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EPC Synthesis of 5-Substituted 2-Oxo-cyclopentanecarboxylates via Conjugate Addition of Cuprates to Asymmetric Shielded 2-Oxo-cyclopentenecarboxylates

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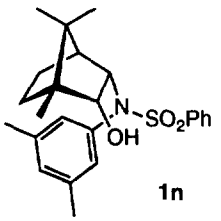
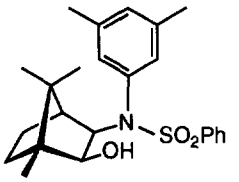
Abstract: Asymmetric shielded 2-oxo-cyclopentenecarboxylates **6n** and **6x** were prepared by transesterification of 2-oxo-cyclopentanecarboxylate **2** with camphor derived concave alcohols **1n** and **1x** and by subsequent introduction of a double bond via phenylselenides. Diastereoselective conjugate addition of equimolar amounts of mixed cuprates at –78 °C and deprotection by ethanolysis gave enantiomerically pure 5-substituted 2-oxo-cyclopentanecarboxylates **13-18** and ***ent*-13-18**, valuable as chiral building blocks in natural product synthesis.

Conjugate additions of cuprates to enoates have been widely employed for asymmetric carbon-carbon-bond formations in syntheses of chiral building blocks.[1] Particularly successful was the conjugate addition of organocopper compounds to enoates of camphor derived chiral auxiliaries.[1-3] Best results were obtained on additions to enoates derived from concave alcohols **1n** and **1x**, which generally proceeded with an extremely high diastereoselectivity (>99%) and in excellent yields (>90%).[3] Recently we extended these studies to cyclic enoates and demonstrated the usefulness of asymmetric protected 2-oxo-cyclohexenecarboxylates for the EPC synthesis of 6-substituted 2-oxo-cyclohexanecarboxylates.[4] In conjunction with a project aiming at the EPC synthesis of (–)-chokol A[5] we have investigated conjugate additions to asymmetric protected 2-oxo-cyclopentenecarboxylates derived from **1n** and **1x** and are now able to present an EPC synthesis of 5-substituted 2-oxo-cyclopentanecarboxylates.

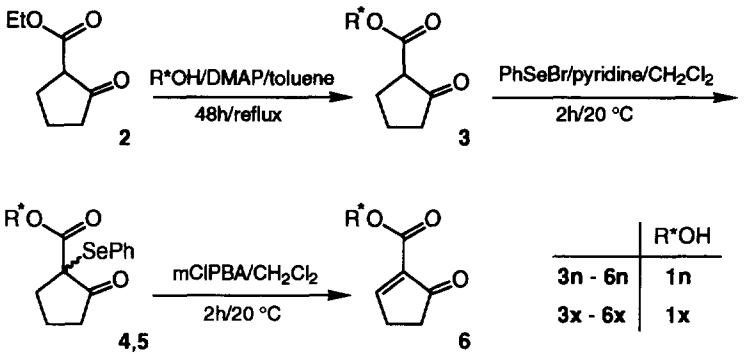


1n



1x

Asymmetric shielded 2-oxo-cyclopentanecarboxylates were readily available from auxiliaries **1n** or **1x** and racemic 2-oxo-cyclopentanecarboxylate **2**. We obtained the well crystallizing esters **3n** (98%) and **3x** (99%) in excellent yields using a DMAP[6] mediated transesterification reaction[7] first reported by Taber.[8] Phenylselenylation[9] of **3n** and **3x** gave mixtures of diastereomeric selenides (**4n**:**5n** = **4x**:**5x** = 80:20) which were separated by chromatography. Oxidative deselenylation of **4n** or **5n** and **4x** or **5x** afforded enoates **6n** and **6x** in good yields (81-90%), respectively.



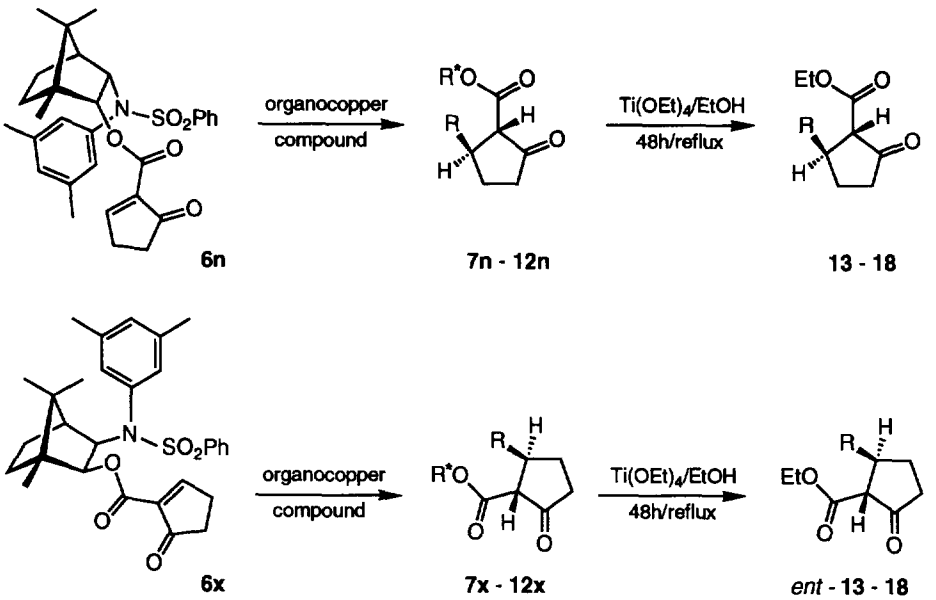
Scheme 1

Preparative scale synthesis of enoates **6n** (75%) and **6x** (78%) was manufactured by a one pot procedure[10] starting from **3n** and **3x** without isolation of the intermediate selenides. In contrast to an anticipation[11] the enoates **6n** and **6x** were stable and could be stored without precautions.

Next we studied the addition of Lipshutz cuprates[12] to **6n** and **6x** (see Table 1) and obtained 5-substituted 2-oxo-cyclopentanecarboxylates **7n-12n** and **7x-12x** in good yields (56-80%)[13,14] and with an extremely high level of diastereoselection. HPLC analysis of unpurified cuprate addition products outlined excellent selectivities (purity of **7x** > 99.5%; **12n** > 98%).[15] Purification of the crude products by flash chromatography and crystallization yielded pure diastereomers according to HPLC and NMR.

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

Enone	R	Cuprate Precursor	Cuprate Adduct	Yield (%)	Ethyl Ester	Yield (%)	$[\alpha]_D^{20}$
6n	CH_3	R-Li	**7n**	73	**13**	76	+94.00
6n	nBu	R-Li	**8n**	80	**14**	88	+81.58
6n	tBu	R-Li	**9n**	59	**15**	93	+94.61
6n	H_2C=CH	R-MgBr	**10n**	68	**16**	82	+85.05
6n	H_2C=C(CH_3)	R-Li	**11n**	63	**17**	81	+69.88
6n	Ph	R-Li	**12n**	56	**18**	79	+18.55
6x	CH_3	R-Li	**7x**	74	*ent*-**13**	75	-95.70
6x	nBu	R-Li	**8x**	69	*ent*-**14**	85	-81.26
6x	tBu	R-Li	**9x**	75	*ent*-**15**	90	-95.69
6x	H_2C=CH	R-MgBr	**10x**	80	*ent*-**16**	82	-85.61
6x	H_2C=C(CH_3)	R-Li	**11x**	75	*ent*-**17**	79	-70.21
6x	Ph	R-Li	**12x**	71	*ent*-**18**	76	-18.30



	R*OH
7n - 12n	1n
7x - 12x	1x

	R
7,13	CH_3
8,14	nBu
9,15	tBu

	R
10,16	H_2C=CH
11,17	H_2C=C-CH_3
12,18	Ph

Scheme 2

Removal of the chiral auxiliary from the sterically highly crowded 2-oxo-cyclopentanecarboxylates **7n-12n** and **7x-12x** was accomplished using a $Ti(OEt)_4$ mediated transesterification reaction[16] which allowed recycling of **1n** and **1x** (78-89%) and gave the enantiomerically pure ethyl esters **13-18** and *ent*-**13-18** in good yields (Table 1). Comparison of the optical rotation of **13**[17] allowed the determination of absolute configuration at C-5', because **13** was previously prepared from (*R*)-pulegone.[18]

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[3] and 2-oxo-cyclohexenecarboxylates.[4]

In conclusion, the present conjugate addition approach to 5-substituted 2-oxo-cyclopentanecarboxylates enable a short and extremely stereoselective route to valuable intermediates in natural product synthesis.

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10. **Typical procedure:** A solution of PhSeBr (4.72 g, 20 mmol) in CH_2Cl_2 (100 ml) was cooled to 0 °C, pyridine (1.61 g, 20.4 mmol) and then a solution of **3n** (10.47 g, 20 mmol) in CH_2Cl_2 were added. The mixture was stirred for 2 h at 20 °C, extracted with 1 M HCl and dried (Na_2SO_4). Then a solution of 3-chloroperbenzoic acid (3.97 g, 23 mmol) in CH_2Cl_2 (100 ml) was added. The mixture was stirred for 2 h at 20 °C, extracted with saturated $NaHCO_3$ and $NaHSO_3$ solution, the organic layer was dried (Na_2SO_4) and the solvent was removed at reduced pressure. Crystallization of the residue from ether gave **6n** (8.14 g, 78%, mp 171 °C).[19]
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13. **Typical procedure:** A stirred solution of lithium 2-thienylcyanocuprate[12] (8 ml, 0.25 M 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 **6n** (1.04 g, 2 mmol) in THF (15 ml) was added and stirring was continued at -78 °C for 2 h. Then a saturated NH_4Cl solution was added, the mixture was stirred at 20 °C for 1 h and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) 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 **7n** (785 mg, 73%, mp 140 °C).[19]
14. ^1H and ^{13}C NMR spectroscopic studies of the keto-enol equilibrium revealed that compounds with a bulky group showed mainly signals of the keto form, while compounds with a planar substituent provided both signals of the keto and the enol form (ratio strongly depending on concentration and choice of the solvent).
15. Diastereomers of **7x** and **12n** with opposite configuration at C-5' have been prepared for HPLC purposes by a sequence which will be published later in a full paper.
16. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982,** 138-141.
17. The optical rotation of **13** ($[\alpha]_D^{25}$ = +68.01 {neat, d_4^{25} = 1.032}) agreed with a previous determination.[18]
18. Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975,** *40,* 1602-1606.
19. All new compounds gave satisfactory spectroscopic data and elementary analyses which will be published later in a full paper.

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