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VERSATILE SYNTHESIS OF ALICYCLIC AND ACYCLIC COMPOUNDS WITH ALTERNATE AND REMOTE C-METHYL SUBSTITUTION PATTERNS VIA ASYMMETRIC SEQUENTIAL OLEFINATION AND ENE REACTIONS

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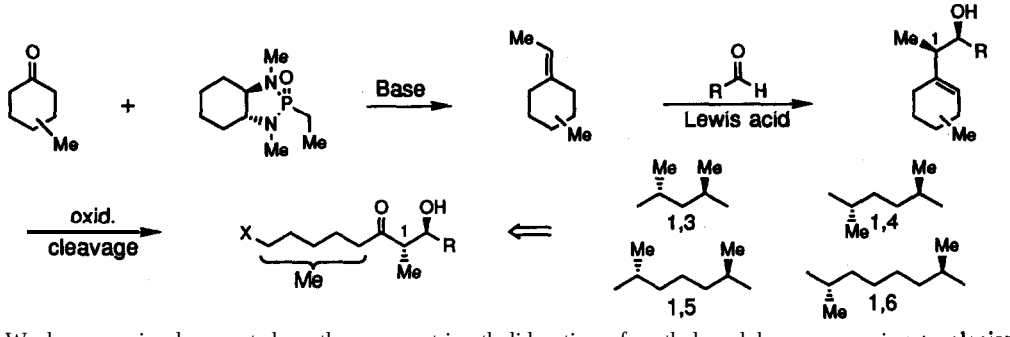
Abstract: Treatment of enantiomerically pure alkyl cyclohexane ethylidene derivatives with 2,3-di-O-benzyl D- and L-glyceraldehyde and related aldehydes in the presence of Lewis acids leads to enantiomerically pure or enriched branched alkylcyclohexenes. These can be oxidized to acyclic motifs with a predetermined C-methyl substitution pattern.

An impressively large number of natural products contain a wide array of carbon and heteroatom appendages in their structures as a result of unique biosynthetic pathways. The C-methyl substitution pattern is ubiquitous in many natural products,[1] and a number of elegant chemical methods are available for the synthesis of such motifs, relying for example, on asymmetric processes,* and on chiron-related approaches.3 In this letter, we report on a novel approach to this problem based on the construction of chiral alicyclic cyclohexenes through the application of sequential asymmetric olefination[4] and ene reactions5 of methyl cyclohexanones. Oxidative cleavage leads to their acyclic counterparts containing stereochemically defined C-methyl groups with 1,3-, 1,4-, 1,5- and 1,6- relationships as exemplified in Figure 1.

Figure 1

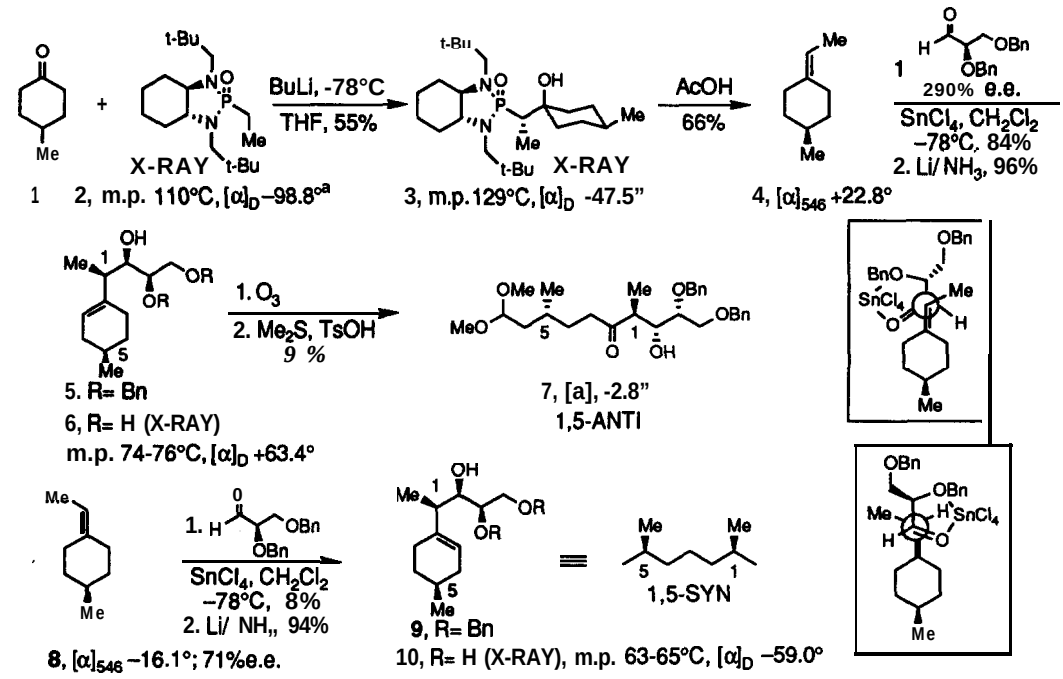


We have previously reported on the asymmetric ethylidenation of methyl cyclohexanones using topologically unique chiral bicyclic phosphonamides, which are easily available from enantiomeric C_2 symmetrical (*R,R*)- and (*S,S*)-1,2-diaminocyclohexanes.[6] Here we show that treatment of 4-methylcyclohexanone with the chiral phosphonamide reagent *(R,R)- 2* leads after careful quenching with water (-78°C→25°C), to a mixture of β-

hydroxy phosphonamides (84:16) which were separated flash chromatography. The structure of the major isomer 3 (55%). was established by direct analogy of the X-ray crystal analysis of the 4-*t*-butyl analog.[7] Remarkably with the N,N'-dineopentyl derivative 2, the anion attacks the ketone from the *pro-R* side, thus reversing the previously observed trend with related (*R,R*)-phosphonamides (ex. N-Me, N-Et, N-Bn, etc.).4 An X-ray structure of the reagent 2 shows that the normally favored *pro-S* face of the anion is indeed shielded by the butyl group, while the *pro-R* face is relatively open, compared to the N,N'-dimethyl analog.6

Treatment of 3 with acetic acid produced (*aS*)-(4-methylcyclohexane) ethylidene 4, with the highest recorded optical rotation;[8] (Scheme 1).

Scheme 1



a. Optical rotations recorded in CHC13 (c 1.0) at 25°C

Reaction of 4 with 2,3-di-O-benzyl-D-glyceraldehyde[9] in the presence of stannic chloride, led to a major product 5 (>90:10) in 63% yield (Scheme 1), whose structure and absolute configuration was deduced from a X-ray crystal structure analysis of the trio1 6. Thus, in addition to localizing the double bond, two new stereogenic centers were also generated in the ene reaction. Of interest is the 1,5-relationship of the C-methyl groups in the major product, which can be exploited as such, or after oxidative cleavage[10] to produce an acyclic motif 7 with an *anti* orientation of the C-methyl groups.

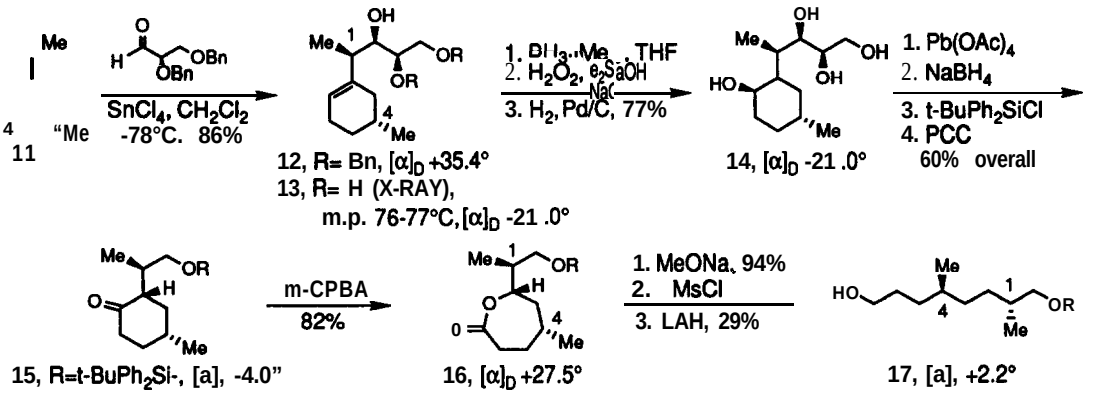
Treatment of the enantiomeric (a*R*)-(4-methylcyclohexane) ethylidene 8 (-71% e.e.) with the same aldehyde, produced the ene product 9 and an isomer 5 (75:25), which upon debenzylation gave the crystalline trio1 10. In this case, a *syn*-1,5-C-methyl substitution pattern results in the cleaved and derivatized acyclic motif by virtue of the position of the double bonds, in the cyclic product. The observed stereochemistry of the major products 5 and 9 can be rationalized (and predicted) by considering a sterically more favored enantiofacial approach of the tin-chelated aldehyde[11] on the (*aS*)- and (*aR*)-exocyclic olefins 4 and 8 respectively (Scheme 1).

Application of the same protocol to **(Z,R)-(3-methylcyclohexane) ethylidene**[6] **11** gave the ene product 12 in 82% yield (Scheme 2). Once again the structure was unambiguously established by X-ray crystallography of the corresponding **triol** 13. In this case the oxidative cleavage was done using a sequence of reactions to produce synthetically useful trisubstituted cyclohexanes,[12] and ultimately an eight-carbon, differentially substituted diol 17 in which a **1,4-*anti*-C-methyl** substitution pattern is obtained.

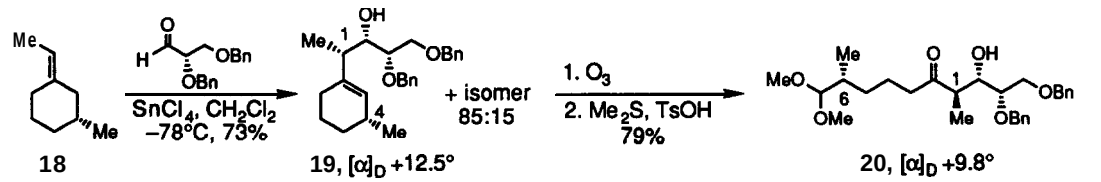
An ene reaction between **(*E*,*R*)-(3-methylcyclohexane)** ethylidene 18 and **2,3-di-O-benzyl-L-glyceraldehyde**[13] gave a major product, whose structure is proposed to be 19, based on the precedents shown above (Scheme 3). By virtue of the position of the double bond, the C-methyl groups are disposed in an **1,6-*anti*** orientation after oxidative cleavage to the acyclic derivative 20. Finally, the ubiquitous propionate and deoxypropionate motifs harboring **1,3-*syn*** or ***anti*-** arrangements of C-methyl groups can be obtained from appropriately paired **(2-methylcyclohexane)** ethylidene,[14] and D-or L-glyceraldehyde derivatives as shown in Scheme 4. Here the products are accompanied by starting material, possibly due to a steric crowding of the chelated intermediate as depicted in Scheme 4. Oxidative cleavage in each case led to acyclic chains containing ***syn*-** and ***anti*-1,3-C-methyl** groups as in 23 and **25**.[15]

The formation of chelated **intermediates**[11] is an important prerequisite for ensuring stereoselectivity and for positioning the double bond in these ene reactions. Thus, reaction of 0-benzyl glycolaldehyde with 18 gave two products in which the double bond had the same position. resulting from a preferential abstraction ***anti*** to the ethylidene group. As expected, there was no face selectivity in view of the absence of a stereocontrolling element. The importance of chirality next to the aldehyde was demonstrated by the successful and highly stereoselective ene reactions with **O-benzyl (*R*)-** or (S)-lactaldehyde with 18.

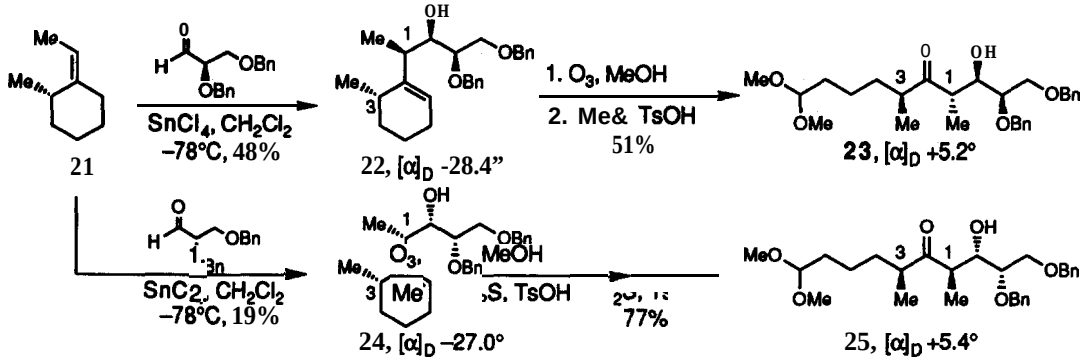
Scheme 2



Scheme 3



Scheme 4



It is **clear that this methodology is uniquely suited for the synthesis of polysubstituted cyclohexenes and related carbocycles, as well as their reduced variants, which are not readily available by other methods. Acyclic counterparts with pre-determined *syn-*** and **anti-arrangements** of C-methyl groups are accessible by oxidative cleavage. Application to natural product synthesis and in the design of enzyme inhibitors are evident.

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