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

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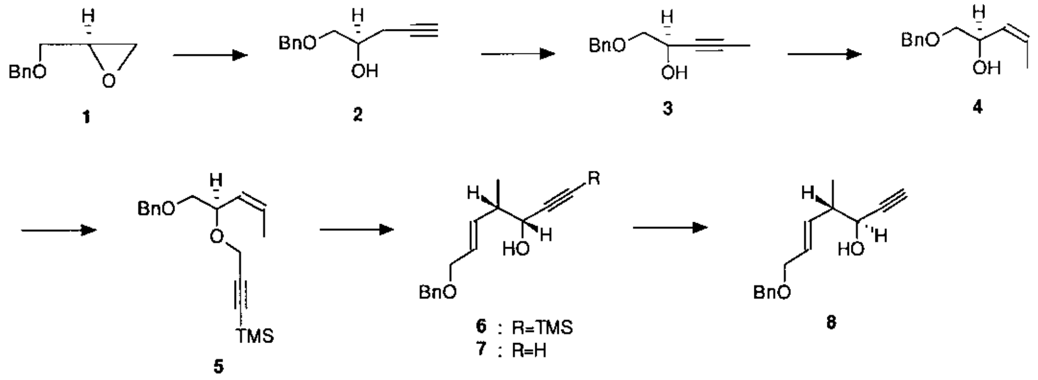
Abstract———An enantiocontrolled route to the aggregation pheromone of European elm bark beetle (**12**), the sex pheromone of cigarette beetle serricornin (**15**), and the spiroketal segment (**24**) of the sixteen-membered macrolide antibiotics milbemycins and avermectins is described using the intermediates 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 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

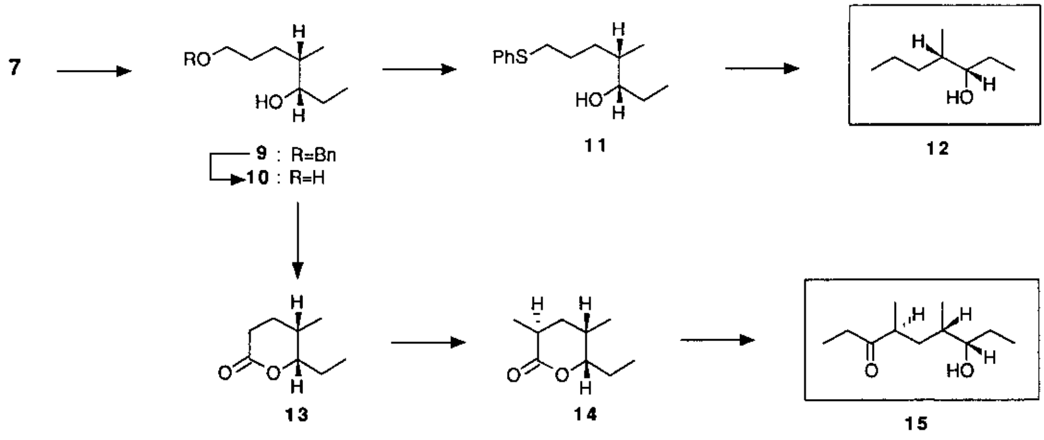


Scheme 1

macrolide antibiotics milbemycins and avermectins.

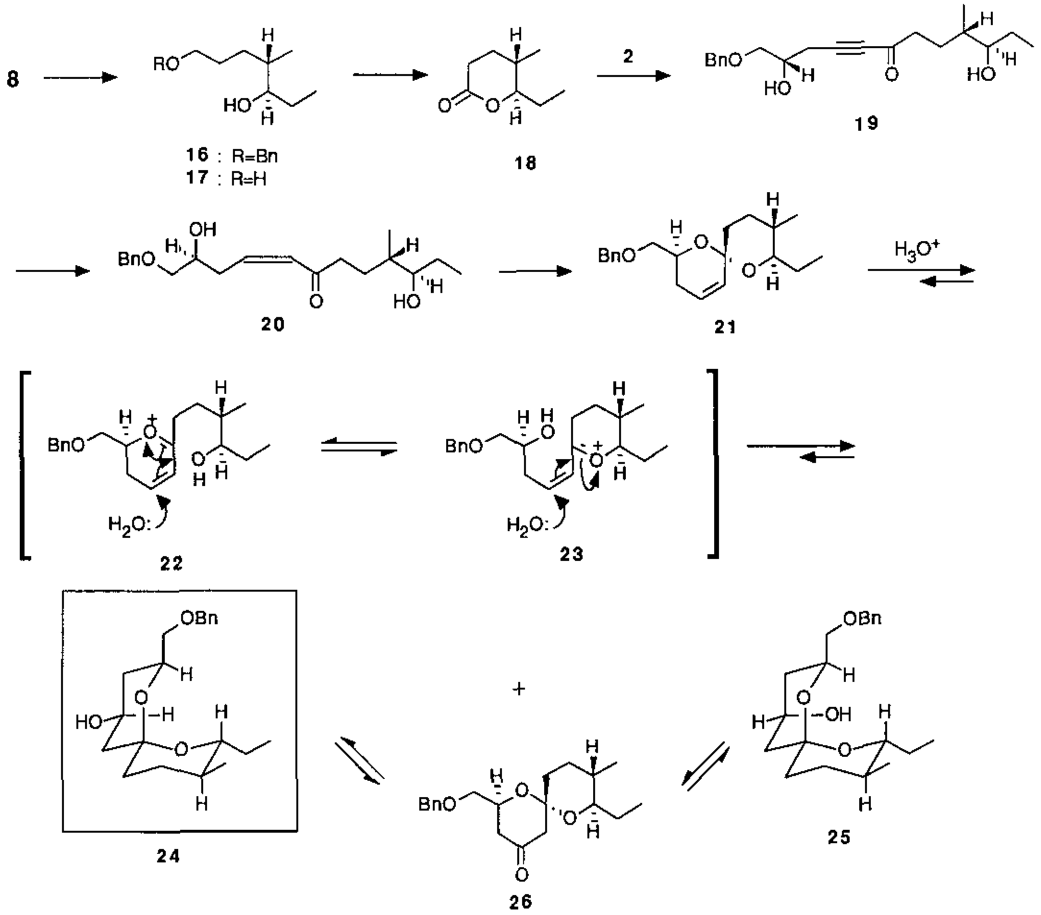
First, the erythro-alcohol (**7**) was catalytically hydrogenated to the saturated alcohol (**9**), $[\alpha]_D^{29}$ -10.85° (c 1.032, $CHCl_3$), (98%), of which the benzyl group was removed by Birch reduction to give the diol (**10**), $[\alpha]_D^{30}$ -16.53° (c 1.028, $CHCl_3$), (95%). Treatment 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 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



Scheme 3

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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