane extract of the New Mexican *isocoma wrightii*, a toxic plant also named Jimmyweed or Rayless Goldenrod.[6] Independently, Bohlmann and co-workers isolated the same natural product from the roots of *berkheya radula* (Harv.) De Willd. and named it berkheyaradulene.[7] In 1979, Bohlmann *et al.* described the isolation of (–)-β-isocomene (**6**) from various species of the South African genus *berkheya* (family: *asteraceae*).[8] Since then, (–)-isocomene (**5**) and (–)-β-isocomene (**6**) have been identified in the extracts or essential oils of more than 20 plants.[9] The relative configuration of (–)-isocomene (**5**) was determined by a single-crystal X-ray analysis of the dihydroxylated derivative.[6] In 1993, Fitjer *et al.* assigned the absolute configuration based on rearrangement experiments of compounds with known absolute configuration.[10] Biogenetically, isocomenes have been suggested to derive from farnesyl pyrophosphate *via* a sequence of rearrangements involving cationic intermediates.[11] The three consecutive quarternary carbon atoms of these angular triquinane sesquiterpenes represent a major challenge and thus, several synthetic approaches have been developed.[12–14]

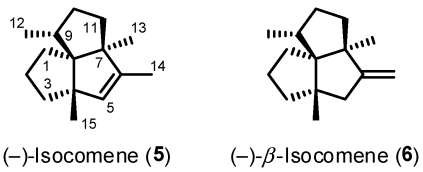
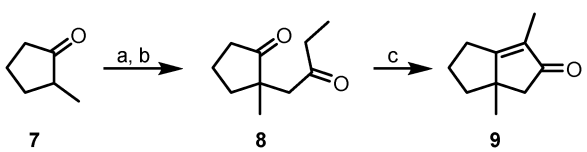


Fig. 1 Structure of the isocomene sesquiterpenes.

Results and discussion

The diquinane precursor for our [3 + 2] cycloaddition was obtained *via* a known three-step sequence starting from 2-methylcyclopentanone (**7**).[15] Mukaiyama–Michael addition of the silyl enol ether of **7** to 2-nitrobut-1-ene and subsequent Nef reaction led to the diketone **8**. In contrast to the literature procedure,[15b,c] the Nef reaction was induced by addition of aqueous HCl. Intramolecular aldol condensation afforded the enone **9** (Scheme 2).



Scheme 2 Synthesis of enone **9**. *Reagents and conditions*: (a) 1.2 equiv. TMSCl, 2.4 equiv. Et_3N, DMF, 153 °C, 90 h, 78%; (b) 1.1 equiv. $SnCl_4$, CH_2Cl_2, 1.5 equiv. 2-nitrobut-1-ene, –78 °C, 1 h to 0 °C, 3 h; then 10% HCl, 60 °C, 12 h, 41%; (c) 5.0 equiv. KOH, EtOH, 78 °C, 12 h, 88%.

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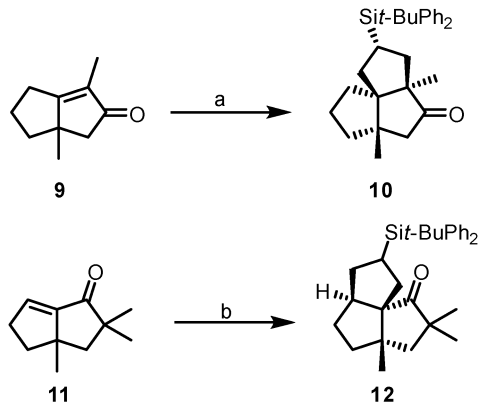
† Part 21 of 'Cycloadditions of Allylsilanes'; for Part 20, see: ref. 16b.

‡ Electronic supplementary information (ESI) available: 2D NMR spectra of compound **18**. CCDC reference number 646230. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00051e

The triquinane framework was constructed by Lewis acid-promoted reaction of allyl-*tert*-butyldiphenylsilane (**1**) with enone **9** (Scheme 3). Remarkably, using our [3 + 2] cycloaddition an arrangement of three contiguous quarternary carbon atoms has been assembled in 85% yield on a multi-gram scale. Cycloadduct **10** was obtained as a single diastereoisomer with the silyl moiety *anti* to the carbonyl substituent. The stereochemistry of **10** has been unequivocally confirmed by an X-ray crystal structure determination (Fig. 2). Comparison with the cycloaddition leading to our recent total synthesis of (±)-cameroonanol (conversion of **11** to **12**)[16] shows that the present reaction requires more harsh conditions and provides better results.



Scheme 3 Comparison of the [3 + 2] cycloadditions of **9** and **11**. *Reagents and conditions*: (a) 1.2 equiv. $TiCl_4$, 4.0 equiv. allyl-*tert*-butyldiphenylsilane (**1**), CH_2Cl_2, 40 °C, 10 d, 85%; (b) 1.2 equiv. $TiCl_4$, 2.0 equiv. allyl-*tert*-butyldiphenylsilane (**1**), CH_2Cl_2, −78 °C, 1 d, 43% (*anti*/*syn* = 7 : 1).

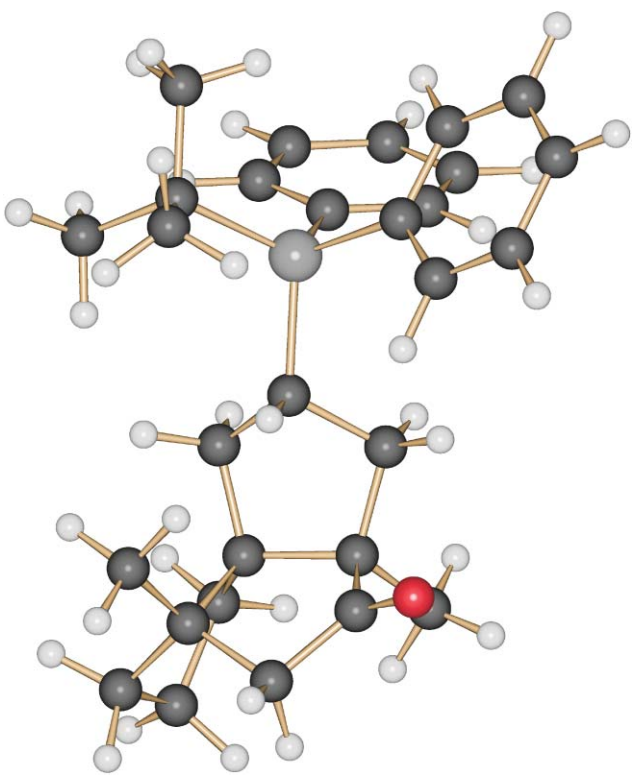
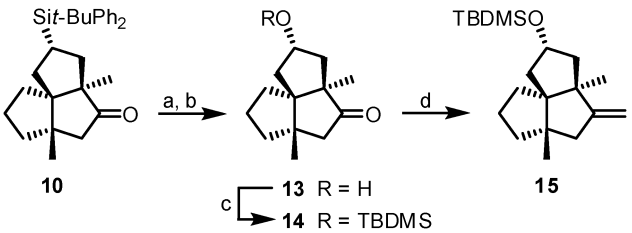


Fig. 2 Molecular structure of the silylcyclopentane **10** in the crystal.

We envisaged introducing the methyl group at C-9 by an α-alkylation of a C-10 ketone. Using our modified protocol for the Fleming–Tamao oxidation, the carbon–silicon bond of **10** was oxidised to the corresponding alcohol (Scheme 4). In our seminal studies, we have shown that excellent overall yields can be achieved only by double protodesilylation of the *tert*-butyldiphenylsilyl group to the corresponding *tert*-butyldifluorosilyl group prior to the oxidation step. Thus, treatment of cycloadduct **10** with boron trifluoride–acetic acid complex in refluxing 1,2-dichloroethane for almost 2 days followed by oxidation with hydrogen peroxide in the presence of caesium fluoride gave the alcohol **13** in high yield (86%).



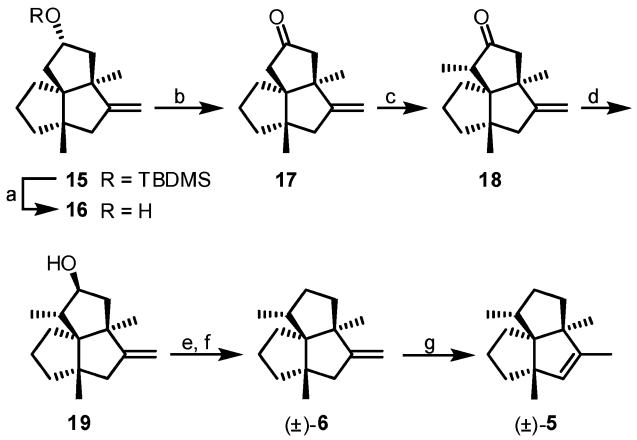
Scheme 4 Modified Fleming–Tamao oxidation and methylenation. *Reagents and conditions*: (a) 10 equiv. BF_3·2AcOH, 1,2-$C_2H_4Cl_2$, 83 °C, 46 h; (b) 2.0 equiv. $KHCO_3$, 6.0 equiv. CsF, 20.0 equiv. H_2O_2, THF–MeOH (1 : 1), 65 °C, 12 h, 86% (two steps); (c) 1.5 equiv. TBDMSCl, 3.0 equiv. imidazole, CH_2Cl_2, 25 °C, 2 h, 94%; (d) 8.3 equiv. Ph_3PMeBr, 7.4 equiv. BuLi, *p*-xylene, 138 °C, 2 d, 83%.

In order to establish the exocyclic double bond of β-isocomene (**6**), we converted the keto group at C-6 to a methylene unit. Since all attempts to achieve methylenation failed in the presence of the free hydroxy group, alcohol **13** was protected as *tert*-butyldimethylsilyl ether **14**. Titanium-based reagents, like the Tebbe reagent[17] or Petasis' reagent (dimethyltitanocene),[18] are generally useful for the methylenation of sterically encumbered ketones, but failed to give good yields of the methylene derivative **15** (Table 1). Wittig olefination in toluene under reflux afforded better results. Finally, using the Wittig reagent in *p*-xylene under reflux provided **15** in 83% yield.

Deprotection of **15** followed by oxidation with TPAP/NMO afforded the ketone **17** (Scheme 5).[19] Steric hindrance caused by the angular methyl group at C-7 was expected to lead to preferential deprotonation at C-9 of **17** and provide the 9,10-enolate. Previous studies of the isocomene skeleton have shown that electrophiles attack from the *exo*-face.[20] Standard alkylation procedures gave low yields and inseparable mixtures of products with no detectable excess of the desired isomer. In 1989, Noyori *et al.* described an improved protocol for alkylation by using a coordinating co-solvent and catalytic amounts of dimethylzinc.[21] This protocol presumably effects transmetallation to a zinc enolate. Thus, deprotonation of **17** was achieved with LiHMDS at room temperature followed by addition of DMPU and 10 mol% of

Table 1 Methylenation of compound **14** to the methylene derivative **15**

Reaction conditions	**15**, Yield
5.0 equiv. Tebbe's reagent, benzene–THF (5 : 1), 80 °C, 3.5 d	27%
5.0 equiv. Petasis' reagent, toluene, 75 °C, 24 h	38%
8.0 equiv. Ph_3PMeBr, 8.0 equiv. BuLi, toluene, 111 °C, 2 d	68%
8.3 equiv. Ph_3PMeBr, 7.4 equiv. BuLi, *p*-xylene, 138 °C, 2 d	83%



Scheme 5 Synthesis of the isocomenes. *Reagents and conditions*: (a) 2.8 equiv. TBAF, 8.5 equiv. H_2O, THF, 65 °C, 24 h, 97%; (b) 5 mol% TPAP, 2.5 equiv. NMO, 4 Å MS (500 mg $mmol^{-1}$), CH_2Cl_2, −16 °C to 25 °C, 16 h, 95%; (c) 1. 1.0 equiv. LiHMDS, THF, 25 °C, 2 h; 2. 3.0 equiv. DMPU, 10 mol% Me_2Zn, 5.0 equiv. MeI, −78 °C to 25 °C, 16 h, 49%; (d) 1.0 equiv. $LiAlH_4$, THF, −78 °C, 3 h, 86%; (e) 2.3 equiv. MsCl, 3.0 equiv. EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 °C, 2 h; (f) 7.7 equiv. $LiAlH_4$, Et_2O, 35 °C, 3 h, (78% over two steps); (g) cat. *p*-TsOH·H_2O, CH_2Cl_2, 25 °C, 3 h, 100%.

dimethylzinc. Subsequent alkylation with iodomethane provided compound **18** along with two isomers and two double alkylation products. The regio- and stereochemistry of **18** was assigned based on 2D NMR experiments (HSQC, HMBC and NOESY, see ESI‡). Several methods to remove the oxygen functionality at C-10 failed (Wolff–Kishner reduction or conversion to a thioketal). Finally, ketone **18** was stereoselectively reduced to alcohol **19** using lithium aluminium hydride. Subsequent mesylation and nucleophilic displacement with lithium aluminium hydride led to (±)-*β*-isocomene [(±)-**6**]. Purification by flash chromatography provided (±)-*β*-isocomene [(±)-**6**] in highly pure form (see elemental analysis) and for the first time as colourless crystals (m.p. 76–82 °C). The spectroscopic data of our synthetic (±)-*β*-isocomene [(±)-**6**] are in full agreement with those reported by Bohlmann *et al.* for the natural product (Table 2).[8] Proton-catalysed isomerisation of (±)-*β*-isocomene [(±)-**6**] following a literature procedure afforded quantitatively (±)-isocomene [(±)-**5**].[13a,13b]

Conclusions

In conclusion, we have developed a new route to the synthetically challenging triquinane (±)-*β*-isocomene [(±)-**6**] *via* a Lewis acid-promoted [3 + 2] cycloaddition of allyl-*tert*-butyldiphenylsilane (**1**). The high utility of our method is emphasised by the efficient construction of compound **10** with an arrangement of three contiguous quarternary carbon centers. Further transformation of the silylcyclopentane **10** has been achieved by using our modified Fleming–Tamao oxidation. The present approach provides (±)-*β*-isocomene [(±)-**6**] in a total number of 12 steps and 5% overall yield based on commercially available 2-methylcyclopentanone (**7**). A comparison with previous total syntheses of (±)-*β*-isocomene [(±)-**6**] emphasises the efficiency of our approach.[13] Although several previous syntheses of (±)-*β*-isocomene [(±)-**6**] were reported,[13] this is the first time that (±)-*β*-isocomene [(±)-**6**] has been obtained as a solid compound. Following Sato's route, enone **9** is also available in enantiomerically pure form.[15e] Therefore, our approach also provides an enantioselective access to (−)-*β*-isocomene (**6**).

Table 2 Comparison of the ^{1}H NMR and ^{13}C NMR data for *β*-isocomene (**6**) reported by Bohlmann with those of our synthetic material ($CDCl_3$)

	δ (H)[a]	δ (H)[b]	δ (C)[a]	δ (C)[b]
(C-1)H_2	*not reported*	1.20–1.67	24.0	24.0
(C-2)H_2	*not reported*	1.20–1.67	30.2	30.3
(C-3)H_2	*not reported*	1.20–1.67	42.8	42.8
C-4	—	—	49.6	49.4
(C-5)H_2	2.10; 2.35[c]	2.09; 2.33[d]	48.1	48.0
C-6	—	—	162.8	162.3
C-7	—	—	55.1	54.8
C-8	—	—	66.9	66.6
(C-9)H	2.00	1.98	40.5	40.4
(C-10)H_2	*not reported*	1.20–1.67	34.7	34.5
(C-11)H_2	*not reported*	1.20–1.67	41.7	41.7
(C-12)H_3	0.92[e]	0.91[e]	18.0	18.0
(C-13)H_3	1.10	1.09	24.2	24.2
(C-14)H_2	4.62; 4.65	4.60; 4.62	100.9	100.7
(C-15)H_3	0.99	0.98	23.6	23.4

[a] Reported by Bohlmann.[8] [b] Present study. [c] $^2J_{5A,5B} = 14.5$ Hz, $^4J_{5,14} = 2.0$ Hz. [d] $^2J_{5A,5B} = 14.5$ Hz, $^4J_{5,14} = 2.4$ Hz. [e] $^3J_{9,12} = 7.0$ Hz.

Experimental

General

All reactions were carried out using dry solvents in oven-dried glassware under an argon atmosphere. Tetrahydrofuran, dichloromethane and diethyl ether were dried using a solvent purification system (MBraun-SPS). Toluene and *p*-xylene were dried over sodium. All other chemicals were used as received from commercial sources. Flash chromatography was performed using silica gel from Acros Organics (0.063–0.200 mm). Thin layer chromatography was performed with TLC plates from Merck (60 F_{254}) using anisaldehyde solution for visualisation. Melting points were measured on an Electrothermal IA9100 melting point apparatus. Infrared spectra were recorded on Bruker IFS 88 or Thermo Nicolet Avatar 360 FT-IR spectrometers. NMR spectra were recorded on a Bruker DRX 500 spectrometer. Chemical shifts δ are reported in ppm with the deuterated solvent as internal standard. The following abbreviations have been used: s: singlet, d: doublet, dd: doublet of doublets, dt: doublet of triplets, quint: quintet, m: multiplet. Mass spectra were recorded on a Finnigan MAT-95 spectrometer (electron impact, 70 eV) or by GC-MS-coupling using an Agilent Technologies 6890 N GC System equipped with a 5973 Mass Selective Detector (EI, 70 eV). Elemental analyses were measured on an EuroVector EuroEA3000 elemental analyser. X-ray analysis: STOE IPDS area detector. Software: STOE software, SHELXS-97 (G. M. Sheldrick, 1990), SHELXL-97 (G. M. Sheldrick, 1997), Schakal-99 (E. Keller, 1999).

(2*SR*,3a*RS*,5a*SR*,8a*RS*)-Decahydro-2-(*tert*-butyldiphenylsilyl)-3a,5a-dimethylcyclopenta[*c*]pentalen-4-one (10)

A solution of (*RS*)-2,5-dimethylbicyclo[3.3.0]oct-1(2)en-3-one (**9**) (3.0 g, 20 mmol) in anhydrous dichloromethane (20 mL) was added to a solution of $TiCl_4$ (2.6 mL, 4.5 g, 24 mmol) in anhydrous dichloromethane (180 mL) at −10 °C. After stirring for 10 min

at room temperature, allyl-*tert*-butyldiphenylsilane (**1**) (22.4 g, 80 mmol) was added and the mixture was heated at reflux for 10 d. After cooling to room temperature the reaction mixture was added to a saturated solution of ammonium chloride and vigorously stirred for 15 min (the mixture turned yellow). The aqueous layer was separated and extracted with dichloromethane two times. The combined organic layers were dried over sodium sulfate and the solvent was removed. Purification of the residue by flash chromatography (SiO_2; petroleum ether–diethyl ether, 20 : 1) afforded a colourless oil, which slowly crystallised upon standing to give **10** as colourless crystals, yield: 7.3 g (85%), m.p. 112 °C. IR (KBr): ν = 3071, 3048, 3015, 2958, 2858, 1733, 1589, 1487, 1471, 1427, 1412, 1392, 1372, 1362, 1327, 1259, 1193, 1157, 1107, 1029, 1008, 999, 917, 820, 795, 739, 701, 686, 646, 622, 608 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 1.06 (s, 9 H), 1.21 (s, 3 H), 1.29–1.61 (m, 8 H), 1.67 (ddd, J = 13.5, 7.1, 3.1 Hz, 1 H), 2.21–2.25 (m, 2 H), 2.28 (d, J_{AB} = 17.3 Hz, 1 H), 2.36 (d, J_{AB} = 17.3 Hz, 1 H), 7.33–7.42 (m, 6 H), 7.54–7.58 (m, 4 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 18.60 (C), 19.83 (CH_3), 21.64 (CH), 23.23 (CH_2), 23.72 (CH_3), 28.47 (3 CH_3), 35.46 (CH_2), 40.17 (CH_2), 43.21 (CH_2), 44.92 (CH_2), 45.83 (C), 53.14 (CH_2), 59.61 (C), 62.43 (C), 127.48 (4 CH), 129.11 (2 CH), 133.76 (C), 134.12 (C), 136.47 (2 CH), 136.53 (2 CH), 223.74 (C═O). MS (EI): m/z (%) = 430 (1) [M^+], 373 (100) [(M–tBu)$^+$], 199 (23), 183 (51), 181 (6), 135 (6). HRMS: m/z calcd for $C_{29}H_{38}OSi$: 430.2692, found: 430.2701. Elemental analysis calcd for $C_{29}H_{38}OSi$: C 80.87, H 8.89; found: C 80.64, H 8.26.

Crystallographic data for compound 10. $C_{29}H_{38}OSi$, crystal size: 0.60 × 0.40 × 0.40 mm^3, M = 430.68 g mol^{-1}, monoclinic, space group $P2_1/c$, λ = 0.71073 Å, a = 13.4071(14), b = 12.1653(9), c = 16.2492(17) Å, β = 109.414(11)°, V = 2499.6(4) Å^3, Z = 4, ρ_c = 1.144 g cm^{-3}, μ = 0.112 mm^{-1}, T = 200(2) K, θ range = 2.14–25.85°; reflections collected: 18979, independent: 4787 (R_{int} = 0.0393), 432 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0481, wR_2 = 0.1275; maximal residual electron density: 0.424 e Å^{-3}. CCDC 646230.‡

(2*SR*,3a*RS*,5a*SR*,8a*RS*)-Decahydro-3a,5a-dimethyl-2-hydroxycyclopenta[*c*]pentalen-4-one (13)

Boron trifluoride–acetic acid complex (5.47 g, 4.04 mL, 29.1 mmol) was added to a solution of **10** (1.25 g, 2.91 mmol) in dry 1,2-dichloroethane (50 mL) and the mixture was heated at reflux for 46 h. After cooling to room temperature the mixture was neutralised by addition of a saturated solution of sodium bicarbonate. The aqueous layer was separated, extracted with dichloromethane three times and the combined organic layers were dried over sodium sulfate. The solvent was removed and the residue was dissolved in a mixture of THF (35 mL) and methanol (35 mL). CsF (2.65 g, 17.5 mmol), $KHCO_3$ (582 mg, 5.82 mmol), and a solution of 35% hydrogen peroxide in water (5.33 mL, 58.2 mmol) were added, and the mixture was heated at reflux for 12 h. After cooling to room temperature, water (50 mL) was added. The aqueous layer was separated and extracted with diethyl ether three times. The combined organic layers were dried over sodium sulfate and the solvent was removed. Purification of the residue by flash chromatography (SiO_2; hexane–*tert*-butyl methyl ether, 1 : 1) afforded **13** as a colourless oil, yield: 523 mg (86%). IR (film): ν = 3431, 2953, 2870, 1732, 1455, 1412, 1376, 1341, 1298, 1270, 1155, 1128, 1075, 1003, 952, 924, 891, 851 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.09 (s, 3 H), 1.14 (s, 3 H), 1.39–1.49 (m, 2 H), 1.52 (ddd, J = 13.6, 6.2, 1.3 Hz, 1 H), 1.57–1.75 (m, 3 H), 1.64 (ddd, J = 13.6, 6.7, 1.2 Hz, 1 H), 2.08–2.18 (m, 3 H), 2.21 (d, J_{AB} = 17.7 Hz, 1 H), 2.28 (d, J_{AB} = 17.7 Hz, 1 H), 4.11 (quint, J = 6.0 Hz 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.12 (CH_3), 22.96 (CH_2), 23.00 (CH_3), 35.58 (CH_2), 41.29 (CH_2), 45.48 (CH_2), 46.23 (C), 49.07 (CH_2), 50.19 (CH_2), 57.46 (C), 61.44 (C), 71.76 (CH), 223.43 (C═O). MS (EI): m/z (%) = 208 (29) [M^+], 166 (8), 151 (54), 147 (8), 124 (100), 109 (5), 107 (6), 106 (12), 96 (18), 95 (23), 94 (14). HRMS: m/z calcd for $C_{13}H_{20}O_2$: 208.1463, found: 208.1467.

(2*SR*,3a*RS*,5a*SR*,8a*RS*)-Decahydro-2-(*tert*-butyldimethylsilyloxy)-3a,5a-dimethylcyclopenta[*c*]pentalen-4-one (14)

Imidazole (0.98 g, 14.4 mmol) and *tert*-butyldimethylchlorosilane (1.1 g, 7.2 mmol) were added to a solution of the alcohol **13** (1.0 g, 4.8 mmol) in dichloromethane (50 mL) at room temperature. A colourless precipitate was formed upon addition of the silane, which disappeared subsequently. The mixture was stirred for 2 h at room temperature and quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous layer was separated and extracted with dichloromethane three times. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. Purification of the residue by flash chromatography (SiO_2; petroleum ether–diethyl ether, 10 : 1) afforded **14** as a colourless oil, yield: 1.45 g (94%). IR (ATR): ν = 2953, 2929, 2857, 1734, 1471, 1462, 1411, 1367, 1252, 1155, 1109, 1077, 1039, 1006, 960, 934, 911, 859, 833, 773, 700, 670, 633 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.86 (s, 9 H), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.37–1.41 (m, 1 H), 1.47–1.53 (m, 2 H), 1.55–1.59 (m, 1 H), 1.62 (ddd, J = 13.4, 4.5, 1.8 Hz, 1 H), 1.68–1.72 (m, 2 H), 1.95 (ddd, J = 13.4, 5.3, 0.9 Hz, 1 H), 2.01 (dd, J = 13.4, 4.8 Hz, 1 H), 2.15–2.19 (m, 1 H), 2.21 (d, J_{AB} = 17.5 Hz, 1 H), 2.25 (d, J_{AB} = 17.5 Hz, 1 H), 4.04 (quint, J = 5.2 Hz, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –4.88 (2 CH_3), 18.00 (C), 21.19 (CH_3), 22.67 (CH_3), 22.96 (CH_2), 25.79 (3 CH_3), 35.67 (CH_2), 41.01 (CH_2), 46.19 (CH_2), 46.25 (C), 49.49 (CH_2), 49.84 (CH_2), 57.39 (C), 61.73 (C), 72.55 (CH), 223.70 (C═O). MS (EI): m/z (%) = 322 (1) [M^+], 307 (4), 267 (6), 265 (100), 195 (10), 173 (18), 143 (29), 133 (13), 95 (16), 91 (13), 75 (94), 73 (21). Elemental analysis calcd for $C_{19}H_{34}O_2Si$: C 70.75, H 10.62; found: C 70.92, H 10.73.

(2*RS*,3a*SR*,5a*SR*,8a*RS*)-Decahydro-2-*tert*-butyldimethylsilyloxy-3a,5a-dimethyl-4-methylenecyclopenta[*c*]pentalene (15)

A 1.47 M solution of butyllithium in hexane (32 mL, 47 mmol) was added to a suspension of methyltriphenylphosphonium bromide (19 g, 53 mmol) in anhydrous *p*-xylene (100 mL) at room temperature. The resulting clear, yellow solution was heated at reflux and a solution of the ketone **14** (2.05 g, 6.36 mmol) in anhydrous *p*-xylene (20 mL) was added *via* perfusor over a period of 2.5 h. Subsequently, the reaction mixture was heated at reflux for 2 d. After cooling to room temperature, a saturated aqueous solution of ammonium chloride was added. The aqueous layer was separated and extracted with diethyl ether three times. The

combined organic layers were washed with water and brine, dried over magnesium sulfate and the solvent was evaporated. Pentane was added and the insoluble parts were removed by filtration (Celite; pentane). After evaporation of the solvent, the residue was purified by flash chromatography (SiO_2; petroleum ether–diethyl ether, 40 : 1) to afford **15** as a colourless oil, yield: 1.70 g (83%). IR (ATR): ν = 3073, 2950, 2928, 2856, 1655, 1471, 1462, 1369, 1252, 1092, 1074, 1039, 1005, 938, 912, 879, 862, 833, 772, 697, 674 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.86 (s, 9 H), 0.97 (s, 3 H), 1.13 (s, 3 H), 1.34–1.39 (m, 2 H), 1.40–1.54 (m, 5 H), 1.88 (ddd, J = 12.8, 6.0, 1.4 Hz, 1 H), 1.92–1.98 (m, 2 H), 2.14 (dt, J_{AB} = 14.8, J = 2.1 Hz, 1 H), 2.20 (d, J_{AB} = 14.8 Hz, 1 H), 4.02 (quint, J = 6.1 Hz, 1 H), 4.68 (m, 1 H), 4.70 (m, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –4.81 (CH_3), –4.79 (CH_3), 18.15 (C), 23.67 (CH_3), 23.84 (CH_2), 24.46 (CH_3), 25.90 (3 CH_3), 36.51 (CH_2), 40.98 (CH_2), 45.61 (CH_2), 47.31 (CH_2), 49.04 (C), 52.30 (CH_2), 52.62 (C), 63.04 (C), 72.22 (CH), 102.43 (CH_2), 161.72 (C). MS (EI): m/z (%) = 320 (1) [M^+], 305 (2), 265 (7), 263 (100), 187 (10), 133 (12), 75 (94), 73 (13).

(2*RS*,3a*SR*,5a*SR*,8a*RS*)-Decahydro-3a,5a-dimethyl-4-methylene-2-hydroxycyclopenta[*c*]pentalene (16)

Water (813 µL, 813 mg, 45.2 mmol) and a 1 M solution of TBAF in THF (15 mL, 15 mmol) were added to a solution of the silyl ether **15** (1.70 g, 5.30 mmol) in anhydrous THF (50 mL). The mixture was heated at reflux for 24 h. After cooling to room temperature the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous layer was separated and extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was evaporated. Purification of the residue by flash chromatography (SiO_2; petroleum ether–diethyl ether, 1 : 1) provided **16** as a colourless oil, yield: 1.06 g (97%). IR (ATR): ν = 3263, 3073, 2948, 2866, 1651, 1440, 1372, 1354, 1316, 1124, 1087, 1048, 936, 877, 676 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (s, 3 H), 1.14 (s, 3 H), 1.34–1.41 (m, 2 H), 1.43–1.55 (m, 5 H), 1.92–1.96 (m, 1 H), 2.00 (ddd, J = 12.9, 6.3, 1.4 Hz, 1 H), 2.09 (ddd, J = 13.2, 5.8, 1.3 Hz, 1 H), 2.15 (dt, J_{AB} = 15.0, J = 2.1 Hz, 1 H), 2.21 (d, J_{AB} = 15.0 Hz, 1 H), 4.09 (m, 1 H), 4.70 (m, 1 H), 4.71 (m, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 23.79 (CH_2), 23.81 (CH_3), 24.49 (CH_3), 36.47 (CH_2), 41.23 (CH_2), 45.18 (CH_2), 47.37 (CH_2), 49.07 (C), 52.08 (CH_2), 52.91 (C), 63.23 (C), 71.67 (CH), 102.79 (CH_2), 161.14 (C). MS (EI): m/z (%) = 206 (6) [M^+], 191 (10), 188 (14), 173 (40), 164 (18), 163 (16), 160 (11), 159 (15), 148 (71), 147 (59), 146 (22), 145 (43), 133 (41), 131 (34), 123 (23), 121 (24), 120 (29), 119 (43), 117 (22), 109 (20), 107 (34), 105 (55), 95 (100). Elemental analysis calcd for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.60, H 10.81.

(3a*SR*,5a*SR*,8a*RS*)-Decahydro-3a,5a-dimethyl-4-methylenecyclopenta[*c*]pentalen-2-one (17)

Powdered 4 Å molecular sieves (1.3 g), *N*-methylmorpholine *N*-oxide (755 mg, 6.4 mmol) and tetrapropylammonium perruthenate (46 mg, 130 µmol) were added to a solution of alcohol **16** (531 mg, 2.6 mmol) in anhydrous dichloromethane (25 mL) at –16 °C. The cooling was removed and the reaction mixture was stirred at room temperature for 16 h. After filtration (SiO_2; diethyl ether) **17** was obtained as a colourless oil, yield: 504 mg (95%). IR (ATR): ν = 3077, 2947, 2868, 1737, 1659, 1447, 1400, 1376, 1184, 1003, 943, 882, 827, 675 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (s, 3 H), 1.16 (s, 3 H), 1.40–1.47 (m, 3 H), 1.54–1.58 (m, 2 H), 1.78 (m, 1 H), 2.12 (d, J = 19.3 Hz, 1 H), 2.20 (dd, J = 19.1, 1.8 Hz, 1 H), 2.31 (d, J = 16.0 Hz, 1 H), 2.35 (d, J = 19.3 Hz, 1 H), 2.46 (dt, J = 16.0, 2.5 Hz, 1 H), 2.55 (d, J = 19.1 Hz, 1 H), 4.75 (m, 1 H), 4.78 (m, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.54 (CH_3), 24.64 (CH_2), 26.49 (CH_3), 37.25 (CH_2), 44.63 (CH_2), 47.06 (CH_2), 48.15 (C), 48.30 (CH_2), 52.22 (C), 52.95 (CH_2), 60.99 (C), 104.30 (CH_2), 157.05 (C), 218.79 (C═O). MS (EI): m/z (%) = 204 (23) [M^+], 189 (11), 175 (11), 171 (14), 162 (31), 161 (33), 160 (18), 147 (62), 146 (32), 133 (30), 120 (24), 119 (41), 105 (39), 95 (100). Elemental analysis calcd for $C_{14}H_{20}O$: C 82.30, H 9.87; found: C 82.19, H 9.92.

(1*SR*,3a*SR*,5a*SR*,8a*RS*)-Decahydro-1,3a,5a-trimethyl-4-methylenecyclopenta[*c*]pentalen-2-one (18)

A solution of ketone **17** (100 mg, 490 µmol) in anhydrous THF (2 mL) was added to a solution of lithium bis(trimethylsilyl)amide (82 mg, 490 µmol) in anhydrous THF (6 mL) and the mixture was stirred at room temperature for 2 h. The solution was cooled to –78 °C. DMPU (*N*,*N*′-dimethyl-1,3-propylene urea) (194 µL, 140 mg, 1.47 mmol), a 1 M solution of dimethylzinc in heptane (49 µl, 49 µmol) and iodomethane (153 µL, 349 mg, 2.45 mmol) were added. The cooling was removed and the mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of a saturated solution of ammonium chloride (10 mL) and water (10 mL). The aqueous layer was separated and extracted with dichloromethane three times. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. Purification of the residue by flash chromatography (SiO_2; pentane–diethyl ether, 20 : 1) afforded 67 mg of a colourless oil. According to GC-MS analysis the mixture contained 78.2% of the desired product **18** (52.4 mg, 240 µmol, 49%). The ratio of **18**/monoalkylated isomer 1/monoalkylated isomer 2/double alkylated products = 78.2 : 14.0 : 3.6 : 4.2. IR (ATR): ν = 3072, 2950, 2871, 1736, 1656, 1454, 1407, 1377, 1188, 1086, 1020, 884 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (s, 3 H), 1.07 (d, J = 7.5 Hz, 3 H), 1.19 (s, 3 H), 1.49–1.59 (m, 3 H), 1.60–1.65 (m, 3 H), 2.17 (d, J = 18.9 Hz, 1 H), 2.35–2.43 (m, 3 H), 2.44 (dd, J = 18.9, 1.3 Hz, 1 H), 4.75 (s, 1 H), 4.79 (s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 13.70 (CH_3), 24.09 (CH_2), 24.29 (CH_3), 25.92 (CH_3), 29.86 (CH_2), 42.47 (CH_2), 47.44 (CH_2), 48.25 (CH), 50.11 (C), 51.16 (C), 51.79 (CH_2), 64.18 (C), 104.37 (CH_2), 158.83 (C), 221.19 (C═O). MS (EI): m/z (%) = 218 (16) [M^+], 203 (7), 190 (3), 175 (10), 161 (10), 147 (23), 119 (11), 109 (100), 108 (18).

(1*SR*,2*SR*,3a*SR*,5a*SR*,8a*RS*)-Decahydro-2-hydroxy-1,3a,5a-trimethyl-4-methylenecyclopenta[*c*]pentalene (19)

A 1 M solution of lithium aluminium hydride in anhydrous THF (500 µL, 500 µmol) was added at –78 °C to a solution of **18** (105 mg, 481 µmol) in anhydrous THF (10 mL) and the resulting mixture was stirred for 3 h at –78 °C. After warming to room temperature, the excess hydride was deactivated by addition of water. The precipitate was dissolved by addition of aqueous HCl (10%). Diethyl ether was added (27 mL), the organic layer was

separated and washed with a saturated aqueous solution of sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and the solvent was removed. Purification of the residue by flash chromatography (SiO_2; pentane–diethyl ether, 5 : 1) afforded the alcohol **19** as a colourless oil, yield: 91 mg (86%).

IR (ATR): ν = 3300, 3075, 2951, 2869, 1654, 1456, 1371, 1357, 1327, 1155, 1132, 1083, 1042, 1030, 1011, 975, 930, 875 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.8 Hz, 3 H), 0.97 (s, 3 H), 1.05 (s, 3 H), 1.31–1.46 (m, 3 H), 1.48–1.74 (m, 5 H), 1.77 (dd, J = 12.0, 6.0 Hz, 1 H), 2.10 (d, J = 14.6 Hz, 1 H), 2.42 (dt, J = 14.6, 2.4 Hz, 1 H), 3.53 (dt, J = 6.1, 10.4 Hz, 1 H), 4.69 (m, 2 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 14.69 (CH_3), 23.44 (CH_3), 23.58 (CH_2), 23.85 (CH_3), 28.42 (CH_2), 39.01 (CH_2), 45.59 (CH_2), 47.09 (CH), 50.20 (C), 50.54 (CH_2), 51.28 (C), 64.35 (C), 78.00 (CH), 102.84 (CH_2), 160.87 (C). MS (EI): m/z (%) = 220 (2) [M^+], 205 (7), 202 (15), 187 (100), 178 (56), 174 (12), 173 (14), 161 (15), 160 (19) 159 (34), 147 (33), 146 (23), 145 (40), 134 (82), 133 (27), 131 (23), 121 (21), 120 (29), 119 (35), 109 (65). Elemental analysis calcd for $C_{15}H_{24}O$: C 81.76, H 10.98; found: C 81.88, H 11.03.

(±)-β-Isocomene [(±)-6]

N-Ethyldiisopropylamine (128 µL, 93 mg, 720 µmol) was added to a solution of the alcohol **19** (53 mg, 240 µmol) in anhydrous dichloromethane (7 mL). After cooling to 0 °C, methanesulfonyl chloride (44 µL, 63 mg, 552 µmol) was added and the reaction mixture was stirred for 2 h at 0 °C. A saturated aqueous solution of sodium bicarbonate was added, the aqueous layer was separated and extracted with dichloromethane three times. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2; pentane–diethyl ether, 5 : 1). The resulting mesylate was taken up in anhydrous diethyl ether (7 mL), lithium aluminium hydride (70 mg, 1.85 mmol) was added and the suspension was heated at reflux for 3 h. After cooling to room temperature, the reaction was quenched by careful addition of ice water. The precipitate was dissolved by addition of aqueous HCl (10%) and the resulting mixture was extracted with diethyl ether three times. The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over sodium sulfate, and the solvent was removed. Purification of the residue by flash chromatography (SiO_2; pentane–diethyl ether, 100 : 1) afforded a colourless oil, which slowly crystallised upon standing to give (±)-β-isocomene [(±)-**6**] as colourless crystals, yield: 38 mg (78%), m.p. 76–82 °C. IR (ATR): ν = 3073, 2925, 2869, 2854, 1655, 1460, 1376, 1260, 1106, 1024, 878 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, J = 7.0 Hz, 3 H), 0.98 (s, 3 H), 1.09 (s, 3 H), 1.20–1.67 (m, 10 H), 1.98 (m, 1 H), 2.09 (d, J = 14.5 Hz, 1 H), 2.33 (dt, J = 14.5, 2.4 Hz, 1 H), 4.60 (m, 1 H), 4.62 (m, 1 H). ^1H NMR (500 MHz, CD_2Cl_2): δ = 0.92 (d, J = 7.0 Hz, 3 H), 0.99 (s, 3 H), 1.10 (s, 3 H), 1.22–1.68 (m, 10 H), 2.00 (m, 1 H), 2.10 (d, J = 14.4 Hz, 1 H), 2.34 (dt, J = 14.4, 2.4 Hz, 1 H), 4.60 (m, 1 H), 4.63 (m, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 17.99 (CH_3), 23.40 (CH_3), 24.01 (CH_2), 24.20 (CH_3), 30.27 (CH_2), 34.54 (CH_2), 40.43 (CH), 41.66 (CH_2), 42.80 (CH_2), 47.99 (CH_2), 49.37 (C), 54.77 (C), 66.64 (C), 100.65 (CH_2), 162.30 (C). ^{13}C NMR and DEPT (125 MHz, CD_2Cl_2): δ = 18.08 (CH_3), 23.53 (CH_3), 24.27 (CH_3), 24.33 (CH_2), 30.55 (CH_2), 34.87 (CH_2), 40.83 (CH), 41.95 (CH_2), 43.15 (CH_2), 48.23 (CH_2), 49.68 (C), 55.14 (C), 67.01 (C), 100.79 (CH_2), 162.76 (C). MS (EI): m/z (%) = 204 (21) [M^+], 189 (68), 175 (12), 162 (15), 161 (35), 149 (22), 148 (29), 147 (49), 134 (28), 133 (42), 122 (29), 121 (44), 120 (31), 119 (40), 109 (68), 108 (100), 107 (60). Elemental analysis calcd for $C_{15}H_{24}O$: C 88.16, H 11.84; found: C 88.28, H 11.98.

(±)-Isocomene [(±)-5]

p-Toluenesulfonic acid hydrate (7 mg, 37 µmol) was added to a solution of (±)-β-isocomene [(±)-**6**] (23 mg, 113 µmol) in dichloromethane (5 mL) and the suspension was stirred at room temperature for 3 h. The solid was removed by filtration (SiO_2; dichloromethane) and the solvent was evaporated to afford (±)-isocomene [(±)-**5**] as a colourless oil, yield: 23 mg (100%). IR (ATR): ν = 3020, 2927, 2866, 2853, 1672, 1458, 1443, 1375, 1002, 940, 845 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, J = 7.2 Hz, 3 H), 1.026 (s, 3 H), 1.030 (s, 3 H), 1.14–1.43 (m, 5 H), 1.48–1.58 (m, 4 H), 1.55 (d, J = 1.3 Hz, 3 H), 1.70–1.73 (m, 1 H), 1.99 (m, 1 H), 4.85 (m, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 13.00 (CH_3), 17.27 (CH_3), 23.16 (CH_3), 23.71 (CH_3), 24.01 (CH_2), 31.91 (CH_2), 33.62 (CH_2), 37.22 (CH_2), 39.88 (CH), 42.60 (CH_2), 56.61 (C), 59.86 (C), 63.75 (C), 132.66 (CH), 142.81 (C). MS (EI): m/z (%) = 204 (10) [M^+], 189 (16), 175 (7), 162 (100), 161 (17), 147 (49), 134 (18), 133 (19), 119 (31), 105 (20), 91 (18). Elemental analysis calcd for $C_{15}H_{24}O$: C 88.16, H 11.84; found: C 88.20, H 11.80.

Acknowledgements

We are grateful to the Wacker Chemie AG, Burghausen, for a generous gift of *tert*-butyldiphenylchlorosilane.

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