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STEREOSELECTIVE CYCLOPROPANATION OF HOMOALLYLIC ALCOHOLS. FORMAL ATTACHMENT OF A CYCLOPROPANE TO A PREEXISTING RING

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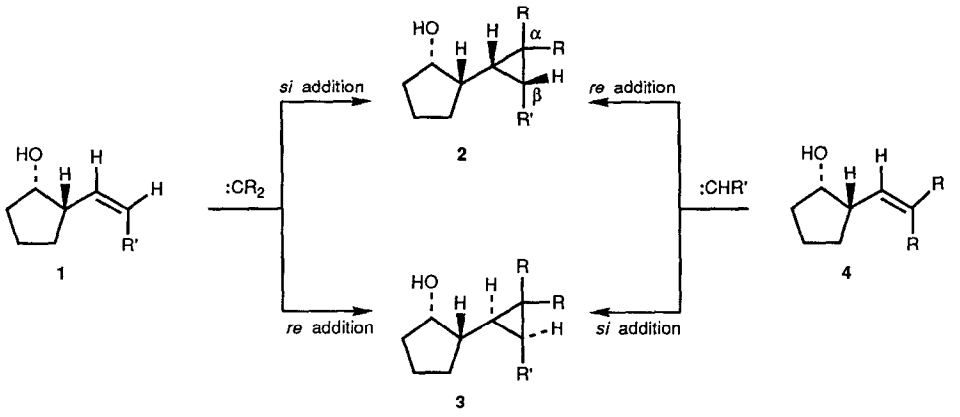
Abstract. Complementary methods for the formal attachment of a cyclopropane to a preexisting ring system that lead to the exclusive formation of either of two possible relative stereochemical relationships are described.

As part of a project directed towards the total synthesis of the ingenane diterpenes,[3,4] we required a method for the stereoselective preparation of cyclopropane **2**. The desired stereochemical relationship could formally be established either *via* the addition of the α carbon in **2** (:CR_2) to the *si* face of **1** or the β carbon in **2** (:CHR) to the *re* face of **4** (Scheme I). While the relative stereochemical relationship of the two stereogenic cyclopropane carbons in the first approach is controlled by the stereoselective *cis* addition of carbene to an alkene,[5] the latter approach (addition of :CHR) is potentially complicated by the need to control the *cis* stereochemistry of the cyclopropane ring, as well as the relationship of the cyclopropane stereochemistry to that of the preexisting ring. In this Letter, we describe complementary approaches for the formation of **2** and its diastereomer, **3**, with complete control of each of the aforementioned relative stereochemical relationships.

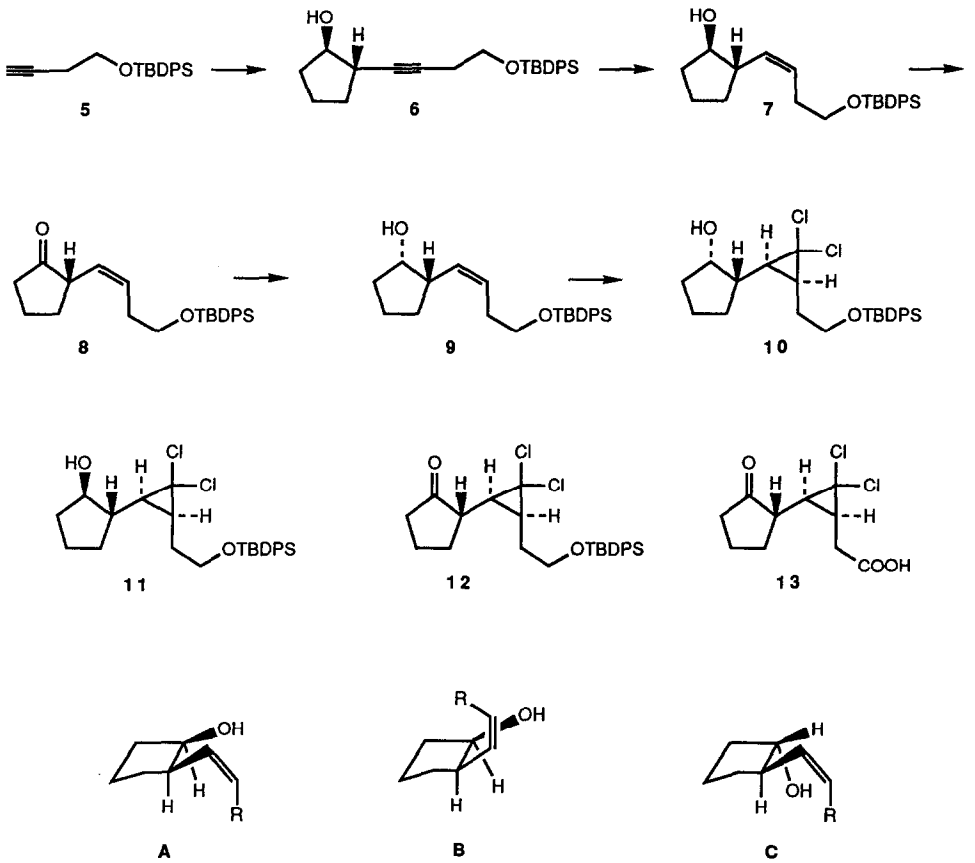
Scheme I



While the stereoselective addition of dichlorocarbene to allylic alcohols has recently been described,[6,7] this reaction had not been extended to homoallylic alcohols. We therefore examined the addition of dichlorocarbene to homoallylic alcohol **9**, prepared as outlined in Scheme II. BF_3-mediated addition[8] of the anion derived from 4-t-butyldiphenylsilyloxy-1-butene[9] to cyclopentene oxide led to the formation of the *trans* 1,2-

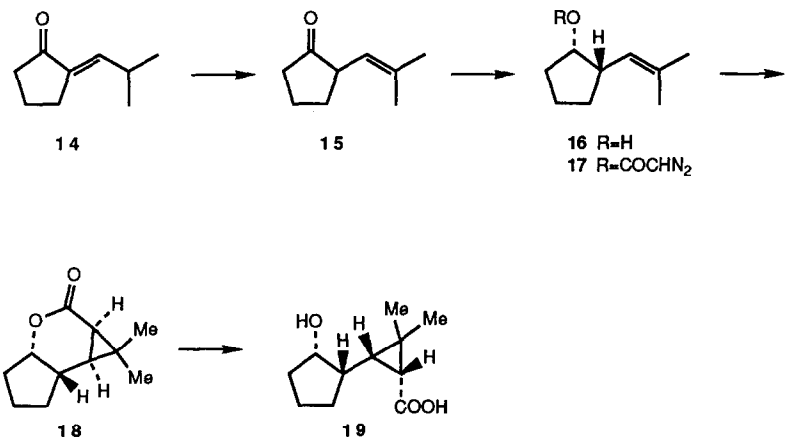
disubstituted cyclopentane **6** in 66% yield. Lindlar reduction of **6** gave **7** (72% yield), which on oxidation using Collins reagent[10] gave ketone **8**. Reaction of **8** with L-Selectride led to the exclusive formation of the *cis* 1,2-disubstituted cyclopentane **9** (68% overall yield from **7**). Addition of dichlorocarbene to **9** ($CHCl_3$, 50% aq. NaOH, cat. Et_3NBzCl, 25°C, 18h, 77% yield) led to the exclusive formation of **10**, the relative stereochemistry of which was confirmed by X-ray analysis of the derived ketoacid **13** (m.p. 132.5-133°C, ethyl acetate).[11] Cyclopropanation of **7** under the same conditions as described for **9** led to a 2.5:1 mixture of **11** (which was converted to the same ketone **12** as was **10** by Swern oxidation) and the diastereomer arising from addition of dichlorocarbene to the *si* face of **7**. The exclusive formation of **10** from **9** can be rationalized by examination of conformations A and B. Hydroxyl-directed addition of dichlorocarbene to the *re* face of **9** via conformation A leads to the formation of **10**. The decrease in stereoselectivity observed in the cyclopropanation of **7** relative to **9** can be accounted for by the greater distance between the hydroxyl and the Z-alkene in *trans* 1,2-disubstituted cyclopentane C vs. *cis*-A.

Scheme II



Given the *re* selectivity observed in these reactions, we reasoned that addition of ":CHR" to **4** (Scheme I) should lead to the establishment of the stereochemical relationship shown in **2**. To ensure the formation of the *cis* cyclopropane stereochemistry (Scheme I), the intramolecular cyclopropanation of **17**, in which the carbene moiety is covalently linked to the hydroxyl as a diazoester, was examined as outlined in Scheme III.[12] Photodeconjugation of **14**[13] (450 W Hanovia lamp, Pyrex filter, MeOH, 25°C, 92% yield)[14] led to the formation of **15**, which on reduction with L-Selectride gave exclusively the *cis* 1,2-disubstituted cyclopentane **16**[15] (79% yield). Acylation of **16** with glyoxylic acid chloride tosylhydrazone using Corey's method[12a] gave diazoester **17**, which on reaction with $Cu(TBS)_2$ (toluene reflux, 57% yield) led to the exclusive formation of lactone **18**, the product of addition to the *re* face of **17**. The relative stereochemistry of **18** was established unambiguously by X-ray crystallographic analysis of the derived hydroxyacid **19** (m.p. 103-103.5°C, ethyl acetate). The exclusive formation of lactone **18** is consistent both with 1) addition to the *re* face of the alkene as observed with **7** and **9** (Scheme II); and 2) the formation of the more stable *cis*-fused bicyclo[4.1.0]heptane moiety in **18**.

Scheme III



The intermolecular addition of dichlorocarbene to **9** to give **10** and the intramolecular cyclization of **17** to provide **18** lead to highly selective and complementary approaches for the establishment of the relative stereochemical relationships shown in **3** and **2** (Scheme I), respectively. The application of this methodology to the stereoselective preparation of cyclopropane-containing photosubstrates for the total synthesis of ingenol is currently underway in our laboratories.

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11 Ketoacid **13** was obtained by desilylation of **10** (TBAF, THF), followed by PDC oxidation (molecular sieves, DMF, 65% overall yield from **10**). The conservation of the relative stereochemistry between the two rings during the PDC oxidation was established by reduction of **13** to the diol corresponding to **10**.

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