

## Versatile Chiral Building Blocks bearing a Secondary Methyl Group from (*S*)-*O*-Benzylglycidol (Benzyloxymethyloxirane)

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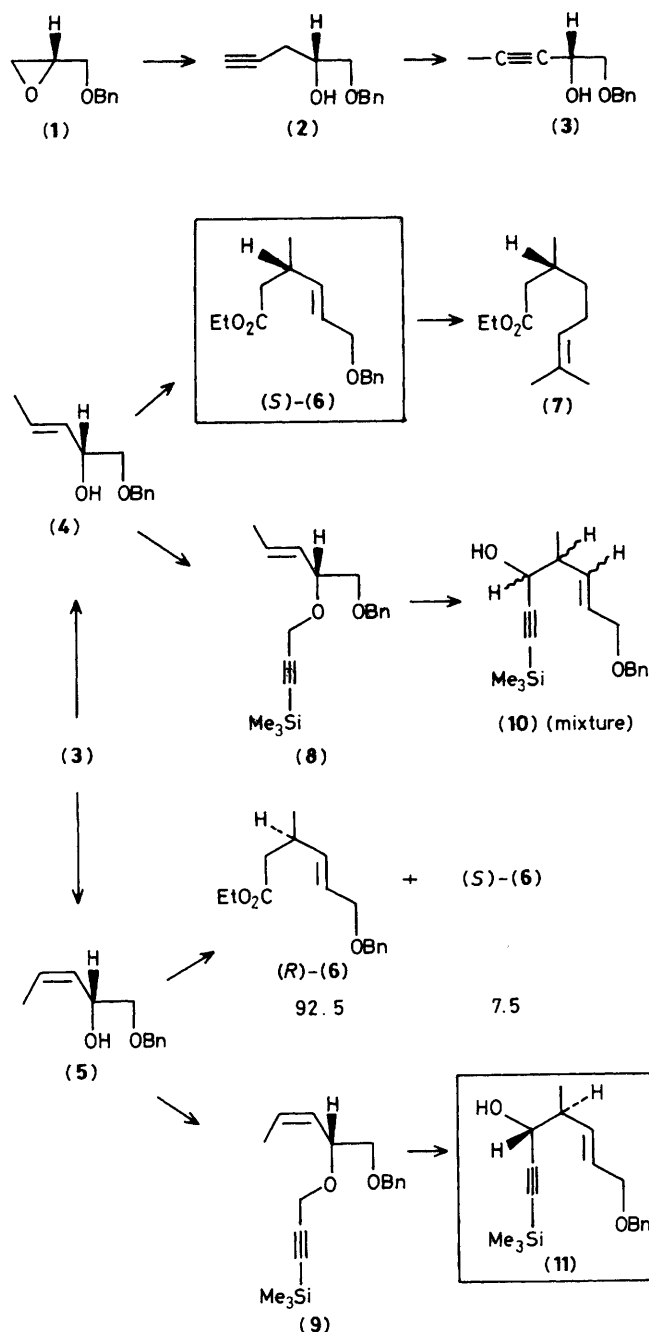
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Versatile chiral building blocks for the construction of chiral natural products bearing a secondary methyl group have been efficiently prepared from (*S*)-*O*-benzylglycidol.

Current investigations in our laboratory are aimed at the effective utilization of the chiral glycerol unit as a precursor for the synthesis of a wide variety of natural products.<sup>1</sup> With this intention, (*S*)-*O*-benzylglycidol (benzyloxymethyloxirane) (*S*)-(**1**)<sup>2</sup> has been converted into the two functionalized

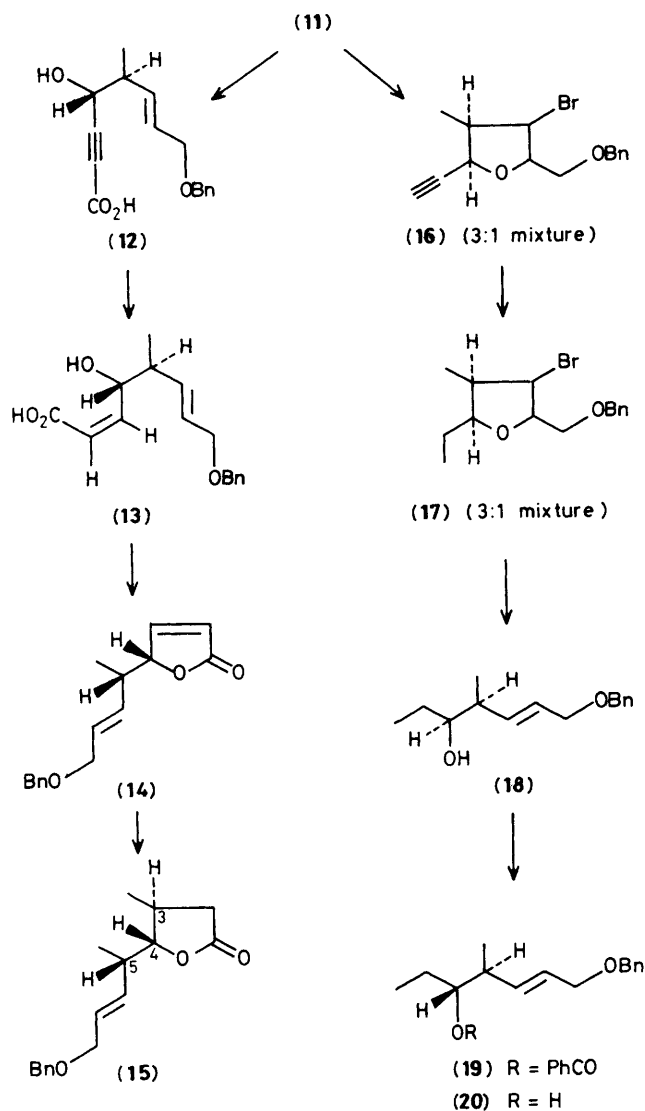
chiral building blocks (*S*)-(**6**) and (3*R*,4*S*)-(**11**) bearing a secondary methyl group, which have considerable potential in natural product synthesis, by successive acetylide addition, acetylene bond migration, and sigmatropic rearrangements.

When the epoxide (*S*)-(**1**) was treated with lithium acety-

Scheme 1. Bn = PhCH<sub>2</sub>.

lithium aluminium hydride gave the pure (*E*)-allyl alcohol (4) in 93% yield, while reduction using Lindlar catalyst afforded the pure (*Z*)-allyl alcohol (5) in 79% yield. The isomeric allyl alcohols (4) and (5) were each treated with triethyl orthoacetate in the presence of acid catalyst<sup>5</sup> to give the enantiomers of the (*E*)- $\beta,\gamma$ -unsaturated ester (6) in 85 and 80% yields, respectively. Studies of the corresponding MTPA esters of each reduction product showed the degree of enantiomeric purity as well as their absolute configurations;<sup>6</sup> the (*E*)-alcohol (4) gave the (*E*)-(*S*)-ester (*S*)-(6) in an enantiomerically pure state, while the (*Z*)-alcohol (5) gave the (*E*)-(*R*)-ester (*R*)-(6) in 85% enantiomeric excess (e.e.). The alcohols (4) and (5) were each converted into the propynyl ethers (8) and (9) in 63 and 65% yields by sequential *O*-alkylation and trimethylsilylation. Treatment of each ether

† Each corresponding methoxy(trifluoromethyl)phenylacetyl (MTPA) ester from the racemic alcohol exhibited distinct  $^1\text{H}$  n.m.r. signals of a 1:1 mixture of diastereoisomers (90 and 500 MHz).

Scheme 2. Bn = PhCH<sub>2</sub>.

lithium aluminium hydride gave the pure (*E*)-allyl alcohol (4) in 93% yield, while reduction using Lindlar catalyst afforded the pure (*Z*)-allyl alcohol (5) in 79% yield. The isomeric allyl alcohols (4) and (5) were each treated with triethyl orthoacetate in the presence of acid catalyst<sup>5</sup> to give the enantiomers of the (*E*)- $\beta,\gamma$ -unsaturated ester (6) in 85 and 80% yields, respectively. Studies of the corresponding MTPA esters of each reduction product showed the degree of enantiomeric purity as well as their absolute configurations;<sup>6</sup> the (*E*)-alcohol (4) gave the (*E*)-(*S*)-ester (*S*)-(6) in an enantiomerically pure state, while the (*Z*)-alcohol (5) gave the (*E*)-(*R*)-ester (*R*)-(6) in 85% enantiomeric excess (e.e.).

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‡ Determined by  $^1\text{H}$  n.m.r. spectroscopy (500 MHz). Satisfactory spectral (i.r.,  $^1\text{H}$  n.m.r. mass) and analytical (combustion and/or high resolution mass spectral) data were obtained for all new isolable compounds.

§ Stereochemical homogeneity was determined by  $^1\text{H}$  n.m.r. analysis of the MTPA ester.

with *n*-butyl-lithium in tetrahydrofuran (THF) at  $-78^{\circ}\text{C}$  led to smooth [2,3] Wittig rearrangement<sup>7</sup> to give the corresponding alcohols; the (*E*)-ether (**8**) afforded a mixture of three isomers of (**10**) in 96% yield in a ratio of 1 : 1.4 : 1, only one of which could be separated by silica gel chromatography, whereas the (*Z*)-ether (**9**) afforded the (*E*)-(3*R*,4*S*)-alcohol (**11**) in 73% yield as a single product in chirally pure form.<sup>8</sup>

Having obtained the two products in enantio- and stereo-isomerically pure forms, a straightforward target using the (*S*)- $\beta,\gamma$ -unsaturated ester (*S*)-(**6**) was (*R*)-ethyl citronellate (**7**).<sup>8</sup> Thus, (*S*)-(**6**) was sequentially hydrogenated, debenzylated, oxidized, and isopropylidenated to give (*R*)-ethyl citronellate (**7**).<sup>¶</sup> To exemplify the potential of the other product, the (*E*)-(3*R*,4*S*)-alcohol (**11**) was separately converted into two key building blocks for the construction of protomycinolide IV, the aglycone of a sixteen membered antibiotic macrolide (Scheme 2).<sup>9</sup> Thus, (**11**) was desilylated and then carboxylated to yield the acid (**12**) which was converted into the butenolide (**14**) by partial reduction followed by lactonization. Treatment of (**14**) with lithium dimethylcuprate allowed conjugate addition in a stereoselective manner from the less hindered face to give the (*E*)-(3*S*,4*S*,5*S*)-lactone (**15**)<sup>‡</sup> selectively in 25% yield from (**11**). Compound (**15**) may also be converted into the Prelog-Djerassi lactonic acid by application of established methodology.<sup>10</sup> Alternatively, (**11**) was sequentially desilylated and treated with *N*-bromosuccinimide (NBS) to give the bromo-ether (**16**) as a 3:1 mixture of epimers, which without separation was hydrogenated on a platinum catalyst to give the saturated ether (**17**) as an epimeric mixture in 79% overall yield. After separation by silica gel chromatography, each epimer was treated with zinc in methanol containing a small amount of hydrochloric acid to give the same alkene (**18**),<sup>‡</sup> both reactions proceeding in excellent yields. In practice, the mixture (**17**) without separation was directly treated in the same way to give (**18**) in 87% yield. Employing the Mitsunobu reaction,<sup>11</sup> the chirality of the secondary hydroxy group of

(**18**) was inverted to give the (*E*)-(4*R*,5*R*)-hexene (**20**)<sup>§</sup> in 58% overall yield *via* the benzoate (**19**). Essentially the same building blocks as (**15**) and (**20**) have been used in the recent synthesis of protomycinolide IV by Tsuchihashi and co-workers.<sup>12</sup>

Thus the two compounds prepared herein should prove to be useful building blocks for a wide variety of optically active natural products bearing a secondary methyl group, in view of their multifunctionality and ready availability.

We thank the Ministry of Education, Science and Culture of Japan for financial support.

Received, 10th November 1986; Com. 1593

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¶ Identical in all respects with authentic material.