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Synthesis of non-racemic unsymmetrical tetrasubstituted vinylallenes

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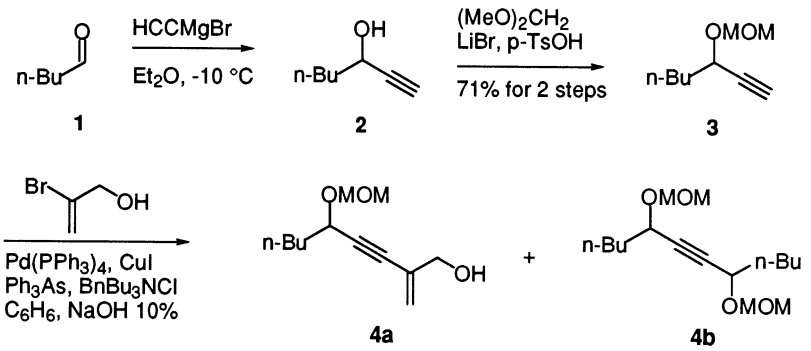
Abstract

Tetrasubstituted chiral vinylallenes are constructed from the enantioselective epoxidation of an enyne followed by an S_N2' addition of a cuprate.

We recently disclosed the use of tetrasubstituted vinylallenes to construct tetrasubstituted exocyclic double bonds.[1] The vinylallenes underwent Diels–Alder cycloadditions under mild conditions even when highly strained alkenes were produced in this way. Vinylallenes have been used in synthesis, mostly as dienes in [4+2]-cycloadditions,[2–11] but tetrasubstituted vinylallenes were used only rarely. We report herein the synthesis of chiral tetrasubstituted vinylallenes that were used as models in our synthetic efforts toward the cytotoxic quassinoids.

Pentanal **1** was reacted with ethynylmagnesium bromide and the resulting alcohol **2** was protected as its methoxymethyl ether (Scheme 1).[†] Initially, we performed Sonogashira's



Scheme 1.

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† All new compounds gave satisfactory IR, NMR and Mass spectral data.

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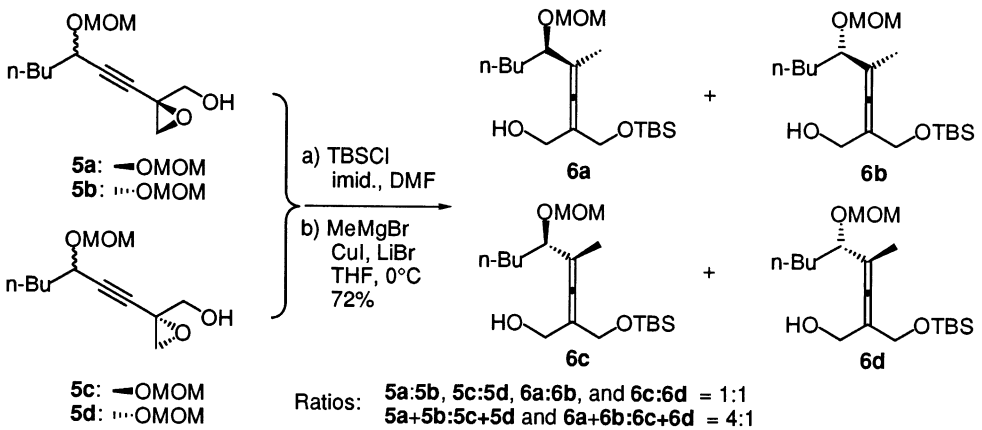
cross-coupling of alkyne **3** with 2-bromo-2-propen-1-ol (Pd^{+2}, CuI, Et_3N) and obtained substantial amounts of by-product **4b** resulting from the homocoupling of alkyne **3** along with the desired enyne **4a**. Rossi's modifications proved superior and under those conditions the ratio of cross versus homocoupling products was >9:1.[12] The allylic alcohol **4a** was epoxidized stereoselectively using Shi's catalyst system and **5** was obtained in 72% yield as a ca 4:1 mixture of **5a**–**b** and **5c**–**d** (55% ee).[13–16] The lack of substituent at position 2 on the alkene may be responsible for the lower enantioselectivity.[16]

The Sharpless asymmetric epoxidation conditions produced **5** in 69% ee but in lower yield. At this stage, the diastereomeric epoxides appear and behave like pairs of enantiomers. The acetylenic unit between the two chiral carbons isolate them so effectively that the two pairs of diastereomers were undifferentiable by proton and ^{13}C NMR. Thus **5** appeared as a single compound by spectroscopy. The (*S*)-(−)-Mosher esters of **5** were prepared and it was found to consist of a ca 4:1 mixture of two epoxides (i.e. [**5a**+**5b**]:[**5c**+**5d**]).‡

The epoxide mixture **5** was submitted to the action of methylcopper in THF to yield 72% of two separable diastereomeric allenic alcohols **6** in a 1:1 ratio each being 54% ee (Scheme 2). The enantiomeric excesses were again checked by making the Mosher esters of each pair of enantiomeric allenyl alcohols. This implies a highly *anti* selective addition of methylcopper on epoxide **5**, a result consistent with what is known on cross-coupling reactions of cuprates with allylic and propargylic epoxides.[17–20]

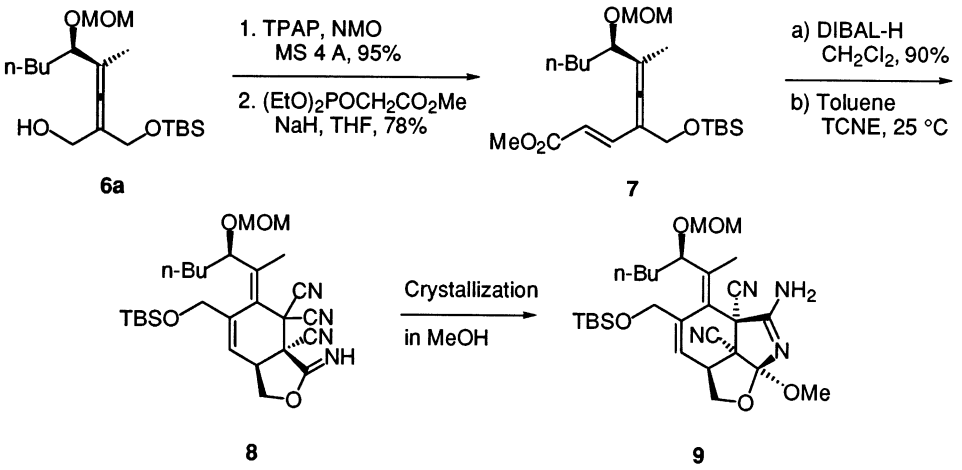


Scheme 2.

While the epoxidation of enyne **4a** proceeded with moderate enantioselectivity, the chiral center on **4a** (bearing the MOM ether) serves to increase substantially the enantiomeric purity of the major allene **6a** obtained. Propargyl alcohol **2** has been prepared in 85% ee.[21] If the sequence of epoxidation–cuprate addition is performed on this material, the enantiomeric ratio **6a**:**6d** becomes 48:1 (ca 98% ee), after separation of the diastereomeric mixture on a normal silica gel column (note that the ratio **6b**:**6c** is ca 1:3).

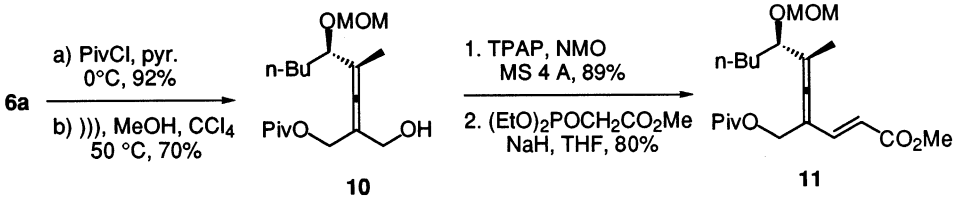
‡ Compounds **5a** and **5b** (or **5c** and **5d**) could not be separated by GC or HPLC and the NMR spectra of their Mosher esters were identical.

To complete the sequence, allene **6a** (54% ee) was oxidized with perruthenate and converted to the desired vinylallene **7** using a Wadsworth–Emmons reaction (Scheme 3). The diisobutylaluminium hydride reduction product of vinylallene **7** underwent a Diels–Alder cycloaddition with tetracyanoethylene at room temperature to give **8** possessing an exocyclic tetrasubstituted double bond and in which the hydroxyl group had cyclized internally to give an iminoester. As expected, the major adduct corresponded to an approach of the dienophile from the least hindered face of the vinylallene.[1] Confirmation of the stereochemistry of the major Diels–Alder adduct, and thus of the vinylallene precursor, was obtained from a single crystal X-ray analysis of an unusual methanolic adduct **9** which occurred when **8** was crystallized from methanol.



Scheme 3.

The pseudo-symmetrical nature of allene **6a** also permitted us to construct the vinylallene with the opposite configuration (Scheme 4). Protection of the alcohol in **6a** as a pivalate ester and deprotection of the silyl ether using ultrasound gave **10** which was submitted to the oxidation/olefination sequence to give **11**. Careful and prompt handling of the allenic alcohols is desirable since they slowly epimerize over time. We have determined that two different mechanisms are responsible for the epimerization depending on the circumstance. First, daylight induces slow epimerization of some allenes presumably via a diradical. We irradiated the aldehyde obtained from **6a** (see Scheme 3) under a 275 W sunlamp and obtained the equilibrium mixture (ca 1:1) of this aldehyde and its epimer (aldehyde corresponding to **6c**) in 1 hour. Second, several basic reaction conditions promote the migration of some protecting groups between the alcohol



Scheme 4.

functions. For example, during an attempt to protect the hydroxyl group in **6a**, deprotonation with NaH led to a 1:1 mixture of **6a** and **6c** instantaneously, probably from a migration of the silyl group. Fortunately, the final vinylallenes **7** and **11** are stable to epimerization.

Acknowledgements

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