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Cis-epoxides via Sharpless' Asymmetric Dihydroxylation Reaction: Synthesis of (+)-Disparlure

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Abstract: (+)-Disparlure, containing an isolated *cis*-epoxide functional group, was synthesized employing the asymmetric dihydroxylation and cyclic sulfate rearrangement-opening reactions as the key steps.

(+)-Disparlure, the sex attractant pheromone of the female gypsy moth, *Lymantria dispar* (L.), has been the target of numerous syntheses,[1] in whch the chirality of the product has been procured employing either enantiopure natural products as starting materials[2] or asymmetric reactions–biological[3] or abiological.[4-6] Among the syntheses in the latter group, the ones employing asymmetric epoxidation (AE)[5] and asymmetric dihydroxylation (AD)[6] offer an interesting comparison of the two, closely related asymmetric processes.

The AE-based strategy for the synthesis of an isolated *cis*-epoxide such as disparlure requires an AE reaction of a (*Z*)-allylic alcohol followed by a chain elongation at the hydroxymethylene terminus. In the case of the disparlure synthesis, Sharpless et al. achieved the chain elongation in three steps: oxidation to aldehyde; Wittig reaction; hydrogenation.[5]

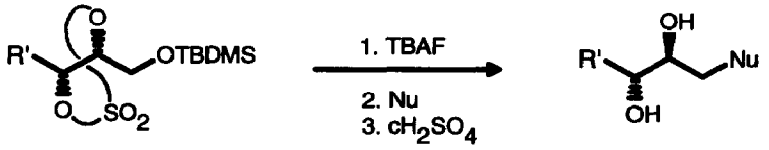
Considering that one great strength of the AD process is its ability to react with isolated olefins,[7] the AD-based strategy may be expected to be more straightforward for the synthesis of an isolated epoxide, since a one-pot procedure has been developed to stereospecifically convert vicinal diols to epoxides.[8] This, however, is true only with a *trans*-epoxide, for the necessary diol intermediate for a *cis*-epoxide is an *erythro*-diol, which would be formed from a (*Z*)-olefin, not an ideal substrate for the AD process.[9] In order to convert an AD product, a *threo*-diol, to *cis*-epoxide, one requires a *regioselective* functionalization of one hydroxyl group, e.g., a succession of reactions involving a regioselective protection of one hydroxyl group; a sulfonation of the other hydroxyl group; deprotection; epoxide formation. This, Keinan et al. ingeniously achieved in their synthesis of disparlure by way of a neighboring group participation: AD of (*E*)-γ,δ-unsaturated ester was followed by an in situ γ-lactonization, thereby differentiating the two hydroxyl groups.[6] The disparlure synthesis was then completed after a chain elongation similar to the one used in the AE-based strategy.

While this method served their purpose well, it may not be applicable as a general solution for the synthesis of *cis*-epoxides. It is apparent that one substituent of the *cis*-epoxide product has to be at least three-carbon long (from γ-lactone), and substituents on or near the starting C,C-double bond may alter the

lactonization pattern. If the in situ cyclization is not regioselective, the regioisomers must be separated as they may eventually lead to the antipodal epoxide products.

Our on-going interest in the synthesis of carbohydrates and related polyhydroxylated compounds recently led us to develop an indirect method to access *erythro*-diols via AD.[10] The key step was a novel, irreversible Payne-type rearrangement-opening reaction (Scheme I). This highly regioselective, one-pot process is also compatible with a variety of substrate types and nucleophiles. Combining the two one-pot processes[10,8] together, one would then have an efficient and general method for the enantioselective synthesis of *cis*-epoxides.

Scheme I



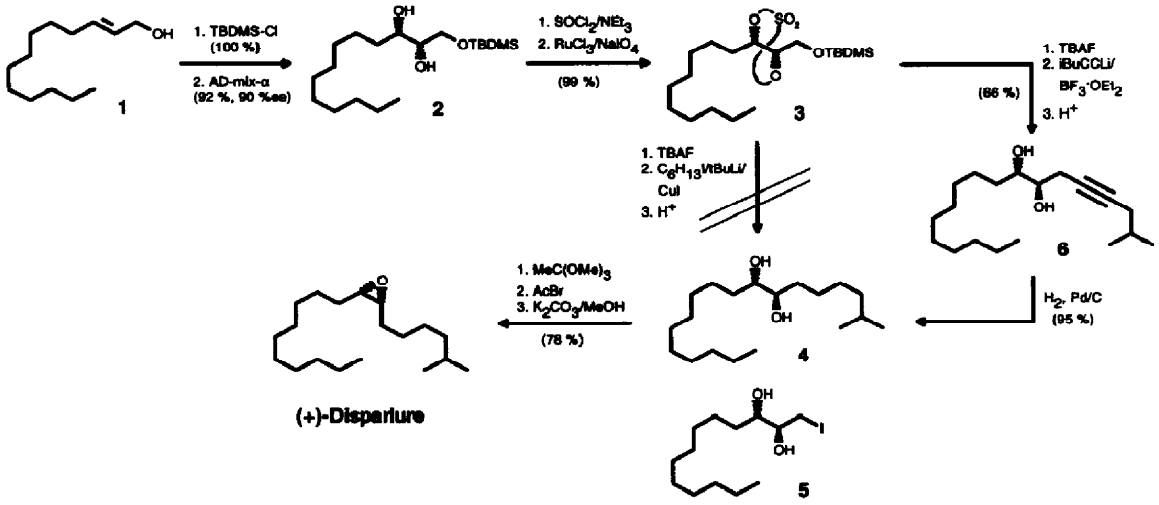
Nu = RS^-, N_3^-, RCO_2^-, NC^-, halides,
H^-, R^-(cuprates), $R-C\equiv C^-$

Thus, (*E*)-2-tridecen-1-ol **1** was TBDMS-protected (100 %) and the product dihydroxylated using AD-mix-α[11] (92 %, 90 %ee,[12] Scheme II). The resulting *threo*-diol **2** was converted to the cyclic sulfate **3** (99 %).[13] The product was treated first with TBAF (trihydrate), and after drying, with the required dialkyl cuprate under anhydrous reaction conditions.[14] After aqueous acidic work-up, however, none of the desired *erythro*-diol **4** was obtained; instead, the only isolated product was an opening product by iodide **5** (quantitative yield). While cuprates, prepared from CuI and commercial alkyllithiums (salt-free), have been successfully used in the cyclic sulfate rearrangement-opening process,[10b] when a dialkyl cuprate is generated from an alkyllithium, which has been prepared in situ from the corresponding alkyl iodide and t-BuLi(2 eq.),[15] as in the present synthesis, a competitive opening by iodide is apparently the only possible reaction pathway.

Therefore, a slight detour was taken and the *erythro*-diol **4** was prepared in two steps from the cyclic sulfate **3**: After the desilylation/rearrangement of **3** using TBAF·$3H_2O$, the dried reaction mixture was treated with 4-methyl-1-pentynyllithium (4-methyl-1-pentyne/n-BuLi). After aqueous acidic work-up, the *erythro*-diol **6** was isolated in 66 % yield, which was then converted to **4** (H_2, Pd/C, 95 %, 70 % recovery after recrystallization from ether-pentane). Conversion of the *erythro*-diol **4** to (+)-disparlure was achieved using the three-step, one-pot procedure ($MeC(OMe)_3$; AcBr; K_2CO_3, 78 %).[8] While this conversion method has been mainly used for the synthesis of *trans*- or terminal epoxides, it worked well in the present case (*erythro*-diol –> *cis*-epoxide), where the steric demand may be greater.[16]

Thus, the route taken in our synthesis of disparlure serves as an efficient alternative for the enantioselective preparation of *cis*-epoxides. With the cyclic sulfate rearrangement-opening process affording *erythro*-diols,[10] and now *cis*-epoxides as well, the synthetic utility of the AD process will be further expanded.

Scheme II



Experimental procedure for the rearrangement-opening step (3 –> 6): The cyclic sulfate **3** (1.0 g, 2.45 mmol) was dissolved in THF (30 mL) and TBAF·3H$_2$O (0.85 g, 2.7 mmol) was added. The mixture was stirred at rt for 5 min. TLC (hexane-EtOAc 4:1) indicated the complete disappearance of the starting material and the presence of base-line material. The solvent was evaporated on a rotary evaporator and the mixture was further concentrated with the aid of dichloromethane (2 X 20 mL). Finally the mixture was dried under high vacuum for 1 h. In the meantime, 4-methyl-1-pentynyllithium was prepared in a second flask using 4-methyl-1-pentyne (1.17 mL, 10 mmol) and n-BuLi (9 mmol) in THF (20 mL) at -30 °C. The solution was cooled to -70 °C, and were added, slowly and simultaneously, the first reaction mixture as a solution in THF (15 mL), and $BF_3{\cdot}OEt_2$ (1.15 mL, 9 mmol). The entire mixture was stirred at -70 °C for 1 h, then warmed to -30 °C, where it was stirred for further 2 h. The reaction was quenched by adding H_2SO_4 (20 %, 20 mL). The mixture was stirred at rt overnight. Extractive work-up (EtOAc - $NaHCO_3$) followed by chromatographic purification (hexane-EtOAc 4:1) yielded **6** as a white solid, mp 65 - 67 °C (0.48 g, 66 %).[17]

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