Stereocontrolled synthesis of *trans*-2-hydroxymethyl-3-methylcyclopentanone from (*S*)-(+)-citronellene

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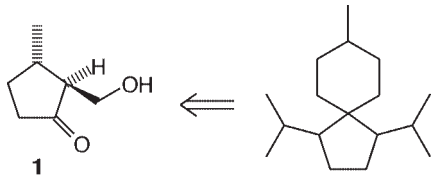
A simple route to *trans*-2-hydroxymethyl-3-methylcyclopentanone was proposed. The compound is a key intermediate in the synthesis of natural spirocyclic sesquiterpene of the acorane series.

Key words: (*S*)-(+)-citronellene, *trans*-2-hydroxymethyl-3-methylcyclopentanone, (*S*)-3-methyl-6-nitrohex-1-ene, silyl nitronates, intramolecular [3+2] cycloaddition, cyclopenta[*c*]isoxazolidine, cyclopenta[*c*]dihydroisoxazole, sesquiterpenes of the acorane series.

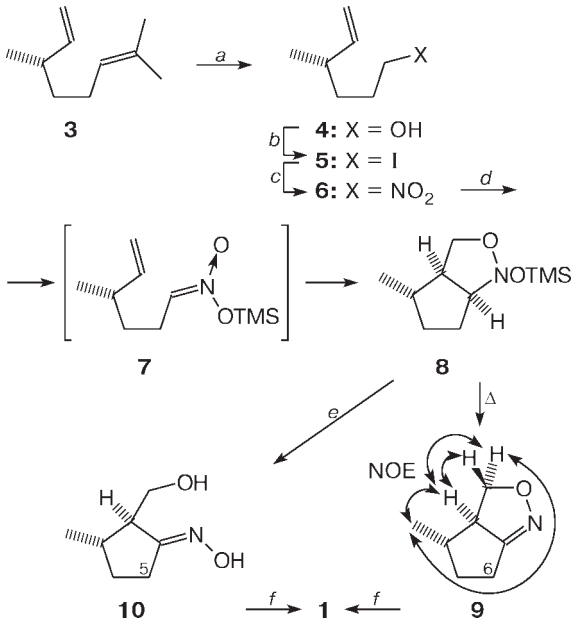
Earlier,[1] we have shown that intramolecular [3+2] cycloaddition of silyl nitronates generated from accessible nitro derivatives of linear monoisoprenoids serves as a basis for a new efficient approach to the stereocontrolled construction of natural cyclopentanoids. In the present work, this reaction was used to obtain cyclopentanone **1**, a known synthetic block for the access to natural compounds containing a cyclopentane fragment. Previously,[2] this has served as a key compound in the synthesis of some spirocyclic sesquiterpenoids of the acorane series **2**, which were found among plant metabolites. It should be noted that the carbon framework of a natural cyclopentanoid, namely, the antibiotic sarcomycin A, is analogous to that in ketone **1**.[3]



1 **2**

Accessible scalemic diene **3** (*ee* ~30%) was used as the starting material for the synthesis of ketone **1**. Compound **3** was converted into alcohol **4** [4] and then into iodide **5** (this has been described previously[5] as a racemate) according to the known procedures. Iodide **5** was treated with $NaNO_2$ in DMF in the presence of $(NH_2)_2CO$ to give nitro olefin **6** (Scheme 1). The reaction of compound **6** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) under the conditions employed earlier[1] yields silyl nitronate **7**, which undergoes intramolecular [3+2] cycloaddition to give *N*-trimethylsilyloxyisoxazolidine **8**. This reaction proved to be virtually diastereospecific since no additional ^1H signals from the TMS and CH_2O groups of possible diastereomers appeared in the ^1H NMR spectrum, as has been observed earlier[1] for related cases. Compound **8** is very labile; upon distillation *in vacuo*, it transformed into dihydroisoxazole **9**. At the same time, treatment of compound **8** without any additional purification with a sus-

Scheme 1



Reagents and conditions: *a*. See Ref. 4. *b*. See Ref. 5.
c. $NaNO_2/(H_2N)_2CO$/DMF, 0 °C.
d. BSA/Et_3N/MeCN/PhH, 85 °C.
e. $KF \cdot 2H_2O$/MeOH/THF, −40 → 20 °C.
f. $[TiCl_3]/H_2O$/MeOH, 20 °C.

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pension of $KF \cdot 2H_2O$ in MeOH (*cf.* Ref. 1) gave oxime **10** in good yield.

Dihydroisoxazole **9** and oxime **10** were converted to the target ketone **1** under the action of $TiCl_3$ at pH 4 (*cf.* Ref. 6), the yield of cyclopentanone **1** being ~80% in both cases.

The structures of new compounds **6** and **8**—**10** were established based on the data from elemental analysis and spectroscopy. In particular, the NOESY spectrum of dihydroisoxazole **9** shows the corresponding nuclear Overhauser effects (NOE) (see Scheme 1). *E*-configuration was assigned to oxime **10** since its ^{1}H NMR spectrum shows a downfield shift of a signal for one of the $C(5)H_2$ protons which is spatially close to the oxime OH group (δ 2.67); this is characteristic of the alicyclic series (*cf.* Ref. 7). Note that signals for the $C(6)H_2$ protons in dihydroisoxazole **9** appear at δ ~2.3.

The ^{1}H NMR spectrum of ketone **1** synthesized according to Scheme 1 is virtually identical with that reported for the compound obtained earlier[2] by a multistep transformation of (*R*)-pulegone; because of its lability, specific optical rotation has not been reported.

Experimental

IR spectra were recorded on a Specord M-80 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 and 50.32 MHz, respectively) in $CDCl_3$. Chemical shifts were referenced to the signals for the solvent (δ_H 7.27 and δ_C 77.0). Mass spectra (EI, 70 eV) were recorded on a Varian MAT 311A instrument. Optical rotation ($[\alpha]_D$) was measured on a JASCO DIP-360 polarimeter. The R_f values are given for a fixed SiO_2 layer (Silufol).

After distillation (b.p. 153—156 °C), (*S*)-(+)-citronellene (**3**) (GLIDCO Organics Co., USA) had $[\alpha]_D^{20}$ +3.6.

Solvents were purified according to standard procedures.

(*S*)-6-Iodo-3-methylhex-1-ene (5). A viscous liquid, b.p. 68 °C (2 Torr) (*cf.* Ref. 5: b.p. 85—87 °C (22 Torr) for (±)-**5**), $[\alpha]_D^{23}$ +5.2 (*c* 3.2, MeOH). ^{1}H NMR, δ: 1.02 (d, 3 H, C(3)Me, J = 6 Hz); 1.42 (m, 2 H, $C(5)H_2$); 1.83 (m, 2 H, $C(4)H_2$); 2.18 (m, 1 H, C(3)H); 3.19 (m, 2 H, $C(6)H_2$); 4.96 (m, 2 H, $C(1)H_2$); 5.70 (m, 1 H, C(2)H). ^{13}C NMR, δ: 6.80 (C(6)); 20.20 (C(3)Me); 31.52 (C(4)); 37.21 (C(5)); 37.42 (C(3)); 113.08 (C(1)); 144.10 (C(2)).

(*S*)-3-Methyl-6-nitrohex-1-ene (6). Iodide **5** (1.6 g, 7.14 mmol) was added dropwise over 5 min to a stirred suspension of $NaNO_2$ (1 g, 14.5 mmol) and $(H_2N)_2CO$ (0.87 g, 14.5 mmol) in 20 mL of DMF at 0 °C. The reaction mixture was stirred at 0 °C for 6 h and poured onto ice (50 g). The product was extracted with light petroleum (b.p. 40—70 °C, 2×50 mL). The combined extract was washed with water (20 mL) and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~1.5 g) was chromatographed on SiO_2 (30 g) in AcOEt—light petroleum (1 : 99). Fractions containing a product with R_f 0.62 (heptane—ether, 95 : 5) were combined and distilled *in vacuo* to give nitro olefin **6** (0.68 g, 67%) as a light yellow liquid, b.p. 62—64 °C (2 Torr), $[\alpha]_D^{25}$ +4.25 (*c* 10.8, MeOH). Found (%): C, 58.67; H, 9.02. $C_7H_{13}NO_2$. Calculated (%): C, 58.72; H, 9.15. IR (thin layer), ν/cm^{-1}: 920, 1000, 1185, 1216, 1378, 1412, 1460, 2280—3000. ^{1}H NMR, δ: 1.03 (d, 3 H, C(3)Me, J = 7 Hz); 1.38 (m, 2 H, $C(5)H_2$); 2.00 (m, 2 H, $C(4)H_2$); 2.18 (m, 1 H, C(3)H); 4.38 (m, 2 H, $C(6)H_2$); 4.98 (dd, 1 H, $C(1)H_{cis}$, J = 10.5 Hz, J = 0.7 Hz); 5.00 (dd, 1 H, $C(1)H_{trans}$, J = 17.2 Hz, J = 1.8 Hz); 5.65 (ddd, 1 H, C(2)H, J = 7.6 Hz, J = 10.5 Hz, J = 17.2 Hz). ^{13}C NMR, δ: 20.24 (C(3)Me); 25.25 (C(5)); 32.81 (C(4)); 37.40 (C(3)); 75.73 (C(6)); 113.80 (C(1)); 143.24 (C(2)). MS, *m/z*: 97 $[M - 46]^+$.

(3a*R*,4*S*,6a*S*)-4-Methyl-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (8). A solution of nitro olefin **6** (0.45 g, 3.15 mmol), BSA (1.28 g, 6.3 mmol), and Et_3N (0.15 g, 1.5 mmol) in 4 mL of benzene and 0.4 mL of MeCN was heated in an atmosphere of argon at 85 °C for 8 h and then partitioned between light petroleum and water. The aqueous layer was separated, and the product was extracted with light petroleum. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to give product **8** (~0.6 g), which can directly be used for the synthesis of oxime **10**. A sample for ^{1}H NMR and mass spectra was purified by filtering its solution in cold hexane (−30 °C) through a short column of SiO_2. ^{1}H NMR, δ: 0.12 (s, 9 H, $SiMe_3$); 1.20 (d, 3 H, C(4)Me, J = 6.8 Hz); 1.40—2.50 (m, 5 H, $C(5)H_2$, $C(6)H_2$, C(4)H); 3.10 (m, 1 H, C(3a)H); 3.90 (dd, 1 H, $C(3)H_\beta$, J = 9.2 Hz, J = 2.0 Hz); 4.23 (m, 1 H, C(6a)H); 4.49 (dd, 1 H, $C(3)H_\alpha$, J_1 = J_2 = 9.2 Hz). MS, *m/z*: 203 $[M]^+$.

(3a*R*,4*S*)-4-Methyl-3a,4,5,6-tetrahydro-3*H*-cyclopenta[*c*]isoxazole (9). Crude product **8** synthesized as described above from nitro olefin **6** (0.45 g, 3.15 mmol) was distilled *in vacuo* to give dihydroisoxazole **9** (0.28 g, 81% from compound **6**) as a colorless liquid, b.p. 65—67 °C (10 Torr), $[\alpha]_D^{20}$ −11.3 (*c* 1.24, MeOH). Found (%): C, 67.27; H, 8.96. $C_7H_{11}NO$. Calculated (%): C, 67.17; H, 8.86. IR (thin layer), ν/cm^{-1}: 800, 840, 900, 1250, 1310, 1380, 1420, 1450, 2800—3000. ^{1}H NMR, δ: 1.08 (d, 3 H, C(4)Me, J = 6.9 Hz); 1.70—2.00 (m, 2 H, $C(5)H_2$); 2.20—2.55 (m, 3 H, $C(6)H_2$, C(4)H); 3.34 (ddd, 1 H, C(3a)H, J = 3 Hz, J = 9.9 Hz, J = 12.5 Hz); 3.78 (dd, 1 H, $C(3)H_\alpha$, J = 8.0 Hz, J = 12.5 Hz); 4.45 (dd, 1 H, $C(3)H_\beta$, J = 8.0 Hz, J = 9.9 Hz). ^{13}C NMR, δ: 19.03 (C(4)Me); 21.24 (C(5)); 37.16 (C(6)); 39.45 (C(4)); 62.78 (C(3a)); 73.36 (C(3)); 171.8 (C(6a)). MS, *m/z*: 125 $[M]^+$.

(1*E*,2*R*,3*S*)-1-Hydroxyimino-2-hydroxymethyl-3-methylcyclopentane (10). A solution of the aforesaid crude product **8** (0.34 g, ~1.7 mmol) in 2 mL of THF was added in one portion at −40 °C to a vigorously stirred suspension of $KF \cdot 2H_2O$ (0.3 g, 3.19 mmol) in 5 mL of MeOH. The reaction mixture was stirred at −40 °C for 1 h, warmed to 20 °C, stirred at this temperature for 1 h, and then diluted with 40 mL of Et_2O. The precipitate that formed was filtered off and washed with Et_2O. The filtrate was concentrated *in vacuo*, and the residue (~0.3 g) was chromatographed on SiO_2 (30 g) in AcOEt—light petroleum (1 : 4) to give oxime **10** (0.18 g, 76%) as colorless crystals, m.p. 73—75 °C (from Bu^tOMe), $[\alpha]_D^{23}$ −44.3 (*c* 1.55, MeOH). Found (%): C, 58.70; H, 9.25. $C_7H_{13}NO_2$. Calculated (%): C, 58.72; H, 9.15. IR (KBr), ν/cm^{-1}: 910, 960, 1010, 1065, 1205, 1300, 1375, 1420, 1480, 1670, 2800—3000, 3000—3500. ^{1}H NMR, δ: 1.09 (d, 3 H, C(3)Me, J = 6.5 Hz); 1.33 (dddd, 1 H, $C(4)H_\beta$, J = 9.0 Hz, J = 12.3 Hz, J = 14.3 Hz, J = 18.0 Hz); 1.78 (dddd, 1 H, C(3)H, J = 6.5 Hz, J = 11.2 Hz, J = 12.3 Hz, J = 17.0 Hz); 2.00 (dddd, 1 H, $C(4)H_\alpha$, J = 2.0 Hz, J = 8.9 Hz, J = 10.2 Hz, J = 14.3 Hz); 2.30 (dddd, 1 H, C(2)H, J = 1.7 Hz,

J = 4.3 Hz, J = 8.0 Hz, J = 17.0 Hz); 2.39 (ddd, 1 H, C(5)H, J = 2.0 Hz, J = 9.0 Hz, J = 19.1 Hz); 2.67 (ddd, 1 H, C(5)H, J = 1.7 Hz, J = 8.9 Hz, J = 19.1 Hz); 3.66 (dd, 1 H, CHOH, J = 8.0 Hz, J = 11.2 Hz); 3.84 (dd, 1 H, CHOH, J = 4.3 Hz, J = 11.2 Hz); 5.00—5.50 (br.s, 2 H, 2 OH). ^{13}C NMR, δ: 19.38 (C(3)Me); 26.68 (C(4)); 31.64 (C(5)); 35.85 (C(3)); 52.42 (C(2)); 62.49 (CH_2O); 169.75 (C(1)). MS, m/z: 143 $[M]^+$.

(2*S*,3*S*)-2-Hydroxymethyl-3-methylcyclopentanone (1). ***A.*** Acetic acid (5 mL) was added to 20 mL of a solution of $TiCl_3$* (~19 mmol). Then, 25% aqueous ammonia was added dropwise with stirring in an atmosphere of argon at 20 °C to pH ~4. Then a solution of dihydroisoxazole **9** (0.13 g, 1 mmol) in 20 mL of MeOH was added, and the reaction mixture was stirred for 1 h and treated with Bu^{t}OMe and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was separated, and the organic layer was washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~0.15 g) was chromatographed on SiO_2 (10 g) in AcOEt—light petroleum (1 : 5) to give ketone **1** (~100 mg, 78%) as a colorless oil, R_f 0.82 (AcOEt—light petroleum, 1 : 4), $[\alpha]_D^{20}$ −13.5 (*c* 2.11, MeOH). ^{1}H NMR, δ: 0.95 (m, 1 H, C(4)H); 1.18 (d, 3 H, C(3)Me, J = 6.1 Hz); 1.20—2.50 (m, 5 H, CH, 2 CH_2); 3.53 (dd, 1 H, CHOH, J = 9.4 Hz, J = 3.7 Hz); 3.66 (dd, 1 H, CHOH, J = 9.4 Hz, J = 4.2 Hz); 7.10 (br.s, 1 H, OH).

B. Under analogous conditions, ketone **1** (102 mg, 80%) was obtained from oxime **10** (0.14 g, 1 mmol). This product was virtually identical (TLC and ^{1}H NMR data) with the sample described above.

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References

1. A. V. Stepanov and V. V. Veselovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1683 [*Russ. Chem. Bull.*, 1997, **46**, 1606 (Engl. Transl.)]; A. V. Stepanov and V. V. Veselovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2357 [*Russ. Chem. Bull.*, 1998, **47**, 2286 (Engl. Transl.)].
2. J. N. Marx and L. R. Norman, *J. Org. Chem.*, 1975, **40**, 1602.
3. Y. Sato, S. Nishioka, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.*, 1963, **11**, 829; J. N. Marx and G. Minaskanian, *J. Org. Chem.*, 1982, **47**, 3306.
4. V. N. Odinokov, O. S. Kukovinets, V. G. Kasradze, A. V. Dolidze, V. R. Akhmetova, E. P. Serebryakov, and G. A. Tolstikov, *Zh. Org. Khim.*, 1993, **29**, 39 [*Russ. J. Org. Chem.*, 1993, **29** (Engl. Transl.)].
5. W. F. Bailey, T. T. Nurmi, J. J. Patricia, and W. Wang, *J. Am. Chem. Soc.*, 1987, **109**, 2442.
6. G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 1971, 195; J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367.
7. I. S. Levina, L. E. Kulikova, A. V. Kamernitskii, A. S. Shashkov, A. N. Smirnov, and E. V. Pokrovskaya, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 649 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51** (Engl. Transl.)].

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* The solution of $TiCl_3$ was prepared by gradual addition (1.5 h) of zinc powder (12.8 g, 0.19 g-at.) to a stirred solution of $TiCl_4$ (6.35 g, 33 mmol) in 30 mL of 10% HCl in an atmosphere of argon at ~5 °C. Then the resulting mixture was kept at 25 °C for 12 h.