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Asymmetric Protected Enoates as Key Intermediates Towards an EPC Synthesis of (+)-Heptelidic Acid

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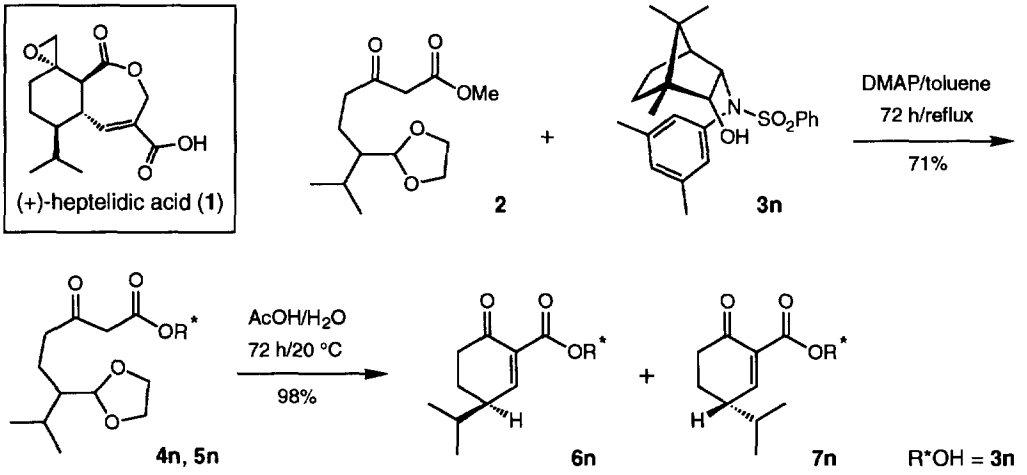
Abstract: Conjugate addition of $(H_2C{=}CH)_2CuLi$ to **6n** and **7n** gave the adducts **9n** (5'R,6'R) and **10n** (5'S,6'R) as single diastereomers, respectively. Finally, the (5'R) configurated enoate **6n** turned out to be valuable as a chiral building block for an EPC synthesis of (+)-heptelidic acid.

The sesquiterpene lactone (+)-heptelidic acid (**1**) first was isolated by Sankyo scientists[1] from cultures of three different strains of fungi as a part of a screening program for new antibiotics. Structure of **1** was resolved by spectroscopic methods[2] and confirmed by x-ray crystal structure analysis.[3] A total synthesis of (±)-heptelidic acid was published by Danishefsky[4] in 1988.

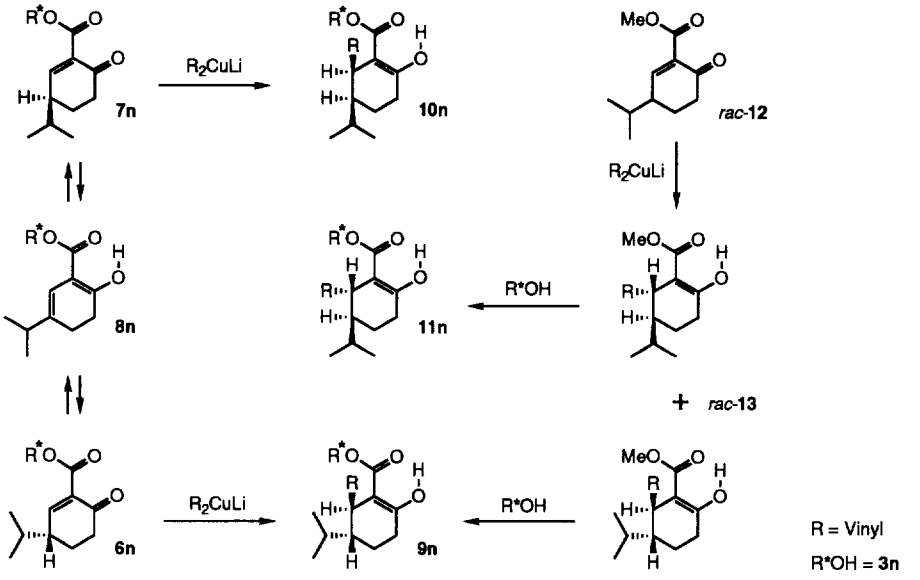


Scheme 1

We started our synthesis from β-ketoester **2**[5] which on transesterification[6] with Helmchen's auxiliary[7] **3n** resulted in a mixture of the diastereomeric esters **4n** and **5n.** Hydrolysis and subsequent acid-catalyzed cyclization[8] gave a mixture of the diastereomeric 2-oxo-5-isopropyl-cyclohexenecarboxylates **6n** and **7n.** After separation by medium pressure chromatography we isolated the crystalline enoates **6n** (70%) and **7n** (79%) in good yields and high purity (>99%, HPLC).[9] Indeed, asymmetric shielded enoates **6n** and **7n** proved to be stable and showed no epimerization *via* the enol form **8n**, even on storage over several weeks.

In conjuction with our recent report on conjugate additions to auxiliary shielded 2-oxo-cyclohexene-carboxylates[10] it was of particular interest to get knowledge about the steric course of cuprate addition to **6n** and **7n.** We first chose the homocuprate $(H_2C{=}CH)_2CuLi$ as a simple nucleophile and obtained single diastereomers **9n** (83%) and **10n** (84%) in excellent yields, respectively.

Attack of the cuprate reagent to asymmetric protected enoate **6n** occured from the less hindered half space of the auxiliary ester *trans* to the vicinal isopropyl group yielding the *trans*-configurated adduct **9n.** In accordance with our expectations both the shielding effect of the auxiliary and the *trans*-directing effect of the isopropyl group synergistically promoted the formation of **9n** at a very high level of diastereoselection.



Scheme 2

Addition of the organocopper compound to the shielded enoate **7n** took place from the less hindered half space of the auxiliary ester *cis* to the vicinal isopropyl group leading to the *cis*-configurated adduct **10n**. Quite obviously shielding effect of the auxiliary was the determinating factor, while steric hinderance by the bulky isopropyl group was tolerated, surprisingly without any detectable decrease of diastereoselectivity.

Course of cuprate addition to the unshielded enoate *rac*-**12** was directed by the isopropyl group at C-5 leading exclusively to the *trans*-configurated adduct *rac*-**13** (5RS, 6RS), like described by Danishefsky.[4] Subsequently, transesterification of *rac*-**13** with **3n** afforded the *trans*-substituted auxiliary esters **9n** and **11n** which were separated by chromatography. Thus we were able to deduct the configuration of **6n** (5'R), **7n** (5'S), **9n** (5'R,6'R), **10n** (5'S,6'R) and **11n** (5'S,6'S) by chemical correlation (Scheme 2).

In conclusion, **6n** turned out to be a valuable building block for an EPC synthesis of (+)-heptelidic acid.

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9. *Preparation and separation of enoates* **6n** *and* **7n**: A mixture of acetals **4n** and **5n** (36.2 g, 56.6 mmol) was dissolved in acetic acid (290 ml), H_2O (40 ml) was added and the reaction mixture was stirred for 72 h. Then CH_2Cl_2 was added, the organic layer was washed with H_2O and a solution of $NaHCO_3$ (5%) and dried with Na_2SO_4. Evaporation of the solvent at reduced pressure gave a 1:1 mixture of raw enoates **6n** and **7n** (32.0 g, 98%), discoloured oil. Separation of the raw product (1.7 g) by MPLC (Lichroprep Si 60, 15-25 µm, 95 g, hexane:EtOAc:AcOH = 80:18:2, flow 1.5 l/h) gave **6n** (595 mg, 70%), colourless crystals from nBuOH, mp 118-120 °C and **7n** (670 mg, 79%), colourless crystals from iPrOH, mp 123-125 °C. HPLC analysis (Lichrospher Si 60, 5 µm, hexane:EtOAc:AcOH = 85:13:2, flow 1.0 ml/min, R_t(**8n**) = 5.2 min, R_t(**6n**) = 20.2 min and R_t(**7n**) = 25.7 min) revealed a purity of ≥99% for enoates **6n** and **7n**.
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