A new version of the conversion of plant polyprenols into (±)-terpenols of the dolichol series

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A two-step method for the chemoselective reduction of the trisubstituted double bond of an α-isoprene unit in plant polyprenols was developed for the preparation of racemic terpenols of the dolichol series of mammals.

Key words: (±)-dolichols, polyprenols, oxidation, polyprenal, reduction of enals.

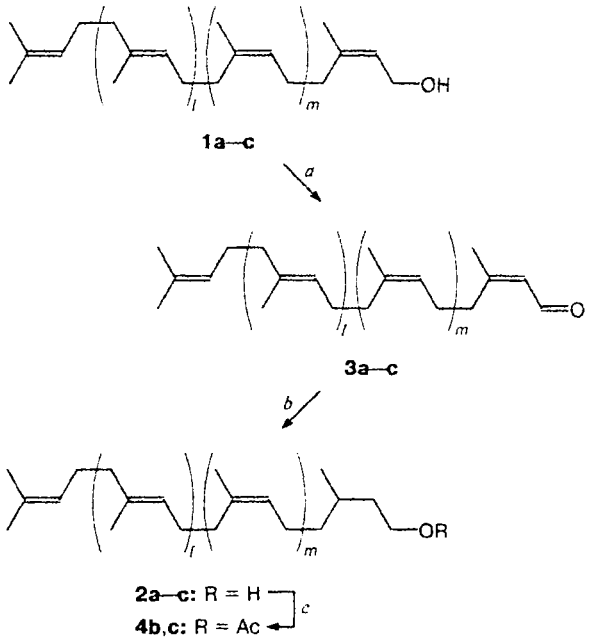
Previously, we proposed a simple method for the three-step transformation of plant polyprenols from coniferous pine needles (**1a**) into 2,3-dihydroterpenols of the dolichol series (**2a**) present in the cells of mammals. These compounds are necessary for the synthesis of intermediates that serve as effective tools for studying biosynthesis of glycoproteins (*e.g.*, see Ref. 2). This method includes oxidation of allylic alcohols **1a** with activated MnO_2 into enals (**3a**) whose double bond can be smoothly hydrogenated with $Na_2S_2O_4$ (sodium dithionite); then, the corresponding saturated aldehydes are subjected to hydride reduction to alcohols **2**. In the present communication, a two-step modified version of the above method is proposed. Our procedure is based on direct reduction of polyprenals **3** with a $NiCl_2 \cdot 6H_2O$—Zn powder system to dolichol-like racemic alcohols **2**. Note that similar conditions ($NiCl_2 \cdot 6H_2O$—Al powder) have been used earlier[3] for chemoselective hydrogenation of the double bond of α,β-enals.

The efficiency of the new procedure is exemplified in the synthesis of (±)-dolichols **2a—c** starting from the native mixtures of polyprenols from pine needles (**1a**), betulaprenols[4] from birch wood (**1b**), and moraprenols[4] from mulberry leaves (**1c**), respectively (Scheme 1).

After two steps, the target products were obtained in an overall yield of more than 80%.

The previously unknown mixtures of isoprenologs **2b,c** and **3b,c** were purified by chromatography and characterized by IR and NMR spectroscopy. In particular, the ^1H NMR spectra of the reaction products contain a set of signals typical of compounds of this class (*cf.* Ref. 1). For each product, the experimental ratio of the integral intensities of diagnostic signals for the methyl groups of *trans*- (δ ~1.6) and *cis*-isoprene fragments (δ ~1.7) correlates with their population in the main isoprenologs constituting these mixtures and with the content of these isoprenologs in the original prenols **1b,c**. Mixtures of prenols **2b,c** were additionally characterized as the respective acetates **4b,c**.

Scheme 1



$l = 2$, $m = 10—13$ (**a**); $l = 2$, $m = 3, 4$ (**b**); $l = 3$, $m = 6, 7$ (**c**)

Reagents and conditions: *a*. MnO_2, CH_2Cl_2, 20 °C; *b*. $NiCl_2 \cdot 6H_2O$/Zn, THF—MeOH, boiling; *c*. Ac_2O/Py/DMAP, CH_2Cl_2, 20 °C.

Experimental

IR spectra (thin layer) were recorded on a Specord M-80 instrument. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer. R_f are given for a fixed SiO_2 layer (Silufol) in a hexane—ether (4 : 1, v/v) system. Column chromatography was performed on silica gel (Kieselgel 60, Merck).

Polyprenols **1b** with a ratio of the main isoprenologs $C_{35}H_{58}O$: $C_{40}H_{66}O \approx 1 : 1$ (*cf.* Ref. 4) were kindly provided by

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A. V. Kuchin (Institute of Chemistry, Komi Research Center, Ural Branch of the Russian Academy of Sciences) and V. I. Roshchin (St.-Petersburg Academy of Wood Technology). Polyprenols **1c** ($C_{55}H_{90}O$: $C_{60}H_{98}O$ ≈ 2 : 1, *cf.* Ref. 4) were provided by S. D. Maltsev (Institute of Organic Chemistry, Russian Academy of Sciences).

Polyprenals 3b. MnO_2 (10.4 g, 120 mmol) was added to a solution of prenols **2b** (5 g, ~9 mmol) in 20 mL of CH_2Cl_2. The resulting suspension was stirred at 20 °C for 5 h and filtered, the solvent was removed *in vacuo*, and the residue was chromatographed on SiO_2 (150 g). Elution with CH_2Cl_2 gave 4.48 g (~90%) of a mixture of aldehydes **3b** as a colorless oil with R_f 0.58. IR, ν/cm^{-1}: 840, 1040, 1100, 1160, 1380, 1450, 1630, 1690 (C=O), 2880—3020. ^{1}H NMR, δ: 1.59 (br.s, *cis*-Me); 1.69 (br.s, *trans*-Me); 1.9—2.2 (m, CH_2, MeC(3)); 2.24 (pseudoq, $H_2C(5)$, J_2 = 6.6 Hz); 2.55 (t, $H_2C(4)$, J = 6.6 Hz); 5.12 (m, HC=); 5.86 (br.d, HC(2), J = 8.3 Hz); 9.93 (d, HCO, J = 8.3 Hz).

Polyprenals 3c were obtained analogously from prenols **2c** (3.3 g, ~4.3 mmol) and MnO_2 (4.5 g, 51.8 mmol) in 35 mL of CH_2Cl_2. The reaction product (~3.2 g) was chromatographed on SiO_2 (70 g). Elution with CH_2Cl_2 gave a mixture of aldehydes **3b** (3.0 g, ~90%) as a colorless oil with R_f 0.60. IR, ν/cm^{-1}: 850, 1040, 1100, 1390, 1450, 1620, 1690 (C=O), 2740—3040. ^{1}H NMR, δ: 1.60 (br.s, *cis*-Me); 1.69 (br.s, *trans*-Me); 1.85—2.2 (m, CH_2, MeC(3)); 2.24 (pseudoq, $H_2C(5)$, J = 6.9 Hz); 2.57 (t, $H_2C(4)$, J = 6.9 Hz); 5.10 (m, HC=); 5.85 (br.d, HC(2), J = 8.4 Hz); 9.93 (d, HCO, J = 8.4 Hz).

(±)-Prenols 2a. $NiCl_2 \cdot 6H_2O$ (1.2 g, 5.05 mmol) was added to a solution of prenals **3a** [1] (0.73 g, ~0.73 mmol) in a mixture of THF (5 mL) and MeOH (5 mL) with vigorous stirring at 20 °C (Ar). Then Zn powder (1 g, 15.30 mg-at.) was added portionwise over 7 min. The reaction mixture was heated to the boiling point, stirred for 2.5 h, and cooled to 20 °C. The precipitate was filtered off, the solvent was removed, and the residue (0.8 g) was chromatographed on SiO_2 (30 g). Elution with a CH_2Cl_2—Et_2O (97 : 3) system gave a mixture of alcohols **2a** (0.68 g, ~93%) as a colorless oil, which is virtually identical (R_f and IR and ^{1}H NMR spectra) with an authentic sample.[1]

(±)-Prenols 2b were obtained analogously from a mixture of prenals **3b** (4.4 g, ~8.3 mmol). The product (4.2 g) was chromatographed on SiO_2 (120 g). Elution with a CH_2Cl_2—Et_2O (95 : 5) system gave alcohols **2b** (3.94 g, ~90%) as a colorless oil with R_f 0.23. IR, ν/cm^{-1}: 840, 1060, 1380, 1660, 2740—3040, 3370. ^{1}H NMR, δ: 0.92 (d, MeC(3), J = 5.9 Hz); 1.10—1.55 (m, HC(2), HC(3), HC(4)); 1.61 (br.s, *cis*-Me); 1.68 (br.s, *trans*-Me); 1.85—2.17 (m, CH_2); 3.66 (m, CH_2O); 5.10 (m, HC=).

(±)-Prenols 2c were obtained analogously from a mixture of prenals **3c** (3 g, ~3.8 mmol). The product (3 g) was chromatographed on SiO_2 (100 g). Elution with a CH_2Cl_2—Et_2O (95 : 5) system gave alcohols **2c** (2.69 g, ~90%) as a colorless oil with R_f 0.35. IR, ν/cm^{-1}: 750, 840, 1060, 1360, 1450, 1660, 2740—3040, 3350. ^{1}H NMR, δ: 0.91 (d, MeC(3), J = 6.1 Hz); 1.10—1.50 (m, HC(2), HC(3), HC(4)); 1.60 (br.s, *cis*-Me); 1.68 (br.s, *trans*-Me); 1.85—2.15 (m, CH_2); 3.65 (m, CH_2O); 5.12 (m, HC=).

Acetates 4b. A solution of alcohols **2b** (2.15 g, ~5 mmol), DMAP (60 mg, 0.5 mmol), Ac_2O (0.66 g, 6.5 mmol), and Py (0.5 g, 6.4 mmol) in 15 mL of CH_2Cl_2 was kept under Ar at 20 °C for 6 h, diluted with hexane (50 mL), washed successively with a saturated solution of $NaHCO_3$, water, and brine, and dried with Na_2SO_4. The solvent was removed *in vacuo*, and the residue (2.4 g) was chromatographed on SiO_2 (100 g). Elution with CH_2Cl_2 gave acetates **4b** (2.0 g, ~93%) as a colorless oil with R_f 0.65. IR, ν/cm^{-1}: 840, 1040, 1150, 1240, 1380, 1450, 1750, 2880—3020. ^{1}H NMR, δ: 0.92 (d, MeC(3), J = 5.9 Hz); 1.15—1.60 (m, HC(2), HC(3), HC(4)); 1.58 (br.s, *cis*-Me); 1.68 (br.s, *trans*-Me); 1.90—2.15 (m, CH_2, MeCO); 4.09 (br.t, H_2CO, J = 6.4 Hz); 5.12 (m, HC=).

Acetates 4c were obtained analogously from alcohols **2c** (2.67 g) as a colorless oil (2.50 g, ~94%) with R_f 0.70. IR, ν/cm^{-1}: 850, 1050, 1260, 1380, 1450, 1730, 2740—3040. ^{1}H NMR, δ: 0.94 (d, MeC(3), J = 5.6 Hz); 1.10—1.60 (m, HC(2), HC(3), HC(4)); 1.61 (br.s, *cis*-Me); 1.70 (br.s, *trans*-Me); 1.90—2.20 (m, CH_2, MeCO); 4.12 (br.t, H_2CO, J = 6.3 Hz); 5.14 (m, HC=).

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