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SYNTHESIS OF (2Z,6Z,10Z,14E,18E)-FARNESYLFARNESOL

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Summary. Nine-step synthesis of the title triterpenol from (E,E)-farnesol using a two-stage cis-C_5-homologation procedure is described.

During recent years, much attention has been given to polyprenols, mainly due to their importance as lipophilic, membrane-soluble carbohydrate carriers in the biosynthesis of both bacterial cell wall polysaccharides and prokaryotic and eukaryotic glycoproteins.[1] Natural sources of polyprenol are rather scarce and therefore much effort has been devoted to the synthesis of these compounds. Additional stimulus for these studies stems from an uncertainty existing in the structure elucidation of some complex polyprenols. Among several alternative synthetic routes to polyprenols, those imitating their biosynthesis[1,2] seem to be of special importance and versatility since they allow a stepwise prenylation, with a predetermined sequence of the introduced Z- and E-prenyl units. At present, the problem of trans-C_5-homologation of the isoprenoid chain seems to be practically solved.[3,4] At the same time, similar biomimetic approach to the synthesis of polyprenols with specifically positioned cis trisubstituted C=C bonds is still lacking and depends largely on the development of a stereospecific cis-C_5-homologation procedure. It has recently been reported that necessary cisoid geometry could be secured by stereospecific alkylation of senecioic or 2-butynoic acids and the possibilities of this approach were illustrated by the synthesis of (Z,Z)-farnesol.[4] Here we wish to demonstrate an alternative approach based on the prenylation of the easily accessible[5] cis isoprenoid synthon 1 followed by the crown ether catalyzed reductive cleavage of the intermediate sulfonamide[6] which led us to the synthesis of triterpenol 11 containing three Z-prenyl units (Scheme).

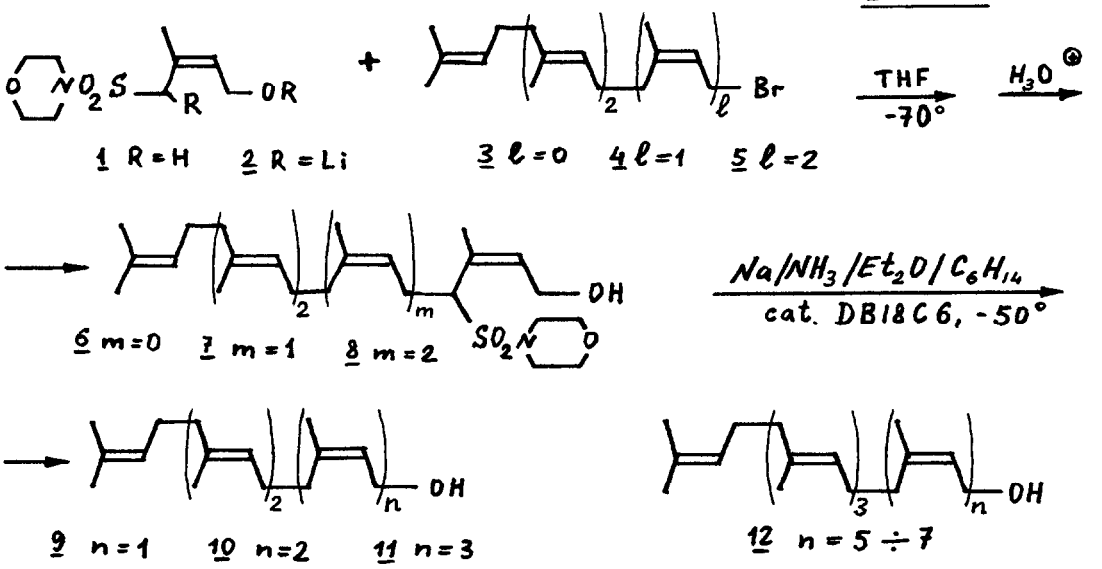
Treatment of the dilithium derivative 2[5] with the bromide 3 /0.9 mol equiv; freshly prepared from (E,E)-farnesol according to[7]/ in THF solution at -70° for 20 min (Ar) followed by quenching of the reaction mixture with H_2O and flash-column chromatography on silica gel (elution with ether) yielded 60% of the hydroxy sulfonamide 6 as an oil, R_f 0.45[8]; $\delta^{CDCl_3}_{TMS}$: 1.59 (bs, 9H, cis-CH_3), 1.67 (bs, 3H, H-C_{16}), 1.87 (bs, 3H, CH_3-C_3), 2.00 (m, 8H, CH_2), 2.62 (m, 2H, H-C_5), 4.12 (m, 3H, CHS, CH_2O), 5.05 (m, 3H, HC=C), 5.84 ppm (bt, J=7 Hz, 1H, H-C_2)[9]; M^+439.

The reductive desulfonylation of 6 was carried out with Na (8 g-at equiv) in the vigorously agitated NH_3-ether-hexane (4:1:4 v/v) emulsion containing 10 mol% of dibenzo-18-crown-6 (DB18C6) at -78° (5 min) and subsequently at -50° (20 min). The specified conditions were essential to minimize both the formation of the double bond isomers[6] and the hydrogenolysis of the allylic C-O bond; the desulfonylation in homogeneous media with the use of Et_2O, THF, DME, or their combinations as co-solvents is invariably accompanied by the hydrogenolysis (up to 60%) of the C-O bond. Usual work-up and subsequent flash-column chromatography on silica gel (gradient elution from hexane to hexane-ether, 1:1 v/v) yielded 68% of the known[10] diterpenol 9 as colourless oil, R_f 0.45[8], M^+290.

In agreement with earlier data,[10] the PMR spectrum (360 MHz) of 9 revealed that the product is contaminated with ~4% of isomeric homoallylic alcohol(s), cf.[6]. However, when treated in ether with PBr_3 and pyridine[7], this product afforded smoothly the structurally homogeneous bromide 4, the impurities being removed due to their decomposition. Repetition of the above sequence with crude bromide 4 produced the hydroxy sulfonamide 7 converted into the sesterterpenol 10 which contained less than 4% of the respective homoallylic alcohol(s). At this step the "self-cleaning" of the mixture was also achieved when 10 was treated with PBr_3 and pyridine to give the individual bromide 5. An additional cycle consisting of the same steps was used to transform 5, via 8, into the title triterpenol 11, its synthesis being performed from (E,E)-farnesol in nine steps with ~2% overall yield (isolated)

Found for 7: R_f 0.50[8]; $\delta^{CDCl_3}_{TMS}$: 1.58 (bs, 9H, cis-CH_3), 1.64 (bs, 6H, trans-CH_3), 1.86 (bs,3H, CH_3-C_3), 2.00 (m, 12H, CH_2), 2.63 (m, 2H, H-C_5), 4.12 (m, 3H, CHS, CH_2O), 5.03 (m, 4H, HC=C), 5.82 ppm (bt, J=7 Hz, 1H, H-C_2)[9] ; M^+507. Found for 8: R_f 0.53[8]; $\delta^{CDCl_3}_{TMS}$: 1.61 (bs, 9H, cis-CH_3), 1.69 (bs, 9H, trans-CH_3), 1.88 (bs, 3H, CH_3-C_3), 2.01 (m, 16H, CH_2), 2.64 (m, 2H, H-C_5), 4.12 (m, 3H, CHS, CH_2O), 5.10 (m, 5H, HC=C), 5.82 ppm (bt, J=7 Hz, 1H, H-C_2)[9] ; M^+575. Found for 10: R_f 0.48[8]; $\delta^{CCl_4}_{TMS}$: 1.57 (bs, 9H, cis-CH_3), 1.64 (bs, 6H, trans-CH_3), 1.73 (bs, 3H, CH_3-C_3), 1.98 (m, 16H, CH_2), 3.94 (bd, J=7 Hz, 2H, CH_2O), 5.04 (m, 4H, HC=C), 5.34 ppm (bt, J=7 Hz, 1H, H-C_2); M^+ 358. Found for 11: R_f 0.52[8]; $\delta^{CCl_4}_{TMS}$: 1.57 (bs, 9H, cis-CH_3), 1.64 (bs, 9H, trans-CH_3), 1.73 (bs, 3H, CH_3-C_3), 2.00 (m, 20H, CH_2), 3.94 (bd, J=7 Hz, 2H, CH_2O), 5.03 (m, 5H, HC=C), 5.34 ppm (bt, J=7 Hz, 1H, H-C_2); M^+426.

SCHEME



Stereochemistry of terpenols 9–11 was ascertained by their NMR spectra. Thus, their PMR spectra contain three diagnostic[11] groups of the broad singlets at δ 1.57, 1.73, and 1.64 ppm. In all cases, the first group was assigned to the nine cis-CH_3 protons of the repeating (E,E)-farnesyl fragment while the second group was attributed to the trans-CH_3 protons of the first Z-isoprenoid unit. Integral intensity of the third group of the signals assigned to the remaining trans-CH_3 protons indicates the presence of one or two additional Z units in 10 or 11, respectively (3H for 9, 6H for 10, and 9H for 11). The same conclusion follows from the analysis of the CMR spectra of 9–11 (in $CDCl_3$) using the diagnostic[12] signals of both CH_3 and CH_2 groups adjacent to the tetrasubstituted carbon as well as from the comparison of our spectral data with those known for four isomeric farnesols[7] and for all-E-geranylgeraniol.[13] Thus, along with the CH_3 signals from the isopropylidene end group (δ 17.7 and 25.7 ppm) the spectra contain cis-, trans-CH_3, cis-, and trans-CH_2 signals ($\delta \sim$ 16.0, 23.5, 32.3, and 39.8 ppm, respectively) in proportions reflecting the number of Z- and E-isoprenoid units in these molecules.

The successful stereospecific synthesis of farnesylfarnesol 11 illustrates the viability of the developed approach which offers new and promising possibilities for the stereospecific total synthesis of various polyprenols, such as betulaprenols[14] and cleomeprenols 12.[15] This work is now under way in our laboratory.

References and Notes

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