Homoconjugate Addition of Grignard Reagents to Spiroactivated Cyclopropanes. An Approach to the Total Synthesis of (±)-Brefeldin A

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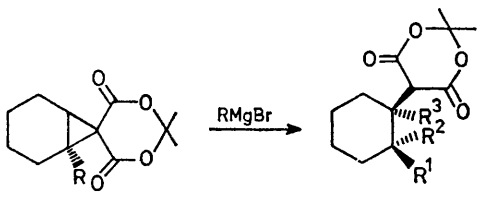
Summary The homoconjugate addition of Grignard reagents to spiroactivated cyclopropanes has been used for the conversion of the readily available cyclopropane (**6a**) into the key intermediate (**4**) for the preparation of (±)-brefeldin A.

IN contrast to the inertness displayed by many electron-deficient cyclopropanes towards nucleophilic opening, 'spiroactivated' cyclopropanes are highly susceptible to attack by a wide range of nucleophiles.[1] We now report the first examples of the homoconjugate addition of organo-

metallic reagents to spiroactivated cyclopropanes and the synthesis of the acylal (**4**) by this method.

Recently, we have described a direct synthesis of spiroactivated cyclopropanes from alkenes *via* irradiation of isopropylidene diazomalonate.[2] The cyclopropanes (**1a**—**c**)

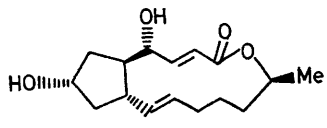


(1)

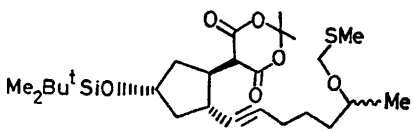
a; R = H
b; R = Me
c; R = Ph

(2)

a; $R^1 = R^3 = H$, $R^2 = PhC{\equiv}C$
b; $R^1 = R^2 = Me$, $R^3 = H$
c; $R^1 = H$, $R^2 = R^3 = Me$
d; $R^1 = Me$, $R^2 = Ph$, $R^3 = H$
e; $R^1 = Ph$, $R^2 = Me$, $R^3 = H$



(3)

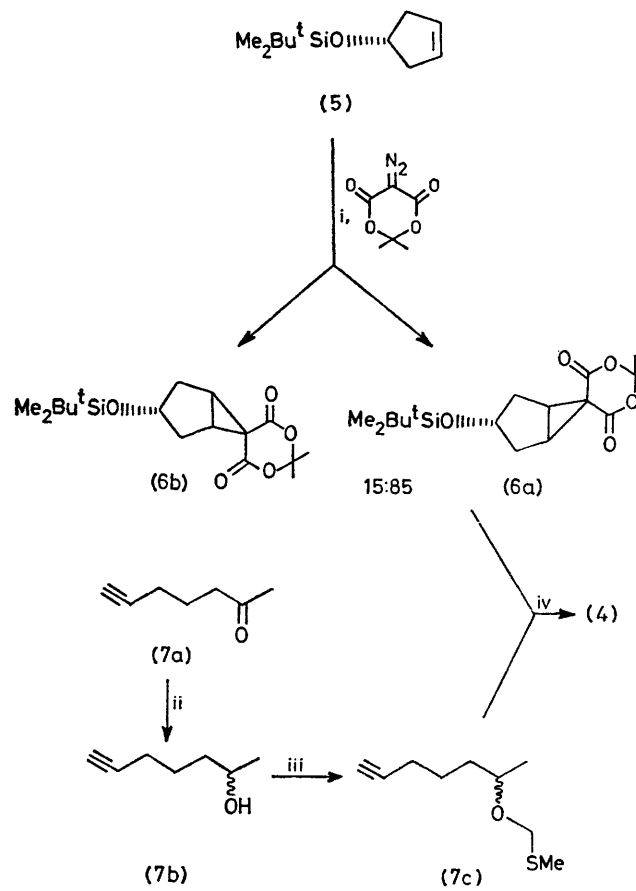


(4)

were prepared from the corresponding alkenes in this manner and treated with a variety of Grignard and other organometallic reagents. The cyclopropane (**1a**) underwent smooth opening upon treatment with 1 equiv. of phenylethynylmagnesium bromide in diethyl ether at 0 °C, affording (**2a**) as the exclusive product (82%).† Similarly, treatment of (**1b**) with 1 equiv. of methylmagnesium bromide in diethyl ether at 0 °C furnished a 3 : 2 mixture of the adducts (**2b**) and (**2c**) (86%).† The addition of 2 equiv. of phenylmagnesium bromide, in CH_2Cl_2‡ containing 1 equiv. of $MgBr_2$ at −20 °C, to (**1b**) produced (**2d**) (m.p. 110—112 °C) as the major product (47%) after column chromatography.† The epimeric adduct (**2e**) (m.p. 117—119 °C) was the exclusive product from treatment of (**1c**) with 1 equiv. of methylmagnesium bromide in diethyl ether at 0 °C (92%).† Surprisingly, efforts to open spiroactivated cyclopropanes with vinylmagnesium halides have failed so far.

The fungal metabolite brefeldin A (cyamin, decumbin) (**3**)[3] exhibits a wide range of biological activity and it has been synthesised recently.[4] We thought that the acylal (**4**) would be a useful intermediate for the synthesis of (±)-brefeldin A.

Irradiation of the cyclopentene (**5**) and 1·5 equiv. of isopropylidene diazomalonate in CH_2Cl_2 at 2537 Å furnished a mixture (83%) consisting of 85% of the desired *trans*-cyclopropane (**6a**) and 15% of the *cis*-isomer (**6b**), readily separable by column chromatography (Scheme).† Reduction of hept-6-yn-2-one (**7a**)[5] with excess of sodium borohydride (in EtOH; 10 °C) gave (**7b**). Sequential treatment



SCHEME. Reagents/conditions: i, CH_2Cl_2, 2357 Å; ii, $NaBH_4$, EtOH, 10 °C; iii, NaH, $HCONMe_2$, then $ClCH_2SMe$, 10 °C; iv, BuLi, Et_2O, 25 °C, then $MgBr_2$, 0 °C.

of (**7b**) with 1 equiv. of sodium hydride and 1 equiv. of chloromethyl methyl sulphide (in dimethylformamide; 10 °C) gave the ether (**7c**) [71% overall from (**7a**)]. Metallation of (**7c**) with 1 equiv. of butyl-lithium in diethyl ether, followed by addition of anhydrous magnesium bromide, gave a solution of the acetylenic Grignard. Addition of 1 equiv. of (**6a**) (0 °C; 2 h) and subsequent neutralization furnished (**4**) (as a mixture of diastereomers at C-15) in 78% isolated yield.†

† The assigned structure was supported by its i.r., 200 MHz n.m.r., and high resolution mass spectra.

‡ All attempted homoconjugate additions of aryl Grignard reagents to spiroactivated cyclopropanes failed with diethyl ether as solvent.

In contrast to the apparent wide scope of the homoconjugate additions of Grignard reagents to spiroactivated cyclopropanes, other organometallic reagents have been less useful. Treatment of (**1a**) under a variety of conditions with lithium dimethylcuprate, methyl-lithium, dimethyl cadmium, dimethylzinc, or aluminium 'ate' complexes has provided only poor yields of the desired adducts.

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