ENANTIOCONTROLLED APPROACH TO NATURAL PRODUCTS UTILIZING (S)-O-BENZYLGLYCIDOL AS COMMON CHIRAL PRECURSOR

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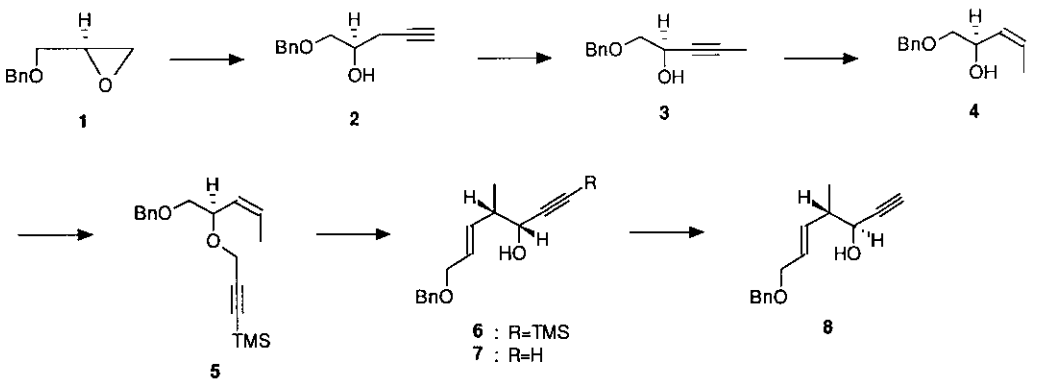
Abstract———An enantiocontrolled route to the aggregation pheromone of European elm bark beetle (**12**), the sex pheromone of cigarette beetle serricornin (**15**), and the spiroketal segment (**24**) of the sixteen-membered macrolide antibiotics milbemycins and avermectins is described using the intermediates derived from (S)-O-benzylglycidol (**1**) as common chiral precursor.

Recently, we disclosed[1,2] efficient preparation of the erythro-acetylene alcohol (**7**) and the threo-acetylene alcohol (**8**) from (S)-O-benzylglycidol[3] (**1**) as starting material. The synthesis involves the following sequence of reactions: (i) formation of the terminal acetylene (**2**) (95%), (ii) rearrangement of **2** to the internal acetylene (**3**) (93%), (iii) reduction of **3** to the Z-olefin (**4**) (100%), (iv) conversion of **4** into the erythro-alcohol (**7**) via **6** by stereospecific [2,3]-Wittig rearrangement[4] of the silylpropargyl ether (**6**) (74%), and (v) Mitsunobu inversion[5] of **7** to the threo-alcohol (**8**) (73%) (Scheme 1). We report here an



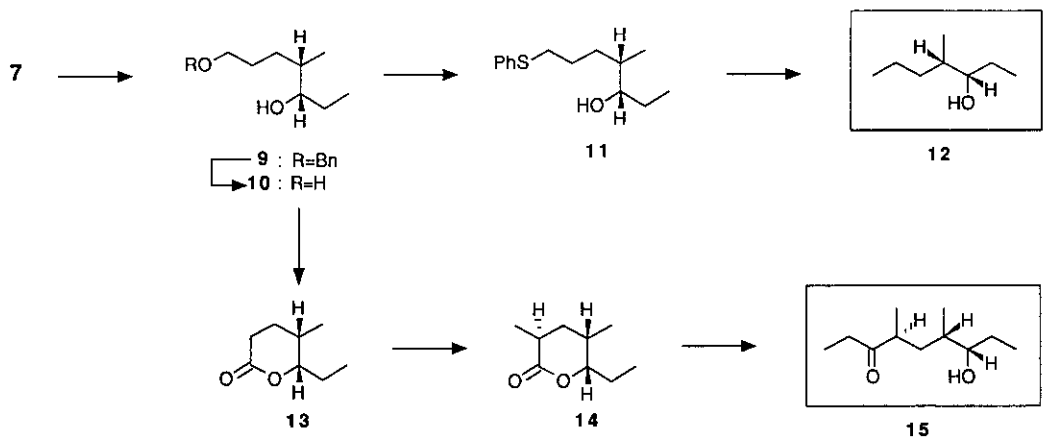
Scheme 1

utilization of these two isomeric alcohols as building blocks for the efficient construction of some biologically active natural products, the aggregation pheromone of European elm bark beetle (**12**), the sex pheromone of cigarette beetle serricornin (**15**), and the spiroketal segment (**24**) of the sixteen-membered

macrolide antibiotics milbemycins and avermectins.

First, the erythro-alcohol (**7**) was catalytically hydrogenated to the saturated alcohol (**9**), $[\alpha]_D^{29}$ -10.85° (c 1.032, $CHCl_3$), (98%), of which the benzyl group was removed by Birch reduction to give the diol (**10**), $[\alpha]_D^{30}$ -16.53° (c 1.028, $CHCl_3$), (95%). Treatment of **10** with diphenyl disulfide in the presence of tri-n-butylphosphine[6] allowed selective sulfide formation at the primary hydroxy center to afford the monosulfide (**11**), $[\alpha]_D^{27}$ -11.70° (c 1.008, $CHCl_3$), (94%). Reductive desulfurization of **11** by Birch reduction furnished the pheromone of elm bark beetle (Scolytus multistriatus)[7] (**12**) in an excellent yield (91%) of which enantiomeric purity was determined to be >99% ee by measurement of ^{1}H-nmr spectra (500 MHz) of both enantiomeric its MTPA esters.[8]

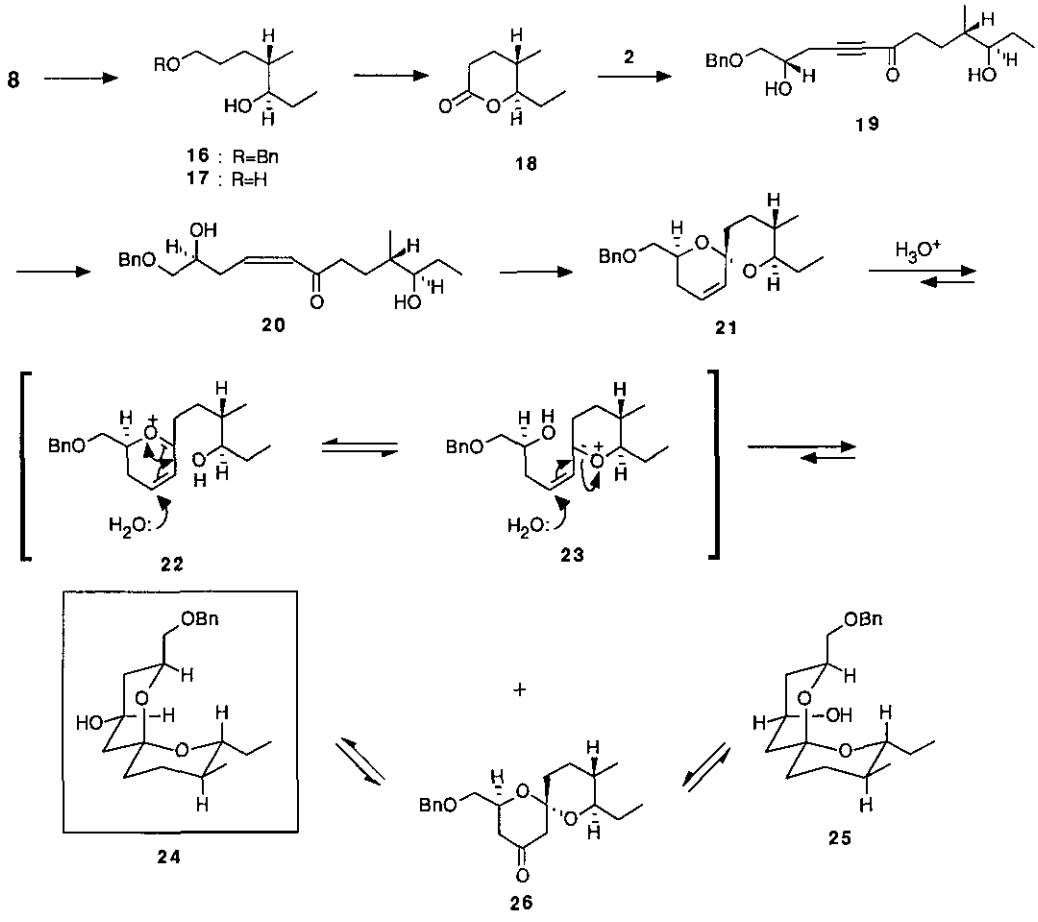
Second, the diol (**10**) was oxidized using silver carbonate on Celite[9] (Fetizon reagent) to give the δ-lactone (**13**), $[\alpha]_D^{24}$ -65.82° (c 1.024, $CHCl_3$), (67%) which has been obtained by fundamentally different route.[10] As described[10] **13** afforded the single alkylation product[11] (**14**), $[\alpha]_D^{24}$ -59.58° (c 0.876, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$ -45.5° (c 0.875, $CHCl_3$)], in 72% yield. Since **14** has already been converted into the sex pheromone of cigarette beetle (Lasioderma serricone) serricornin[11] (**15**), the present synthesis constitutes an alternative approach.



Scheme 2

Third, the threo-alcohol (**8**) was catalytically hydrogenated to the saturated alcohol (**16**), $[\alpha]_D^{22}$ -7.72° (c 1.010, $CHCl_3$), which on hydrogenolytic debenzylation yielded the diol (**17**), $[\alpha]_D^{24}$ -7.93° (c 1.008, $CHCl_3$), in an excellent yield (92% overall). Catalytic oxygenation[12] of **17** brought about selective reaction at the primary hydroxy center to furnish the δ-lactone (**18**), $[\alpha]_D^{26}$ +49.32° (c 1.034, $CHCl_3$), (74%) after acid work-up. Condensation of **18** with the lithium acetylide, generated in situ from the terminal acetylene[2] (**2**), afforded the ketol (**19**), $[\alpha]_D^{26}$ +17.19° (c 1.012, $CHCl_3$), in good yield (82%). Partial hydrogenation yielded the Z-olefin (**20**) which on brief treatment with diluted hydrochloric acid gave the single spiroacetal (**21**), $[\alpha]_D^{27}$ -24.99° (c 1.008, $CHCl_3$), in 61% overall yield. Stirring **21** in a aqueous tetrahydrofuran containing hydrochloric acid[13] (THF/H_2O/conc. HCl=20:5:1 v/v) for 1 week at room temperature afforded a readily

separable (SiO_2 column chromatography) mixture of the equatorial alcohol (**24**), $[\alpha]_D^{26}$ +51.53° (c 1.106, $CHCl_3$), (30%), the axial alcohol (**25**), $[\alpha]_D^{26}$ +50.97° (c 1.236, $CHCl_3$), (53%), and the unchanged **21** (16%). Two isomeric alcohols may be formed via the Michael addition of water to the transient oxonium intermediates, (**22**) and/or (**23**). The stereochemistry of each of the isomeric alcohols was determined by ^{1}H-nmr spectroscopy (500 MHz): only the former showed the carbinol hydrogen at δ 4.19 with double axial-axial couplings (J=11.25 Hz), while the latter showed the carbinol hydrogen at δ 4.11 with all equatorial-equatorial



Scheme 3

couplings. Epimeric relationship between the alcohols, (**24**) and (**25**), was also ascertained by converting them into the same ketone (**26**), $[\alpha]_D^{25}$ +74.25° (c 1.010, $CHCl_3$), (89% from **24** and 95% from **25**) by oxidation with pyridinium chlorochromate (PCC), respectively. The ketone (**26**) regenerated the mixture of the equatorial-(**24**) and the axial-(**25**) alcohols (95%) in ratio of 2.5:1 on reduction with sodium borohydride in dimethoxyethane at -20 °C. The axial isomer (**24**) corresponds to the spiroketal segment of certain members of the sixteen-membered macrolide

antibiotics milbemycins[14] and avermectins,[14] isolated from a cultured Streptomyces strain, which possess highly potent pesticidal activity against a variety of species of mites, beetles, and tent caterpillers without phytotoxity.

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