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

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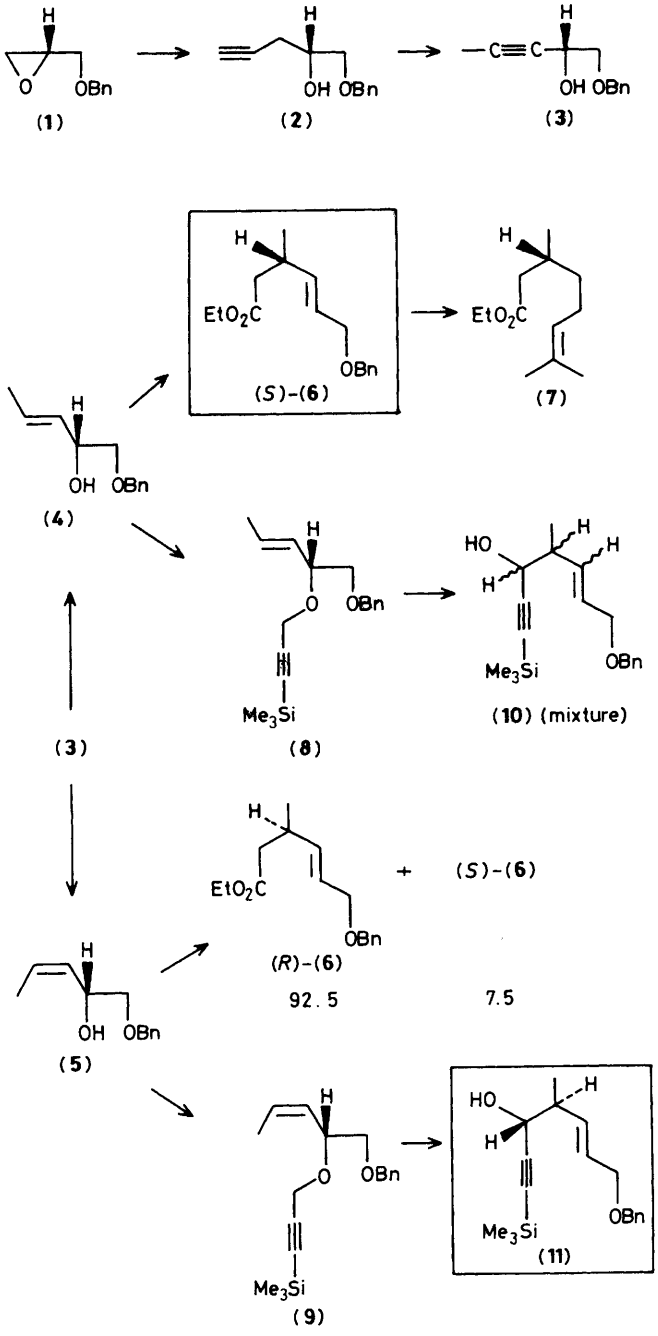
Versatile chiral building blocks for the construction of chiral natural products bearing a secondary methyl group have been efficiently prepared from (*S*)-*O*-benzylglycidol.

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.[1] With this intention, (*S*)-*O*-benzylglycidol (benzyloxymethyloxirane) (*S*)-(**1**)[2] 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.

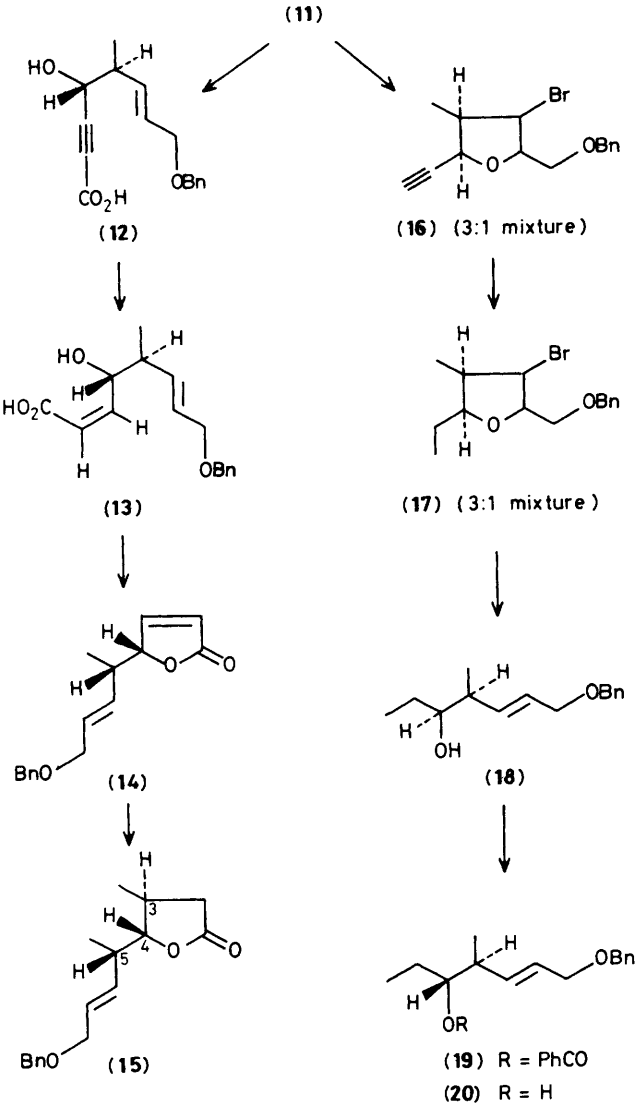
When the epoxide (*S*)-(**1**) was treated with lithium acety-



Scheme 1. Bn = $PhCH_2$.

lide–ethylenediamine complex in dimethyl sulphoxide[3] at 0 °C, the β,γ-acetylenic alcohol (**2**) was obtained in 89% yield (Scheme 1). Treatment of (**2**) with potassium t-butoxide in dimethyl sulphoxide[4] at 0 °C brought about smooth triple bond migration to form the α,β-acetylenic alcohol (**3**) in 93% yield. These conversions could also be carried out in one stage in 79% yield by successive treatment of (**1**) with the acetylide and the butoxide in the same flask. In these conversions preservation of the original chiral integrity was established by ^{1}H n.m.r. studies of the MTPA esters.† Reduction of (**3**) with

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



Scheme 2. Bn = $PhCH_2$.

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[5] to give the enantiomers of the (*E*)-β,γ-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;[6] 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

‡ Determined by ^{1}H n.m.r. spectroscopy (500 MHz). Satisfactory spectral (i.r., ^{1}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}H n.m.r. analysis of the MTPA ester.

with n-butyl-lithium in tetrahydrofuran (THF) at −78 °C led to smooth [2,3] Wittig rearrangement[7] 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.§

Having obtained the two products in enantio- and stereoisomerically pure forms, a straightforward target using the (*S*)-β,γ-unsaturated ester (*S*)-(**6**) was (*R*)-ethyl citronellate (**7**).[8] Thus, (*S*)-(**6**) was sequentially hydrogenated, debenzylated, oxidized, and isopropylidenated to give (*R*)-ethyl citronellate (**7**).¶ 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).[9] 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**)‡ selectively in 25% yield from (**11**). Compound (**15**) may also be converted into the Prelog–Djerassi lactonic acid by application of established methodology.[10] Alternatively, (**11**) was sequentially desilylated and treated with *N*-bromosuccinimide (NBS) to give the bromoether (**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**),‡ 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,[11] the chirality of the secondary hydroxy group of (**18**) was inverted to give the (*E*)-(4*R*,5*R*)-hexene (**20**)§ 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 Tsuchihasi and co-workers.[12]

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.

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¶ Identical in all respects with authentic material.

References

1 S. Takano and K. Ogasawara, *J. Synth. Org. Chem. Jpn.*, 1982, **40**, 1037.
2 *Cf.* S. Takano, M. Akiyama, and K. Ogasawara, *Synthesis*, 1985, 503.
3 *Cf.* E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, and S.-E. Yoo, *J. Am. Chem. Soc.*, 1978, **100**, 4618.
4 *Cf.* L. Brandsma, 'Preparative Acetylenic Chemistry,' Elsevier, Amsterdam, 1971, 143.
5 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741.
6 *Cf.* F. Yasuhara, S. Yamaguchi, R. Kasai, and O. Tanaka, *Tetrahedron Lett.*, 1986, **27**, 4033.
7 N. Sayo, K. Azuma, K. Mikami, and T. Nakai, *Tetrahedron Lett.*, 1984, **25**, 565.
8 F. I. Carroll and A. Philip, *Org. Prep. Proced. Int.*, 1978, **10**, 21.
9 M. Hayashi, M. Ohno, and S. Satoi, *J. Chem. Soc., Chem. Commun.*, 1980, 119; M. Hayashi, H. Ohara, M. Ohno, H. Sakakibara, S. Satoi, K. Harada, and M. Suzuki, *J. Antibiot.*, 1981, **34**, 3857.
10 E. Nakai, E. Kitahara, N. Sayo, Y. Ueno, and T. Nakai, *Chem. Lett.*, 1985, 1725.
11 *Cf.* O. Mitsunobu, *Synthesis*, 1981, 1.
12 K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, and G. Tsuchihashi, *J. Am. Chem. Soc.*, 1986, **108**, 5221.