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Enantioselective Conjugate Addition Greatly Improves the Synthesis of (+)-Confertin

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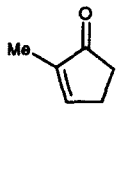
Key Words: enantioselective conjugate addition; chiral ligand-modified organocuprates; total synthesis of (+)-confertin

Abstract: *The five-membered ring building blocks* **2**+**3** *are enantioselectively produced by conjugate addition of a chiral ligand-modified organocuprate to 2-methylcyclopent-2-enone* (**1**) *(chemical yield: 88%; e.e.: 88%) and successfully converted in a multi-step sequence, after final enantioselection by recrystallization of an appropriate intermediate, into the pseudoguaianolide (+)-confertin* (**5**).

In spite of exceedingly high activity in the area of enantioselective conjugate addition to enones[1], the triumphs are few. This is especially true for cyclopentenone(s) and/or unsaturated organocuprates. Cu(I)-mediated 1,4-addition[2] of an isopropenyl Grignard reagent to the cyclopentenone **1** affords a mixture of *rac*-**2**+*rac*-**3** (96:4 after equilibration; 89% yield)[3]. The enantioselective version of this chirogenic[4] reaction step would lead to (**2**+**3**)/(*ent*-**2**+*ent*-**3**) $\neq$ 1. We now report a 88% conversion of **1** into (**2**+**3**)/(*ent*-**2**+*ent*-**3**) = 94:6, using an organocuprate produced when copper(I)thiocyanate is combined with two equiv. each of isopropenyllithium and (*S*)-2-(ethoxymethyl)pyrrolidine (**4c**) in ether[6]. Structurally related pyrrolidine derivatives as chiral, non-transferable ligands were less efficacious (see table 1).

The five-membered ring building blocks (**2**+**3**)[9] have already been utilized in a total synthesis of (+)-confertin (**5**)[3]. They were accessible, however, by a rather lengthy route making use of a stereospecific ring extension of a three-membered ring compound prepared by diastereoselective *Linstead* cyclopropanation. The mixture of (**2**+**3**)/(*ent*-**2**+*ent*-**3**) = 94:6, mentioned above, would be a promising starting material, provided the undesired enantiomer of a successive product can be simply removed by recrystallization at an appropriate stage[10] of the total synthesis, and nonlinear effects or kinetic separation changing the composition of intermediates can be ruled out[11]. Details of the scheme actually reveal that this comes true and indicate in which way the target compound **5** has been synthesized again, this time by a much shorter route[14,15].



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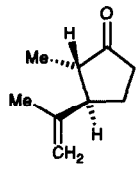

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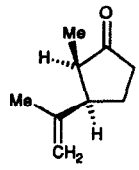

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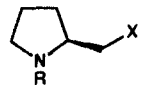
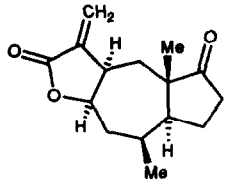


4 **a**: R = H; X = OH
b: R = H; X = OMe
c: R = H; X = OEt
d: R = H; X = OPr
e: R = H; X = $O(CH_2)_2OMe$
f: R = H; X = SMe
g: R = Me; X = OH
h: R = Me; X = OMe



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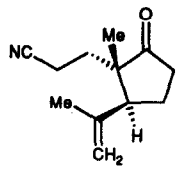

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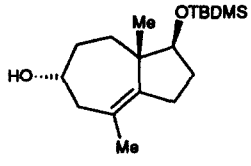

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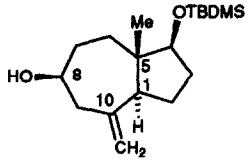

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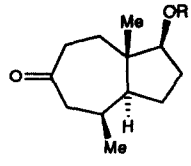
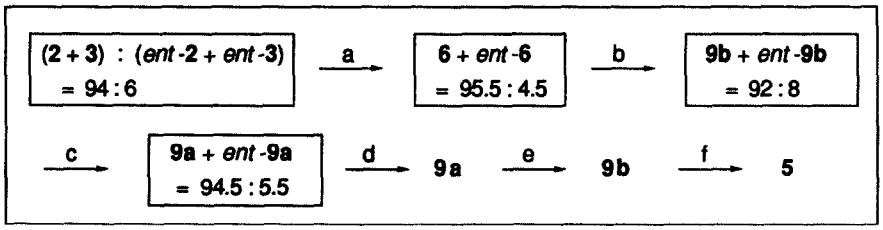


9 **a**: R = H
b: R = TBDMS



a: NaOMe, Et_2O, H_2C=CHCN, rt, 2h, 66%. b: 1. $NaBH_4$, MeOH, rt, 2h, quant. yield; - 2. TBDMSCl, imidazole, DMF, rt, 14h, 97 %; - 3. DIBAH, hexane, -60°C to rt, 4h; Me_2AlCl, CH_2Cl_2, 0°C, 1h, 57 %; - 4. CrO_3, Py, CH_2Cl_2, rt, 2h; H_2, 5 % Rh / Al_2O_3, EtOAc + 3 % AcOH, rt, 48h; CrO_3, Py, CH_2Cl_2, rt, 2.5h, HPLC, 35 %. c: TBAF, THF, 4h, rt, quant. yield. d: crystallization Et_2O / *n* - pentane, 71 %. e: TBDMSCl, imidazole, DMF; rt, 14.5h, quant. yield. f: 1. $LiN(TMS)_2$, THF, -80°C; then HMPT, $BrCH_2CO_2Et$, - 80°C to - 20°C, 100 min, quant. yield; - 2: KOH, MeOH, reflux, 1h; 70 % aq $HClO_4$, EtOAc, Ac_2O, 5 °C, 1h; H_2, 5 % Rh / Al_2O_3, EtOAc, 55 %; - 3. aq KOH, MeOH, rt, 19h; TMSCl, Py, CH_2Cl_2, rt, 15h; MMC, DMF, 140°C, 3.5h; Et_2NH, 37 % aq HCHO, 80°C, 30 min; then NaOAc, AcOH, 80°C, 30 min, 40 %; - 4. CrO_3, Py, CH_2Cl_2, rt, 30 min, 94 %.

Table 1. Enantioselective Version of the Chirogenic Isopropenylation of 2-Methylcyclopent-2-enone (1).

Ligand	4a	4b	4b	4b	4b	4c	4d	4e	4e	4f	4g	4h	4h
CuX[1)]	A	B	B	B	A	A	A	B	A	B	B	B	A
Yield (%)	0	76	60[2)]	66[3)]	81	88	69	22	12	62	0	74	12
$(\alpha)_D^{20}$	-	98.8	81.1	98.8	106.9	117.8	110.4	7.0	52.2	13.5	-	7.8	4.3
Opt. Purity (%)	-	75	61	75	81	89[4)]	83	5	39	10	-	6	3

1) A = CuSCN, B = CuI; 2) in 50 ml ether; 3) in 250 ml ether; 4) The enantiomeric excess according to footnote 7 is equal to 88%.

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2. J.A. Kozlowski in *Comprehensive Organic Synthesis* (Ed. B.M. Trost), Vol. 4, p. 169; Pergamon Press, Oxford 1991.
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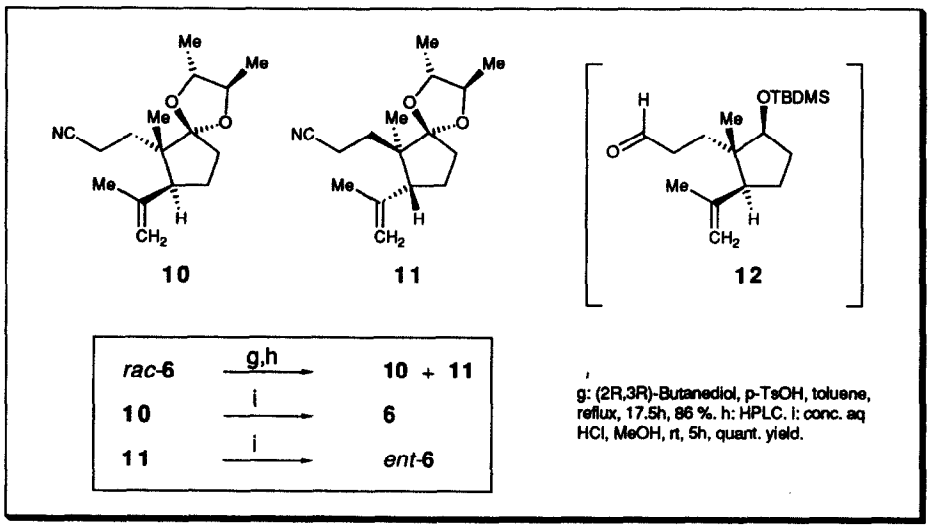
4. This term has been coined and used by A. Eschenmoser[5].
5. S. Drenkard, J. Ferris, A. Eschenmoser, *Helv. Chim. Acta* **1990**, *73*, 1373-1389.
6. Reproducible results were obtained according to the following protocol: Under a nitrogen atmosphere, cuprous thiocyanate (2.76 g, 22.5 mmol), powdered 4Å molecular sieves (3g), and anhydrous diethyl ether (375 ml) are placed in a 500-ml septum-sealed Schlenk vessel equipped with a magnetic stirring bar, and cooled to -45°C. First 29.4 ml (42 mmol) of isopropenyllithium in n-hexane is added by syringe, and the mixture is stirred for 1 h and allowed to warm up to -25°C. Then the mixture is cooled to -60°C and **4c** (5.67 ml, 45 mmol) in 45 ml of anhydrous ether is added by syringe. Stirring is continued for 30 min while the temperature goes up to -50°C. Finally ketone **1** (735 µl, 7.5 mmol) within 5 min is added by syringe at -100°C and the resulting mixture after stirring for 3 h at that temperature is poured into 80 ml of ice water saturated with ammonium chloride, and 100 ml of ether. After stirring for 15 min the mixture is filtered through Celite. The aqueous layer is separated and washed with 100 ml of ether. The combined organic layers are extracted successively with 50 ml each of 2N HCl, saturated aqueous solutions of sodium hydrogencarbonate and sodium chloride. After drying over magnesium sulfate the solvent is removed at a temperature less than 30°C using a rotatory evaporator and the residue is distilled using a Kugelrohr oven at 80°C (0.1 torr) to give 910mg (88%) of product (**2** + **3**):(*ent*-**2** + *ent*-**3**) = 94:6[7,8].

7. The polarimetrically determined optical purity amounts to 89%, the enantiomeric excess (*e.e.*) determined for **3**:*ent*-**3** by use of gas-liquid chromatography (on FS-CYCLODEX beta-1/P, CS-Chromatographie GmbH) is equal to 88%.
8. The chiral, non-racemic ligand **4c** can be reisolated in 80% yield.
9. Both diastereoisomers give one and the same thermodynamically favoured enolate anion.
10. Bicyclic ketone **9a**, but not its derivative **9b**, was accessible from enantiomerically enriched mixtures by recrystallization.
11. There is no denying the fact that an enantiomerically enriched building block has to be converted into the enantiomerically pure target compound, before an accomplished total synthesis can be claimed: non-linear effects[12] or kinetic separation may change enantiomer composition. In order to find out whether this takes place, enantiomerically pure reference compounds were prepared after resolution of **6** and *ent*-**6** mediated by formation and separation of the diastereoisomers **10** and **11**. As a matter of fact, cyclization of the *in situ*-formed aldehyde **12** afforded **7** and **8** without shift in enantiomer composition only under special condition[13].



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13. For details: A. Königer, Dissertation, Frankfurt am Main 1992.
14. Satisfactory spectroscopic and elemental analysis data were obtained using homogeneous samples purified by chromatography or crystallization.
15. The work reported here was generously supported by the Deutsche Forschungsgemeinschaft (Project Qu 15/21), the Fonds der Chemischen Industrie, the Bundesminister für Forschung und Technologie (Project 0318801B), the Bundesminister für Wirtschaft (Project AIF Nr. 7882), and Hoechst AG.

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