A General Method for Iterative Cyclopentannulation: Sequential Use of Claisen Rearrangement and Radical Enyne Closure

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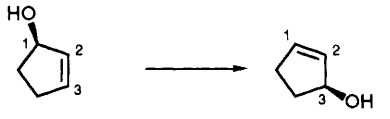
Cycloalkenyl acetylenes **4**, which are easily prepared from allylic alcohols **1**, undergo radical cyclization (**4** → **5**) on treatment with stannyl radicals; the products **5** are themselves convertible into allylic alcohols, so that the annulation sequence can be repeated.

We report a method for cyclopentannulation, based on the reactions summarized in Scheme 1. The starting allylic alcohols **1** can be converted by Claisen[1] (or related[2]) rearrangement into aldehydes (**1** → **2** → **3**). These, in turn, are easily elaborated into terminal acetylenes **4**, which undergo cyclization (**4** → **5**) on treatment with stannyl radicals. Double bond cleavage and dehydrogenation takes the route as far as enones **6**. The procedure is iterative because reduction[3] of enones affords the same compound class (*i.e.*, allylic alcohols) as used at the start (*cf.* **1**). The method of Scheme 1 should accommodate both stereochemcial and regiochemical control. The newly formed ring is annulated on the same face as the hydroxy group of the parent allylic alcohol; that hydroxy group can be inverted by Mitsunobu reaction,[4] and a number of methods are also available[5] for transposition, in the sense of eqn. (1). In principle, therefore, the new ring can be annulated to span C(2)–C(3) in **1** (Scheme 1) or C(1)–C(2).

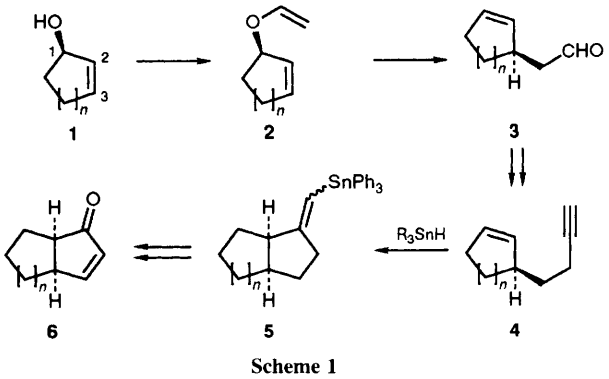


(1)

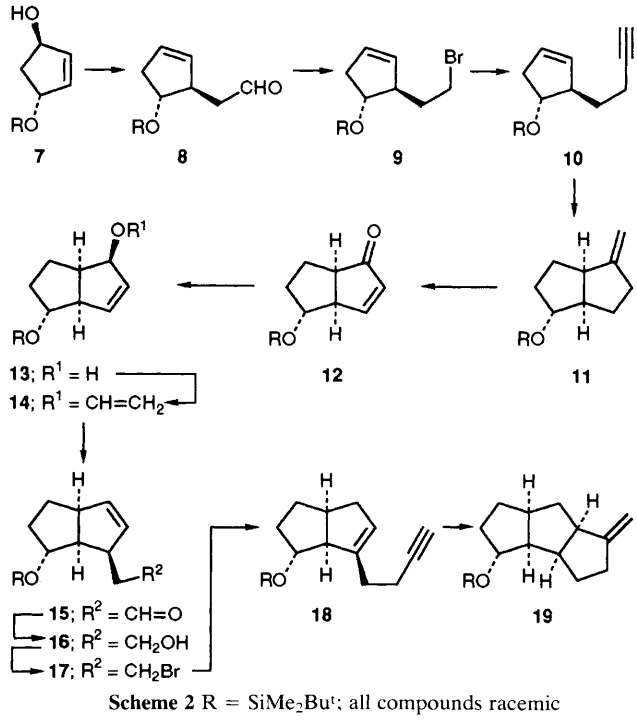
The essential features of the method are illustrated by synthesis (see Scheme 2) of triquinane **19** from allylic alcohol **7**. The silyloxy group in **7**† is a useful, and removable, substituent, whose purpose in this particular example is to raise the molecular mass (and boiling point) of the first few compounds of the sequence; analogous compounds lacking the substituent were too volatile for easy manipulation on a small scale.

Treatment of **7** with an excess of ethyl vinyl ether in the presence of mercury(II) acetate (1 equiv.; reflux, 18 h) gave‡ [80% (99% after correction for recovered **7**)] the expected vinyl ether, which was rearranged[7] (200 °C, 20 min; 90%) to aldehyde **8**. Reduction [–CHO → $-CH_2OH$; $LiAlH_4$, tetrahydrofuran (THF); 90%] followed by reaction with triphenylphosphine–carbon tetrabromide[8] (0 °C to room temp., 30 min; 96%) afforded bromide **9**, and the halogen was then displaced with lithium acetylide [THF–HMPA (hexamethylphosphoramide), −78 °C to room temp., 3 h; 89%]. Addition of triethylborane (1 mol dm^{-3} in hexane, 1.2 mol per mol **10**) to a hexane solution of **10** (0.014 mol dm^{-3}, 1 mol) and tributyltin hydride (0.018 mol dm^{-3}, 1.2 mol per mol **10**) (room temp., 3 h), followed by silica gel chromatography (to effect protodestannylation of the initial product) gave **11** [76% (85% after correction for recovered **10**)]. Double bond cleavage, best done in this case by hydroxylation [OsO_4 (catalytic), 4-methylmorpholine *N*-oxide, 3 h; 99%] and glycol cleavage [$Pb(OAc)_4$, K_2CO_3, 0 °C to room temp., 50 min; 93%], gave the expected ketone, and ring unsaturation was introduced by a standard methods§[9] [lithium diisopropylamide (LDA), PhSSPh; *m*-chloroperbenzoic acid; $(MeO)_3P$, PhMe, reflux; 73%]. Reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; 91%) took the sequence as far as allylic alcohol **13**, from which point the original operations (*cf.* **7** → **11**) were repeated, but with significant technical improvements.

The hydroxy group of **13** is sterically hindered and formation of the corresponding vinyl ether **14** [refluxing ethyl vinyl ether (*ca.* 33 °C), $Hg(OAc)_2$, NaOAc; 72%] requires a long reaction time (48 h). The presence of sodium acetate is also essential to avoid decomposition of the starting material. Thermal rearrangement of the hindered vinyl ether **14** in refluxing decalin led to extensive decomposition, but treatment with an excess of triisobutylaluminium[10] (0.087 mol dm^{-3}



Scheme 1



Scheme 2 R = $SiMe_2Bu^t$; all compounds racemic

† Prepared by Mitsunobu inversion (Ph_3P, $PhCO_2H$, $EtO_2CN{=}N{-}CO_2Et$; 97%; $LiAlH_4$, THF; 94%) of *cis* 4-[(1,1-dimethylethyl)-dimethylsilyloxy]cyclopent-2-en-1-ol (ref. 6).

‡ An excess of anhydrous potassium carbonate must be added before evaporation of the ethyl vinyl ether.

§ Phenylselenenylation under standard conditions was inefficient.

in CH_2Cl_2, −78 °C to room temp., 1 h) caused not only rearrangement (**14** → **15**) but also Meerwein–Ponndorf–Verley reduction to the desired alcohol **16**, isolated in 95% yield (from **14**). Diisobutylaluminium hydride[11] was much less effective for the transformation **14** → **16**. Alcohol **16** was converted into acetylene **18** by the general method used earlier (Ph_3P, CBr_4; 96%; LiC≡CH, THF–HMPA; 93%), and the acetylene cyclized smoothly in refluxing toluene when treated with triphenyltin hydride and azoisobutyronitrile.¶ Again, chromatography of the crude product over silica gel resulted in protodestannylation to afford **19** (79% from **18**). This last experiment took the route to a point where it overlaps with a compound type (*cf.* **11**) used in an earlier step.

The published examples of enyne (and related) cyclization with stannanes are generally[12] cases that benefit[13] from the presence of *gem* disubstitution[14] or of a heteroatom[14c,15] in the chain undergoing ring closure; however, these special features[16] are unnecessary.

All new compounds were characterized by spectroscopic methods, as well as combustion analytical and/or high resolution mass spectral data.

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¶ The conditions used earlier (Et_3B, Bu_3SnH, air) for the cyclization did not work.