Stereoselective Total Synthesis of the Sesquiterpene (±)-β-Isocomene

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Abstract: Application of the Lewis acid mediated [3+2] cycloaddition of allyl-*tert*-butyldiphenylsilane combined with a modified Fleming–Tamao oxidation provides a stereoselective route to the triquinane sesquiterpene (±)-β-isocomene.

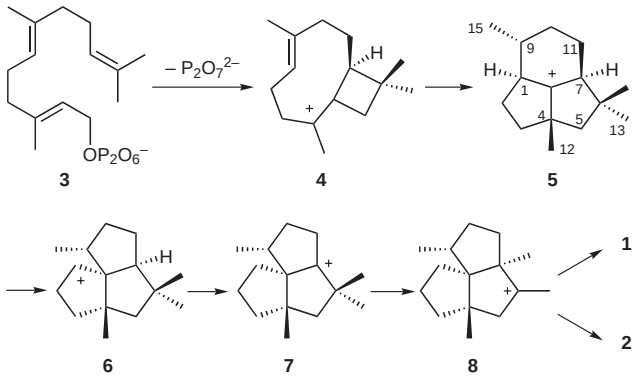
Key words: cycloadditions, Lewis acids, silicon, stereoselective synthesis, terpenoids

The sesquiterpene (–)-β-isocomene (**1**) was isolated first by Bohlmann and co-workers in 1979 during their investigation of various species of the South African genus *Berkheya* (family: *asteraceae*, Figure 1).[1] The natural product was found along with other sesquiterpenes in the roots of *B. rhapontica* (DC.) Hutch. & Burtt Davy, *B. setifera* (DC.) and *B. sp. novum aff. bipinnatifada*. The isomeric (–)-isocomene (**2**) was isolated first by Zalkow et al. in 1977 from the hexane extract of *Isocoma Wrightii*, a toxic plant, also known as Rayless Goldenrod or Jimmyweed, which is native to New Mexico and Texas (Figure 2).[2] The relative configuration was established by transformation of the natural product into the corresponding diol and subsequent single-crystal X-ray analysis. In the same year (–)-isocomene (**2**) was isolated by Bohlmann et al. from the roots of the South African *Berkheya radula* (Harv.) De Willd. and named berkheyaradulene.[3] However, the name (–)-isocomene prevailed. Since then, both natural products have been found in various plants.[4,5] The absolute configuration was assigned in 1993 by Fitjer et al. based on rearrangement experiments of compounds with known absolute configuration.[6] For the biogenesis of the isocomenes a cascade of rearrangement steps starting from farnesyl pyrophosphate (**3**) has been proposed (Scheme 1).[5–7] The intermediate presilphiperfolanyl cation (**5**) is considered as the crucial precursor for all triquinanes and represents the parent compound for atom numbering. Due to their unique skeleton, both natural products have received considerable attention in organic synthesis.[8–10] An asymmetric synthesis of **2** was reported by Rawal et al. in 1996.[9] Due to the exocyclic methylene group at C-6, β-isocomene is the more challenging target. So far four total syntheses of (±)-β-isocomene [(±)-**1**] have been described. The acid-catalyzed isomerization of (±)-β-isocomene [(±)-**1**] affords the thermodynamically more stable isomer (±)-isocomene [(±)-**2**].[10]

1 (–)-β-isocomene **2** (–)-isocomene

Figure 1 Triquinane sesquiterpene natural products of the isocomene type

Figure 2 *Isocoma wrightii* (Courtesy of Texas Cooperative Extension, Texas A&M University System)



3 **4** **5** **6** **7** **8**

Scheme 1 Biogenetic pathway to the isomeric isocomenes **1** and **2**

We described the formation of five-membered carbocyclic rings by a formal [3+2] cycloaddition of sterically hindered allylsilanes and α,β-unsaturated ketones.[11,12] This new methodology found diverse applications in organic synthesis.[13] Exploitation of the silylcyclopentanes for natural product synthesis is feasible by the Fleming–

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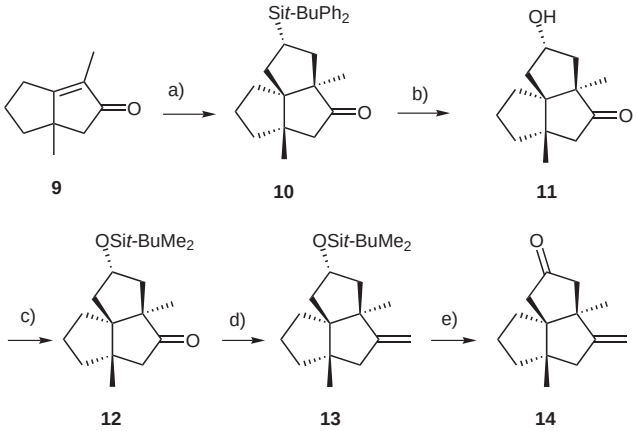
Tamao oxidation.[14] Even highly hindered silyl groups [e.g. triphenylsilyl, *tert*-butyldiphenylsilyl and di(isopropyl)phenylsilyl] can be converted into the corresponding hydroxy groups by using our modified protocol for this reaction.[15] Herein, we report an application using our [3+2] cycloaddition of allyl-*tert*-butyldiphenylsilane to the stereoselective total synthesis of (±)-β-isocomene [(±)-**1**].

Our approach to (±)-β-isocomene [(±)-**1**] started from the known enone **9**,[16] prepared by Yoshikoshi's method via Henry reaction and subsequent intramolecular aldol condensation.[16b] Since an enantioselective synthesis of enone **9** has been reported,[16d] our approach would open up an access to enantiopure **1** as well. The Lewis acid mediated [3+2] cycloaddition of **9** and allyl-*tert*-butyldiphenylsilane provided the tricyclic compound **10** as a single diastereoisomer in high yield (85%; Scheme 2).[17] The *anti* configuration of **10** was unequivocally proven by an X-ray crystal-structure determination (Figure 3).[18] This assignment has been confirmed by comparison with the stereochemical results of our previous studies.[12] Remarkably, our cycloaddition establishes the decahydrocyclopenta[*c*]pentalene skeleton with three consecutive quaternary carbon atoms in a single step. Protodesilylation of **10** using boron trifluoride–acetic acid complex followed by oxidation of the resulting difluorosilane with buffered hydrogen peroxide in the presence of cesium fluoride (modified Fleming–Tamao oxidation)[15] afforded alcohol **11**.[17] Since methylenation in the presence of the free hydroxy group was not possible, compound **11** was transformed into the corresponding silyl ether **12**. Wittig olefination furnished compound **13**, bearing the required exocyclic double bond. Generation of the Wittig reagent by addition of butyllithium to methyltriphenylphosphonium bromide and subsequent slow addition of the ketone while heating in *p*-xylene at reflux was required for this transformation. The next task was the introduction of the missing methyl group at C-9. Thus, the silyl ether was cleaved followed by oxidation of the resulting alcohol to the ketone **14** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as stoichiometric oxidant.[19]

A regio- and stereoselective alkylation was envisaged for the introduction of the final methyl group. Due to the steric hindrance caused by the angular methyl group at C-7, we expected a preferential deprotonation at C-9 leading to the 9,10-enolate. Attack of the electrophile should occur from the *exo*-face of the molecule, previously observed for various transformations at the 9,10-double bond of the isocomene skeleton.[20] Deprotonation with LiHMDS at room temperature followed by treatment of the resulting enolate with iodomethane in the presence of *N*,*N*′-dimethyl-1,3-propyleneurea (DMPU) and catalytic amounts of dimethylzinc[21] led to compound **15** (Scheme 3). After removal of starting material by flash chromatography, the desired product **15** was isolated along with two monoalkylated isomers and two double alkylation products.[22] The regio- and stereochemistry of the alkylation product **15** was assigned based on 2D NMR experiments (COSY, HSQC, HMBC, and NOESY). Finally, the oxo group of **15** had to be removed. Wolff–Kishner reduction and thioketalization of the ketone failed. Thus, compound **15** was reduced to the alcohol **16** using lithium aluminum hydride. The relative configuration of **16** was assigned based on 2D NMR experiments (COSY, HSQC, HMBC, and NOESY). Transformation into the corresponding mesylate and subsequent nucleophilic displacement with lithium aluminum hydride afforded (±)-β-isocomene [(±)-**1**]. The natural product was quantitatively isomerized to (±)-isocomene [(±)-**2**] using a literature procedure.[10b] The



Scheme 2 *Reagents and conditions*: a) 1. $TiCl_4$, CH_2Cl_2, r.t., 10 min; 2. allyl-*tert*-butyldiphenylsilane, reflux, 10 d (85%); b) 1. BF_3·2AcOH, 1,2-$C_2H_4Cl_2$, reflux, 46 h; 2. CsF, $KHCO_3$, H_2O_2, THF–MeOH (1:1), reflux, 12 h (86%, two steps); c) *t*-$BuMe_2SiCl$, imidazole, CH_2Cl_2, r.t., 2 h (94%); d) 1. $MePPh_3Br$, *n*-BuLi, *p*-xylene, r.t.; 2. **12**, *p*-xylene, reflux, 48 h (83%); e) 1. TBAF, H_2O, THF, reflux, 24 h, (97%); 2. TPAP, NMO, CH_2Cl_2, r.t., 16 h (95%).

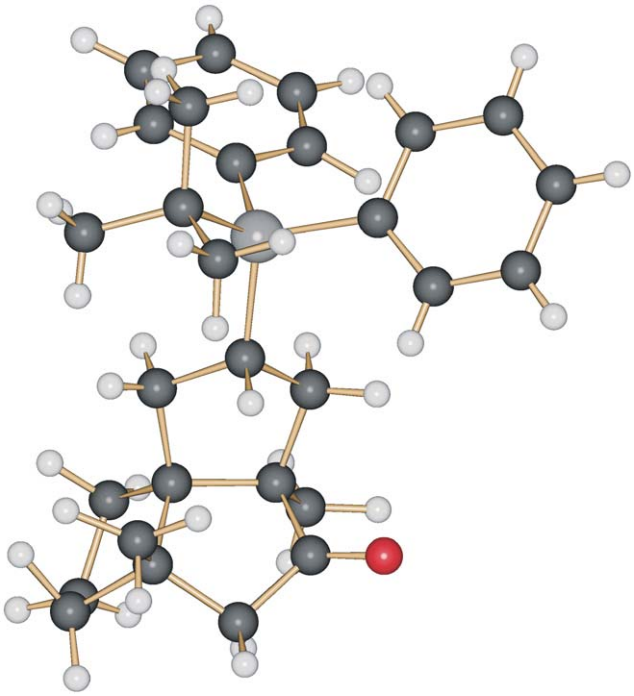
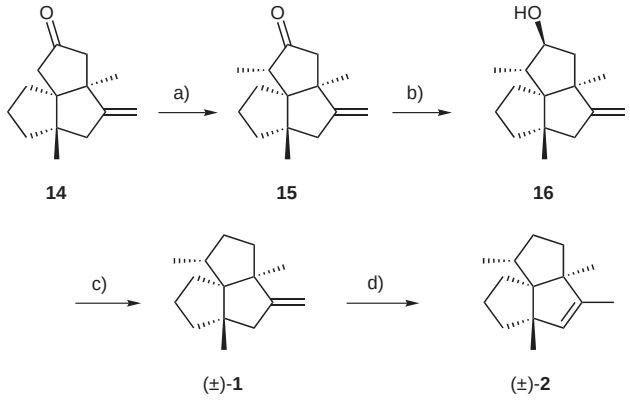


Figure 3 Molecular structure of compound **10** in the crystal.



Scheme 3 *Reagents and conditions*: a) 1. LiHMDS, THF, r.t., 2 h; 2. MeI, $ZnMe_2$, DMPU, THF, –78 °C to 25 °C, 16 h (49%); b) $LiAlH_4$, THF, –78 °C, 3 h (86%); c) 1. MsCl, EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 °C, 2 h; 2. $LiAlH_4$, Et_2O, reflux, 3 h (78%, two steps); d) PTSA·H_2O, CH_2Cl_2, r.t., 3 h (100%).

spectroscopic data of our synthetic (±)-β-isocomene [(±)-**1**] and (±)-isocomene [(±)-**2**] are in full agreement with those reported for the natural products.[1–3,17]

In conclusion, our Lewis acid promoted [3+2] cycloaddition of allyl-*tert*-butyldiphenylsilane followed by the modified Fleming–Tamao oxidation represents a powerful method for natural product synthesis. The efficiency of this cyclopentannulation is emphasized by the fact that a sterically hindered arrangement of three contiguous quarternary carbon centers is constructed in high yield (85%). We obtained (±)-β-isocomene [(±)-**1**] for the first time as a solid (colorless crystals, mp 76–82 °C) in 9 steps and 17% overall yield based on enone **9**.

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(17) Characteristic Spectroscopic Data of **10**, **11**, (±)-**1**, and (±)-**2**: Compound **10**: colorless crystals, mp 112 °C. ^{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). Anal. Calcd (%) for $C_{29}H_{38}OSi$: C, 80.87; H, 8.89. Found: C, 80.64; H, 8.26.

Compound **11**: colorless oil. ^{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).

(±)-β-Isocomene [(±)-**1**]: colorless crystals, mp 76–82 °C. IR (ATR): ν = 3073, 2925, 2869, 2854, 1655, 1460, 1376, 1260, 1106, 1024, 878 cm^{-1}. ^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, 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). Anal. Calcd (%): for $C_{15}H_{24}O$: C, 88.16; H, 11.84. Found: C, 88.27; H, 11.98.

(±)-Isocomene [(±)-**2**]: colorless oil. 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). Anal. Calcd (%) for $C_{15}H_{24}O$: C, 88.16; H, 11.84. Found: C, 88.20; H, 11.80.

(18) Crystal data for **10**: $C_{29}H_{38}OSi$, crystal size: $0.60 \times 0.40 \times 0.40$ mm^3, M_r = 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_{calcd} = 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). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0481, wR_2 = 0.1275 [$I > 2\sigma(I)$]; maximal residual electron density: 0.424 e $Å^{-3}$. CCDC 646230 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(22) Ratio of compound **15**/monoalkylated isomer **1**/monoalkylated isomer **2**/dialkylated product **1**/dialkylated product **2** = 78.2:14.0:3.6:2.2:2.0.