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Highly Stereocontrolled Sequential Asymmetric Michael Addition Reactions with Cinnamate Esters – Generation of Three and Four Contiguous Stereogenic Centers on Seven-Carbon Acyclic Motifs

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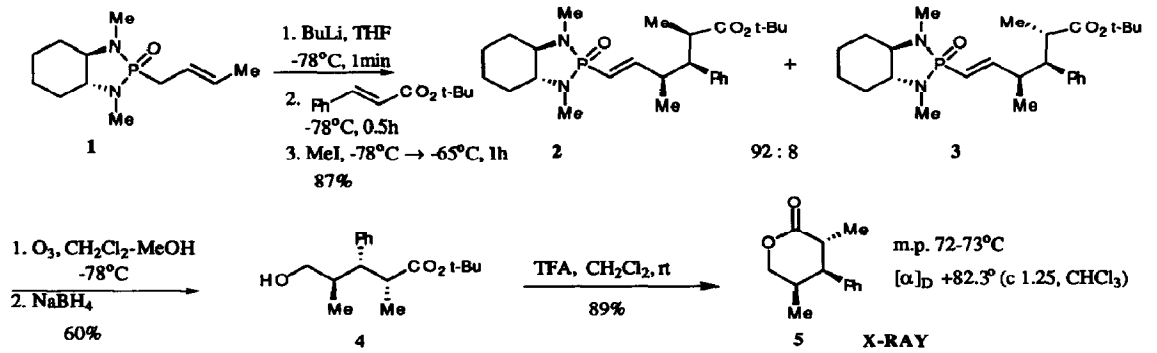
Abstract: The reaction of allyl and crotyl bicyclic chiral phosphonamide anions with two cinnamate esters leads to a sequential Michael reaction with excellent diastereoselectivity. The option to quench enolates with methyl iodide greatly enhances the versatility of the reaction in the synthesis of acyclic seven-carbon chains with vicinal and alternating C-methyl and C-phenyl substituents.

In spite of the remarkable advances in asymmetric C-C bond forming reactions by conjugate additions over the past twenty years,[1] there is a need to develop methods that lead to molecules harboring alkyl, aryl, and related substituents *on consecutive carbon atoms*. To achieve this objective with a high degree of stereochemical control, thus leading to enantiomerically pure or enriched compounds with a pre-determined pattern of substitution is a veritable challenge.[2] To extend the methodology for stereochemical control in *acyclic molecules* with carbon-based substituents is an even greater ambition. A major problem in the synthesis of such molecules is to ensure a high degree of organization in the transition state such that the stereochemical outcome of the reaction(s) is preparatively acceptable.

In a previous publication,[3] we reported on a versatile asymmetric conjugate addition reaction, in which anions of chiral α-allyl and α-crotylphosphonamides could be added to cyclic and acyclic α,β-unsaturated carbonyl compounds with excellent diastereoselectivity. We now extend this powerful methodology to include an asymmetric Michael reaction of the anion derived from the crotyl phosphonamide reagent **1** to t-butyl cinnamate followed by addition of methyl iodide, where adducts **2** and **3** are formed in a ratio of 92 to 8 and in excellent yield (Scheme 1). Ozonolysis of the mixture reduction of the ozonide and chromatographic separation gave the hydroxy

Scheme 1

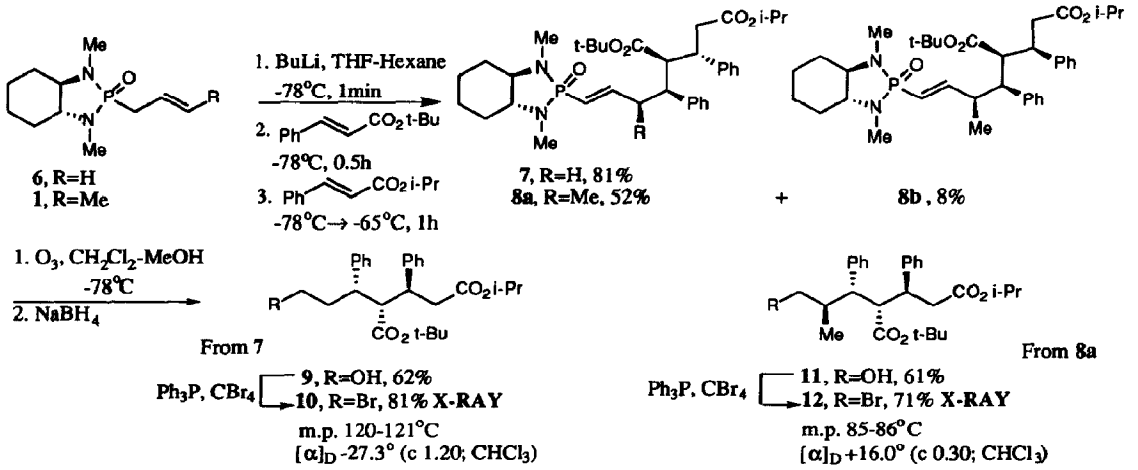


ester derivative **4** as a single isomer. Treatment with TFA in dichloromethane led to the crystalline lactone **5**, the structure of which was unequivocally proved by single crystal X-ray analysis. Thus, the γ-phosphonamide crotyl anion of **1** was transferred to t-butyl cinnamate with very high diastereoselectivity,[3] and the resulting enolate was trapped with a high degree of selectivity generating an acyclic motif containing *three contiguous carbon substituents*.

We now wish to extend the utility of these reactions to examples in which *two consecutive* asymmetric Michael additions can take place with cinnamate esters and with excellent diastereoselectivity.[4,5]

Thus, addition of one equivalent of t-butyl cinnamate to the anion of the allyl phosphonamide reagent **6** in THF-hexane at -78°C, followed by addition of isopropyl cinnamate led to virtually a single diastereoisomer **7** in excellent yield. Ozonolysis and reduction of the resulting ozonide led to hydroxy ester **9** (Scheme 2). A single crystal X-ray analysis of the corresponding bromide **10** confirmed the structure and stereochemical outcome of the sequential double Michael addition reaction. The same reaction with the crotyl reagent **1** gave an 87:13 mixture (^{31}P, ^{13}C NMR) of diastereomers **8a** and **8b** respectively. Ozonolysis of the mixture, reduction, followed by chromatographic separation gave the alcohol **11** corresponding to the major isomer **8a**. Conversion to the bromide and X-ray crystallographic analysis confirmed the structure as being **12**. *Thus, three and four contiguous stereogenic centers can be created from two cinnamyl esters in remarkably efficient and highly stereocontrolled sequential Michael reactions.*

Scheme 2

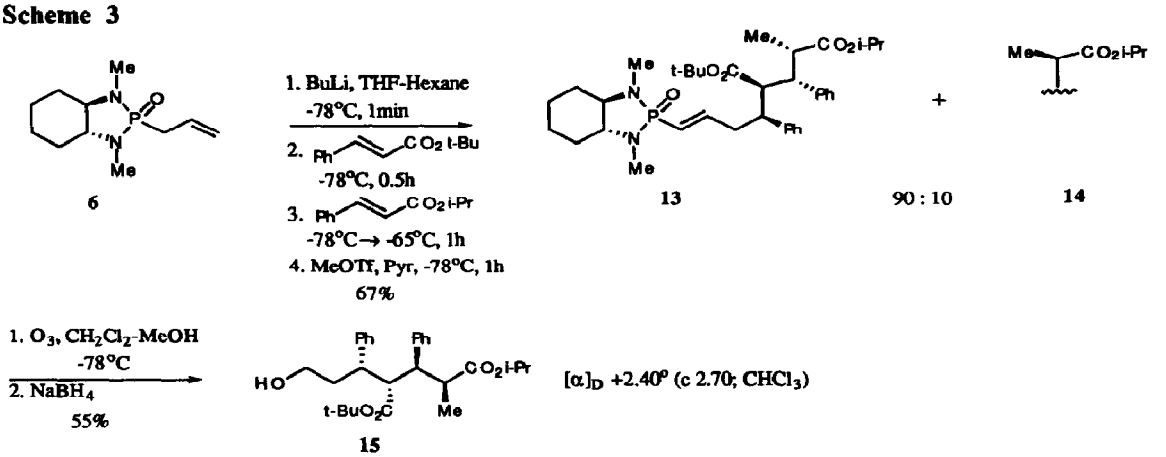


Following the same protocol as above, and quenching the enolate with methyl iodide led primarily to the double addition product **7** without C-methylation. However, using methyl triflate led to a 90:10 mixture of diastereomers **13** and **14** in 67% yield (Scheme 3). Ozonolysis, reduction, and chromatographic separation gave the hydroxy ester **15** as a single isomer, *harboring four contiguous stereogenic centers.*

Attempts to C-methylate the enolates derived from **8a, b** formed from a double addition sequence, or from the isolated adducts with methyl triflate under a variety of conditions led mainly to recovery of starting materials (**8a, b**). Using methyl iodide in the presence of TMEDA (BuLi, THF-hexanes -78° → -30°C), led to the expected C-methylation product albeit in low yield and poor selectivity for the enolate alkylation step (~30%, 1:1 at C-2).

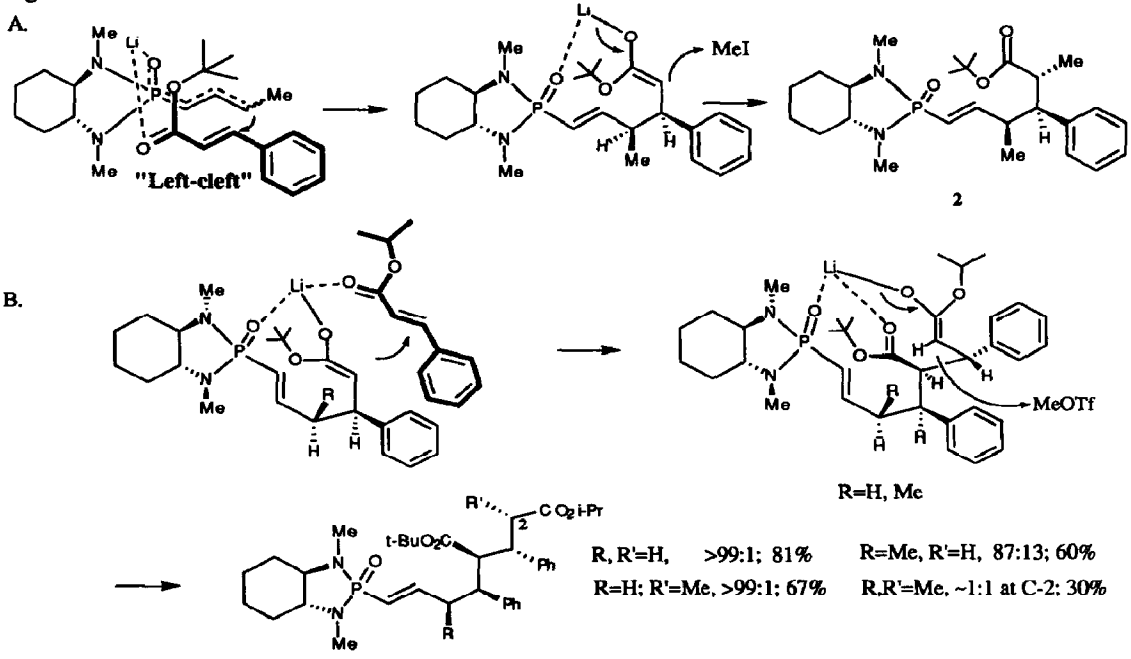
The unsuccessful attempts to obtain *five* contiguous stereogenic centers in high stereochemical purity may reflect the extreme congestion in a Li-chelated intermediate.

Scheme 3



The remarkable stereochemical outcome of these single and double Michael-enolate alkylation reactions (Schemes 1-3) can be rationalized based a model for the possible structure of the enolate resulting from the respective addition reactions (Figure 1A,B). Inspection of molecular models shows that initial attack of the allyl reagent on the *Si* face of t-butyl cinnamate coordinated to phosphorus and "anchored" in the left-cleft of the reagent[3] as shown in Figure 1A, leads to a Li chelated enolate which is then alkylated from the more readily

Figure 1



accessible *pro-R* side to give the observed major product **2**. The alternative coordination mode with the t-butoxy group pointing "downward" would require the ester to adopt an *S-cis* configuration. The double Michael addition (Figure 1B) presumably involves anchoring the isopropyl cinnamate on the Li-chelated enolate intermediate resulting from the first addition. Interestingly, the facial selectivity of the enolate carbon atom is opposite to that of the alkylation reaction. This may be due to the Li coordination which is absent in the alkylation, with a possible contribution from the stacking of the aromatic rings in the transition state. The slightly lower selectivity in the case of the crotyl reagent (Scheme 2, **8a, b**) is more difficult to explain, and may be due to aggregation and steric congestion. A methyl iodide quench of the enolate resulting from the double addition product with the allyl reagent leads to a highly enriched C-2 methylated product **13** whose origin can be explained by an approach from the more accessible face of the resulting chelated enolate (Figure 1B). The relative inefficiency and lack of stereoselectivity of C-2 methylation of **8a** may be due to the highly hindered nature of the Li coordinated adducts, and the effect of the TMEDA respectively.

The tri- and tetra-substituted ω-hydroxy esters obtained from the initial addition products after oxidative cleavage and reduction should be preparatively useful chirons for the synthesis of a variety of pharmacologically important molecules in view of their symmetry and substitution pattern.[6,7] They also represent further examples of chemically asymmetrized chirons that are normally obtained by enzymatic procedures in variable enantiomeric purities as their dicarboxylic acid monoester counterparts.[8]

Attempts to extend this double asymmetric Michael addition reaction to other acyclic esters by varying the first and second acceptors and to further probe the possible effects of the π-stacking are under study.[9]

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