3-Substituted and 2,3-Disubstituted Cyclopentanones via an Asymmetric Tandem 1,4-Addition/Dieckmann Cyclization¹

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Abstract: A new stereoselective method for the synthesis of 3-substituted and 2,3-disubstituted cyclopentanones is described. The key step is the 1,4-addition of a cuprate to a chiral Michael-acceptor derived from (–)-8-phenylmenthol or the Helmchen auxiliary followed by Dieckmann cyclization of the obtained chiral enolates. The resultant 2,3-cyclopentanones can be transformed after methanolysis and demethoxycarbonylation to the related 3-substituted cyclopentanones.

Key words: asymmetric synthesis, cyclopentanones, cuprate, chiral auxiliary, 1,4-addition, Dieckmann cyclization, natural products

2,3-Disubstituted and 2,2',3-trisubstituted cyclopentanones such as jasmonic acid and its related compounds,² chokol A,³ sarkomycin,⁴ dactylol,⁵ confertin,⁶ 11-deoxyprostaglandines⁷ and steroids⁸ are attractive target molecules in organic synthesis due to their biological activity and pharmaceutical importance. Consequently, a number of methods have been applied for the asymmetric construction of cyclopentanones.⁹ Since some conjugate addition/cyclization reactions have been reported¹⁰ in connection with our own studies in steroid synthesis¹¹ we have developed a versatile applicable method for the asymmetric synthesis of 3-substituted-2-carbomethoxy- and 3-substituted-cyclopentanones. We were able to synthesize two different chiral enoates **5a** and **5b**, which allowed the conjugate addition of various organocopper compounds. The intermediates **6** of this addition led via an intramolecular cyclization (Dieckmann cyclization) to 2,3-disubstituted cyclopentanones **7** in good yields and with high diastereoselectivity (Scheme 1). These gave upon methanolysis the enantiopure 2-carbomethoxycyclopentanones **8** (Scheme 2), which can be used as starting materials in the synthesis of natural products containing a cyclopentane moiety.

The (–)-8-phenylmenthol-derived Michael-acceptor **5a** was prepared in a Wittig–Horner reaction from methyl-4-oxo-butanoate **4** and the diethoxy phosphonic ester **3a** in 87% yield; as a by-product the corresponding *cis*-isomer of **5a** was isolated in 4% yield. Compound **4** was obtained in two steps by an improved synthesis according to Saji.¹² Compound **3a** was prepared in a Michael–Arbuzov reaction from the chloroacetate **2a**, an intermediate in the syn-

thesis of (–)-8-phenylmenthol.¹³ The other chiral acceptor **5b** was synthesized in a similar way starting from **1** and alcohol **B** – the Helmchen auxiliary – in 51% yield over 3 steps. While reaction of the organocuprates $\text{RCuLi}\cdot n\text{Bu}_3\text{PBF}_3$, which were prepared according to Oppolzer¹⁴ from MeLi or PhLi, copper(I)iodide, tributyl phosphine and $\text{BF}_3\cdot\text{Et}_2\text{O}$, with **5a** gave the cyclopentanones **7a** and **7b** in goods yields and with high diastereoselectivity, the analogue organocuprate $t\text{-BuCuLi}\cdot n\text{-Bu}_3\text{P}\cdot\text{BF}_3$ generated from $t\text{-BuLi}$ did not react (Table 1, entry 3). We were able to synthesize the cyclopentanone **7c** by changing from copper(I)iodide to copper(I)cyanide.¹⁵ In this case the use of the tributyl phosphine is not necessary, which makes the purification of the synthesized cyclopentanone by column chromatography easier. Next, we studied the reaction of allylcuprates with **5a** by choosing three different cuprate adducts, but unfortunately the 3-allyl-substituted cyclopentanone **7d** could not be obtained. In the course of our synthetic studies towards

Scheme 1

Table 1 1,4-Addition/Dieckmann Cyclization of Cuprates with the Chiral Acceptors¹⁷

Entry	R	5, R*	Cuprate	7 (%)	de (%) ^a
1	CH ₃	A	RCuLi· <i>n</i> -Bu ₃ P·BF ₃	7a (79)	78
2	Ph	A	RCuLi· <i>n</i> -Bu ₃ P·BF ₃	7b (67)	76
3	<i>t</i> -Bu	A	RCuLi· <i>n</i> -Bu ₃ P·BF ₃	—	—
4	<i>t</i> -Bu	A	R ₂ Cu(CN)Li ₂ ·BF ₃	7c (85)	75
5	CH ₂ =CH ₂ CH ₂	A	RCuLi· <i>n</i> -Bu ₃ P·BF ₃	—	—
6	CH ₂ =CH ₂ CH ₂	A	R ₂ CuLi ₂ · <i>n</i> -Bu ₃ P·BF ₃	—	—
7	CH ₂ =CH ₂ CH ₂	A	R ₂ Cu(CN)Li ₂ ·BF ₃	—	—
8	CH ₂ =CH	A	RCuLi· <i>n</i> -Bu ₃ P·BF ₃	—	—
9	CH ₂ =CH	A	R ₂ CuLi ₂ · <i>n</i> -Bu ₃ P·BF ₃	7e (78)	82
10	CH ₂ =CH	B	R ₂ Cu(CN)Li ₂ ·BF ₃	7f (79)	78
11	CH ₂ =CH	B	R ₂ Cu(CN)Li ₂ ·BF ₃ ^b	7f (88)	89
12	CH ₂ =CH	B	R ₂ Cu(CN)Li ₂ ·BF ₃ ^c	7f (78)	89

^a Determined by ¹³C NMR spectroscopy.^b The cuprate was added at –95 °C.^c The cuprate was added at –116 °C.

the sesquiterpenes *chokols* we investigated the synthesis of the 2-carbomethoxy-3-vinyl-cyclopentanone **8e** (Scheme 2, Table 2, entries 4 and 5) starting from the previous using chiral acceptor **5a** and the camphor derivative **5b** by reaction with a vinylcuprate. The Oppolzer organocuprate (CH₂=CH)CuLi·*n*-Bu₃P·BF₃ generated from vinylolithium¹⁶ did not react with **5a**, but the reaction of the cuprate (CH₂=CH)₂CuLi₂·*n*-Bu₃P·BF₃ yielded 78% of the 3-vinyl-β-keto-ester **7e** with 82% de. Similarly, the chiral enoate **5b** derived from the Helmchen auxiliary,^{9b} after reaction with vinylcuprates also gave the vinyl-cyclopentanone **7f** in good yields and with high diastereoselectivity. Indeed, addition of (CH₂=CH)₂Cu(CN)Li₂·BF₃¹⁵ at –85 °C to **5b** afforded **7f** in 79% yield and with 78% de. We also observed that the yield and the diastereomeric excess of **7f** can be increased (88% yield and 89% d.e.) by addition of the cuprate at –95 °C. However, addition at lower temperatures (–116 °C) had no effect on the de, but the yield decreased to 78%.

Methanolysis of the cyclopentanones **7** at 120 °C in a sealed tube afforded the 2-carbomethoxycyclopentanones **8** in 86–95% ee and, in addition, enantiomerically pure (–)-8-phenylmenthol **A** or camphor alcohol **B**, the chiral

auxiliaries, in 83–95% yield. Obviously, the major diastereomers **7** undergo a methanolysis much faster than their C-3 epimers, so that the β-keto esters **8** can be obtained virtually in enantiomerically pure form. As a by-product of the methanolysis an almost 1:1 mixture of **7** and its epimers was obtained in 6–11%. The enantiomeric excess and the absolute configuration of **8a** at C-3 were determined by comparison of its optical rotation with an authentic sample prepared from (*R*)-pulegone.¹⁸ The absolute configuration of **8b**¹⁹ and **8c**²⁰ was determined by comparison of the optical rotation of the prepared 3-substituted-cyclopentanones **9** with the reported value. For the determination of the absolute configuration of **8e** we compared the optical rotation of our 2-carbomethoxy-3-vinylcyclopentanone **8e**¹⁷ with the reported value of the same compound ([α]_D²⁰ = +85.05) synthesized from Helmchen and co-workers.^{9b} The enantiomeric excess of the cyclopentanones **8b–e** and **9b–e** was obtained by determination of the diastereomeric excess of the diastereomeric ketals **10** by analysis of their ¹³C NMR spectra.²¹ These were prepared after demethoxycarbonylation of **8** with DABCO²² (1,4-diazabicyclo[2.2.2]octane) in DMSO and reaction of the obtained cyclopentanones **9** with (2*R*,3*R*)-(–)-2,3-butanediol **11**.

Scheme 2

Table 2 Synthesis of the 3-Substituted Cyclopentanones

Entry	7, R	8 (%)	R*OH (%)	ee (%)	9 (%)	10 (%)
1	7a, CH ₃	8a (84)	A (84)	89	—	—
2	7b, Ph	8b (91)	A (95)	> 95 ^b	76	96
3	7c, <i>t</i> -Bu	8c (60)	A (92)	86	89	84
4	7e, CH ₂ =CH	8e (77)	A (83)	> 95 ^b	85	90
5	7f, CH ₂ =CH ^a	8e (78)	B (86)	> 95 ^b	88	94

^a Table 1, entry 11.^b Only one diastereomer was detected.

In summary, we have developed a new access to substituted cyclopentanones by employing a tandem reaction of cuprates with chiral Michael acceptors via an asymmetric 1,4-addition and a Dieckmann cyclization. The prepared 2,3-substituted cyclopentanones were then transformed into the related enantiopure 2-carbomethoxycyclopentanones and 3-substituted cyclopentanones. The synthesis of cyclopentanoid natural products using this new methodology is currently under investigation.

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- (16) Vinylolithium was prepared via reaction of tetravinyltin with *n*-BuLi.
- (17) **Experimental Procedure:** A solution of 10.0 mmol organolithium compound in Et₂O (10 mL) was added to a solution of 5.0 mmol copper(I) cyanide in Et₂O (10 mL) at -80°C . After 2 h stirring 5.0 mmol BF₃·Et₂O were added and the resultant mixture was cooled at -95°C . A solution of 1.0 mmol chiral enoate **5** in Et₂O (10 mL) was added via cannula and the obtained mixture was allowed to warm under stirring to r.t. (18 h). The reaction mixture was quenched with aq sat. NH₄Cl solution (30 mL), extracted with Et₂O (2 × 20 mL), the combined organic layer dried over MgSO₄ and evaporated in vacuum. Purification of the residue by flash chromatography provided the 2,3-substituted cyclopentanone **7**.

Analytical data of selected compounds (Figure 1).

Compound 7e: R_f 0.41 (Et₂O–petroleum ether, 1:5).

IR(film): 3040 (alkene CH), 1740 (C=O), 1725 (OC=O), 1650 (alkene C=C), 1610 (arom. C=C) cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 0.87 (d, ³*J* = 6.5 Hz, 1 H, H-5'), 1.19 (s, 3 H, CH₃), 1.27 (s, 3 H, CH₃), 0.80–1.84 (m, 7 H, H-1', H-3', H-4', H-6'), 1.88–2.40 (m, 3 H, H-4, H-5, H-2'), 3.46 (d, ³*J* = 11 Hz, 1 H, H-2), 2.83–3.05 (m, 1 H, H-3), 4.81 (ddd, ³*J* = 10.5, 10.5, 4 Hz, 1 H, COOCH, H-1'), 5.09 (ddd, *J*_{cis} = 10 Hz, *J* = 1.5, 1.5 Hz, 1 H, CH=CH₂), 5.125 (ddd, *J*_{trans} = 17 Hz, *J* = 1.5, 1.5 Hz, 1 H, CH=CH₂), 5.745 (ddd, *J*_{trans} = 17 Hz, *J*_{cis} = 10 Hz, *J* = 7 Hz, 1 H, CH=CH₂), 7.06–7.20 (m, 1 H, arom. H), 7.23–7.38 (m, 4 H, arom. H). ¹³C NMR (62.5 MHz, CDCl₃): δ = 21.74 [22.75] (CH₃), 25.68 (CH₃), 26.58 (cyclopentane-CH₂), [26.43] 26.65 (cyclohexane-CH₂), 27.37 [27.51] (CH₃), [29.52] 31.28 (CHCH₃, C-5'), 34.52 [34.68] (cyclohexane-CH₂), 37.79 [38.25] (cyclopentane-CH₂), 39.70 [39.87] (C(CH₃)₂), 41.38 [41.73] (cyclohexane-CH₂), 43.73 [46.20] (CHCH=CH₂, C-3), 49.96 [50.48] (C-2'), 60.90 [62.07] (COCHCO, C-2), 75.96 [76.30] (C-1'), 115.78 [116.24] (CH=CH₂), 124.87 [125.18], 125.45 [125.56], [127.84] 127.97 (3 × C-arom.), 138.62 [140.67] (CH=CH₂), 151.51 (C-arom.), 167.34 [168.13] (COO), 210.22 (CO) (signals of the 2*R*,3*S*-configured diastereomer in brackets). EI-MS (70 eV): *m/z* (100) = 119 [PhC(CH₃)₂] (100), 249 (4) [M⁺ – PhC(CH₃)₂], 368 (2) [M⁺]. Anal. Calcd for C₂₄H₃₂O₃ (368.5): C, 78.22; H, 8.75. Found: C, 78.39; H, 8.85.

Compound 7f (Table 1, entry 11): R_f 0.46 (Et₂O–petroleum ether, 1:1); mp: 59–63 °C. IR(nujol): 3060, 3040 (arom. CH), 1750 (C=O), 1730 (OC=O), 1640 (C=C), 1610, 1595 (arom. C=C), 1350, 1165 (CSO₂N) cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 0.82 (s, 3 H, CH₃), 0.88 (s, 3 H, C-1-CH₃), 1.04 (s, 3 H, CH₃), 0.90–2.45 (m, 9 H, CH, CH₂), 2.02 (s, 3 H, arom. CH₃), 2.32 (s, 3 H, arom. CH₃), 3.33 (d, *J*_{trans} = 11.2 Hz, 1 H, H-2'), 3.34–3.50 (m, 1 H, H-3'), 4.25 (ddd, *J* = 8.8 Hz, *J* = 3.4 Hz, ⁴*J* = 1.0 Hz, 1 H, H-3), 5.11 (ddd, *J*_{cis} = 10.6 Hz, ²*J* = 1.2 Hz, ⁴*J* = 1.2 Hz, 1 H, CH=CH₂), 5.27 (ddd, *J*_{trans} = 17.0 Hz, ²*J* = 1.2 Hz, ⁴*J* = 1.2 Hz, 1 H, CH=CH₂), 5.46 (d, *J* = 8.8 Hz, 1 H, H-2), 5.78 (s, 1 H, arom. H), 5.98 (ddd, *J*_{trans} = 17.0 Hz, *J*_{cis} = 10.6 Hz, *J* = 6.6 Hz, 1 H, CH=CH₂), 6.83 (s, 1 H, arom. H), 7.11 (s, 1 H, arom. H), 7.28–7.57 (m, 5 H, arom. H). ¹³C NMR (62.5 MHz, CDCl₃): δ = 14.30 (C-10), 19.41 (C-8), 19.51 (C-9), 19.69 (C-5), 20.98, 21.29 (2 × arom. CCH₃), 26.59 (C-6), 26.62 (C-4'), 38.13 (C-5'), [35.53] 43.46 (C-3'), 45.71 (C-7), 49.38 (C-4), 51.30 (C-1), 59.35 (C-3), 60.77 [63.27] (C-2'), 77.59 (C-2),

115.38 (CH=CH₂), 127.49, 128.12, 129.33, 129.89, 132.46 (arom. C), 138.64 (CH=CH₂), 136.98, 137.05, 138.16, 139.04 (arom. C), 167.88 (CHCOO), 210.70 [212.35] (C=O) (signals of the 2*R*,3*S*-configured diastereomer in brackets). EI-MS (70 eV): *m/z* (%) = 549 (3) [M⁺], 395 (11) [M⁺ – C₈H₁₀O₃], 254 (100) [M⁺ – C₈H₁₀O₃ – SO₂C₆H₅], 105 (22) [C₈H₉⁺]. Anal. Calcd for C₃₂H₃₉O₃NS (549.7): C, 69.92; H, 7.15. Found: C, 69.87; H, 7.28.

Compound 8e (Table 2, entry 5): R_f 0.31 (Et₂O–petroleum ether, 1:2). [α]_D²⁰ +82.3 (c 1.5, CHCl₃). Bp. 65–70 °C (2 torr). IR(film): 3065 (alkene CH), 1750 (C=O), 1730 (OC=O), 1635 (C=C) cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 1.54–1.86 (m, 1 H, CH), 2.16–2.60 (m, 3 H, CH, CH₂), 3.03 (dd, ³*J* = 11.6 Hz, ⁴*J* = 0.6 Hz, 1 H, C-2-H), 3.14–3.29 (m, 1 H, C-3-H), 3.76 (s, 3 H, OCH₃), 5.10 (ddd, ³*J*_{cis} = 10.0 Hz, ²*J* = 1.2 Hz, ⁴*J* = 1.2 Hz, 1 H, CH=CH₂), 5.17 (ddd, ³*J*_{trans} = 17.0 Hz, ²*J* = 1.2 Hz, ⁴*J* = 1.2 Hz, 1 H, CH=CH₂), 5.84 (ddd, ³*J*_{trans} = 17.0 Hz, ³*J*_{cis} = 10.0 Hz, ³*J* = 6.6 Hz, 1 H, CH=CH₂). ¹³C NMR (62.5 MHz, CDCl₃): δ = 27.25 (C-4), 38.12 (C-5), 44.83 (C-3), 52.48 (OCH₃), 60.77 (C-2), 115.95 (CH=CH₂), 135.95 (CH=CH₂), 169.10 (COOCH₃), 210.71 (C-1). EI-MS (70 eV): *m/z* (%) = 168 (86) [M⁺], 137 (85) [M⁺ – OCH₃], 109 (90) [M⁺ – COOCH₃], 81 (100) [M⁺ – C₂H₃O₂ – C₂H₃ – H]. HRMS: *m/z* calcd for C₉H₁₂O₃ (168.2): 168.0786; found: 168.0786.

Compound 10e (Table 2, entry 5): R_f 0.41 (Et₂O–petroleum ether, 1:10). [α]_D²⁰ +3.3 (c 1.4, CHCl₃). IR(film): 3065 (alkene CH), 1635 (C=C) cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 1.21–1.27 (m, 6 H, CH₃), 1.31–2.08 (m, 6 H, CH₂), 2.46–2.74 (m, 1 H, CHCH=CH₂), 3.47–3.66 (m, 2 H, OCH), 4.91 (ddd, ³*J*_{cis} = 10.0 Hz, ²*J* = 1.5 Hz, ⁴*J* = 1.5 Hz, 1 H, CH=CH₂), 5.00 (ddd, ³*J*_{trans} = 17.2 Hz, ²*J* = 1.5 Hz, ⁴*J* = 1.5 Hz, 1 H, CH=CH₂), 5.79 (ddd, ³*J*_{trans} = 17.2 Hz, ³*J*_{cis} = 10.0 Hz, ³*J* = 7.2 Hz, 1 H, CH=CH₂). ¹³C NMR (62.5 MHz, CDCl₃): δ = 16.86 (CH₃), 16.95 (CH₃), 30.57, 37.98 (CH₂), 42.16 (C-7), 44.43 (CH₂), 78.21 (CHCH₃), 78.26 (CHCH₃), 113.07 (CH=CH₂), 116.84 (OCO), 141.98 (CH=CH₂). EI-MS (70 eV): *m/z* (%) = 182 (3) [M⁺], 114 (100) [C₆H₁₀O₂⁺], 54 (26) [C₄H₈⁺]. Anal. Calcd for C₁₁H₁₈O₂ (182.3): C, 72.49; H, 9.95. Found: C, 72.36; H, 9.84.

Figure 1

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