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EPC Synthesis of 6-Substituted 2-Oxo-cyclohexanecarboxylates via Conjugate Addition of Cuprates to Asymmetric Shielded 2-Oxo-cyclohexenecarboxylates

Ernst Urban*,a, Gerhard Riehsa and Guido Knühlb

^a Institut für Pharmazeutische Chemie der Universität Wien, Althanstraße 14, A-1090 Wien, Austria

^b Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Abstract: Asymmetric shielded 2-oxo-cyclohexenecarboxylates **6n** and **6x** were prepared by transesterification of 2-oxo-cyclohexanecarboxylate **2** with camphor derived concave alcohols **1n** and **1x** and by subsequent introduction of a double bond via phenylselenides. Diastereoselective conjugate addition of equimolar amounts of mixed cuprates at -78 °C and deprotection by methanolysis gave enantiomerically pure 6-substituted 2-oxo-cyclohexanecarboxylates **14-19** and *ent*-**14-19**, valuable as chiral building blocks in natural product synthesis.

The conjugate addition of cuprates to asymmetric shielded enoates developed into an important and well known method¹ for assembling structural complex organic molecules. Outstanding results were obtained by Helmchen² on the conjugate addition of organocopper compounds to enoates of camphor derived chiral auxiliaries **1n** and **1x**, which generally proceeded with an extremely high diastereoselectivity (>99%) and in excellent yields (>90%). In conjunction with projects aiming at EPC syntheses of the natural products (-)-chokol A³ and (+)-heptelidic acid,⁴ we investigated preparation of enantiomerically pure 5-substituted 2-oxo-cyclopentanecarboxylates and 6-substituted 2-oxo-cyclohexanecarboxylates starting from asymmetric protected cyclic enoates. In the present communication we want to report on conjugate addition of mixed cuprates to asymmetric protected 2-oxo-cyclohexenecarboxylates derived from the chiral auxiliaries **1n** and **1x**.



Asymmetric shielded 2-oxo-cyclohexanecarboxylates were readily available from auxiliaries 1n or 1x and racemic 2-oxo-cyclohexanecarboxylate 2. We obtained the well crystallizing esters 3n (94%) and 3x (94%) in excellent yields using a DMAP⁵ mediated transesterification reaction⁶ first reported by Taber.⁷ Phenylselenylation⁸ of 3n and 3x gave mixtures of diastereometric selenides (4n:5n = 4x:5x = 60:40) which were separated by chromatography. Oxidative deselenylation of 4n or 5n and 4x or 5x afforded enoates 6n and 6x in good yields (85-91%), respectively. Preparative scale synthesis of enoates 6n (60%) and 6x (68%) was manufactured by a one pot procedure⁹ starting from 3n and 3x without isolation of the intermediate selenides.



Next we studied the addition of Lipshutz cuprates¹⁰ to 6n and 6x (see Table 1) and obtained 6-substituted 2-oxo-cyclohexanecarboxylates 7n-12n and 7x-12x in good yields (62-78%),¹¹ with one significant exception, the reaction of 6n and 6x with the bulky t-butyl-2-thienyl-cyanocuprate which led to mixtures of t-butyl adducts 9n (26%) and 9x (37%) with β -cyano adducts 13n (16%) and 13x (14%), respectively. Nevertheless we were able to prepare 9n (66%) and 9x (56%) in good yields using tBu₂CuLi which proved to be the more reactive cuprate. NMR analysis of unpurified cuprate addition products outlined excellent diastereoselectivities (>95%). After purification of the raw products by flash chromatography and crystallization we were in fact unable, with help of HPLC and NMR, to find more but single diastereomers.

Enone	R	Cuprate Precursor	Cuprate Adduct	Yield (%)	Methyl- ester	Yield (%)	R*OH	Yield (%)
бn	CH ₃	R-Li	7 n	64	14	70	1 n	82
6n	nBu	R-Li	8 n	62	15	90	1 n	79
6 n	tBu	R-Li	9n(13n) ^a	26(16)	16	56	1 n	91
6n	H ₂ C=CH	R-MgBr	10n	70	17	81	1 n	81
бn	$H_2C=C(CH_3)$	R-Li	11n	62	18	77	1 n	71
6n	Ph	R-Li	12n	66	19	80	1 n	82
6 x	CH ₃	R-Li	7 x	78	ent-14	62	1 x	63
6 x	nBu	R-Li	8 x	70	ent-15	76	1 x	88
6 x	tBu	R-Li	9x(13x) ^a	37(14)	ent-16	52	1 x	94
6 x	H ₂ C=CH	R-MgBr	10x	62	ent-17	75	1 x	95
6 x	$H_2C=C(CH_3)$	R-Li	11x	78	ent-18	69	1 x	95
6 x	Ph	R-Li	12x	63	ent-19	78	1 x	91

Table 1. Cuprate Addition to Asymmetric Shielded Enoates and Deprotection by Methanolysis.

^a Separated by flash chromatography; reaction of **6n** and **6x** with tBu₂CuLi gave **9n** and **9x** as single products.





Cleavage of the chiral auxiliary from the sterically highly crowded 2-oxo-cyclohexanecarboxylates 7n-12n and 7x-12x was accomplished by transesterification with MeOH at 125 °C, which allowed recycling of 1n and 1x and gave the enantiomerically pure methylesters 14-19 and *ent*-14-19 in good yields (Table 1).¹²

The steric course of cuprate additions to 6n and 6x can be rationalized by an attack of the organocopper nucleophile from the less hindered halfspace of the *s*-trans enoate reactive species (Scheme 2), as it was found for simpler acyclic enoates by Helmchen². Quite obviously the additional keto function does not seem to influence the reaction, apart from increased reactivity.

In conclusion, the present conjugate addition approach to 6-substituted 2-oxo-cyclohexanecarboxylates enables a short and extremely stereoselective route to valuable intermediates in natural product synthesis.

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- 4. Recently we were successful using conjugate additions of cuprates to an asymmetric protected 2-oxocyclohexenecarboxylate as a key step towards EPC synthesis of (+)-heptelidic acid, following the synthesis of the racemic natural product by Danishefsky, S. J.; Mantlo, N. J. Am. Chem. Soc. 1988, 110, 8129-8133.
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- 9. Typical procedure: A solution of PhSeBr (4.72 g, 20 mmol) in CH₂Cl₂ (100 ml) was cooled to 0 °C, pyridine (1.61 g, 20.4 mmol) and then a solution of 3x (10.75 g, 20 mmol) in CH₂Cl₂ were added. The mixture was stirred for 2 h at 20 °C, extracted with 1 M HCl and dried (Na₂SO₄). Then a solution of 3-chloroperbenzoic acid (3.97 g, 23 mmol) in CH₂Cl₂ (100 ml) was added. The mixture was stirred for 2 h at 20 °C, extracted NaHCO₃ and NaHSO₃ solution, the organic layer was dried (Na₂SO₄) and the solvent was removed at reduced pressure. Crystallization of the residue from ether gave 6x (7.28 g, 68%, mp. 171 °C).¹³
- 10. Lipshutz, B. H.; Koerner, M.; Parker, D. A. Tetrahedron Lett. 1987, 28, 945-948.
- 11. **Typical procedure:** A stirred solution of lithium 2-thienylcyanocuprate¹⁰ (8 ml, 0.25M in THF, 2 mmol) was cooled to -78 °C and treated dropwise with a solution of methyllithium (1.3 ml, 1.55 M in ether/hexane, 2 mmol). The mixture was stirred at -78 °C for 1 h, then a solution of **6x** (1.07 g, 2 mmol) in THF (15 ml) was added and stirring was continued at -78 °C for 2 h. Then a saturated NH₄Cl solution was added, the mixture was stirred at 20 °C for 1 h and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc = 9:1); recrystallization from 2-propanol yielded **7x** (861 mg, 78%, mp. 175 °C).¹³
- 12. Typical procedure: 7x (1.10 g, 2 mmol) was dissolved in methanol (25 ml) and heated in an autoclave (125 °C, 64 h). Then the solvent was evaporated at reduced pressure and 1x (520 mg, 63%) was recovered by crystallization from methanol. Kugelrohr distillation of the filtrate at 100 °C/0.05 mbar afforded *ent*-14 (210 mg, 62%), colourless oil, $[\alpha]_D^{20} = +0.6$ (c = 1.020, CDCl₃, ketone:enol = 63:37).¹³
- 13. All new compounds gave satisfactory spectroscopic data and elementary analyses which will be published later in a full paper.

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