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SYNTHESIS OF HIGHLY SUBSTITUTED, DIASTEREOMERICALLY AND ENANTIOMERICALLY PURE 3-ACYL-TETRAHYDROFURANS FROM 4-HYDROXY-1-ALKENYL-CARBAMATES

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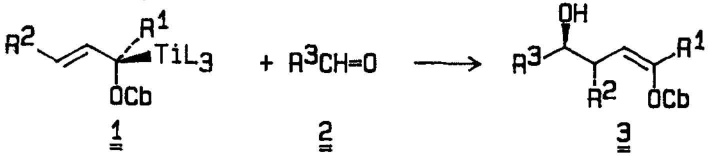
Abstract. The boron trifluoride promoted condensation of (Z)-anti-4-hydroxy-1-alkenyl carbamates and aldehydes (or ketones) yields the title compounds with high twofold diastereofacial selectivity. In all, a new flexible strategy is offered for the construction of cis,trans,trans substituted tetrahydrofurans by coupling allylic carbamates and two (different) aldehydes with only two synthetic steps.

Tetrahydrofuran units are the main structural features of polyether antibiotics; numerous approaches have been worked out for their synthesis.[1] For 3-acyl-tetrahydrofurans, intramolecular cationic cyclizations of acetals derived from 4-hydroxy-1-enol ethers or 3-alken-1,2-diols have been applied by Frauenrath,[2] Overman,[3] and by Linderman,[4] respectively.

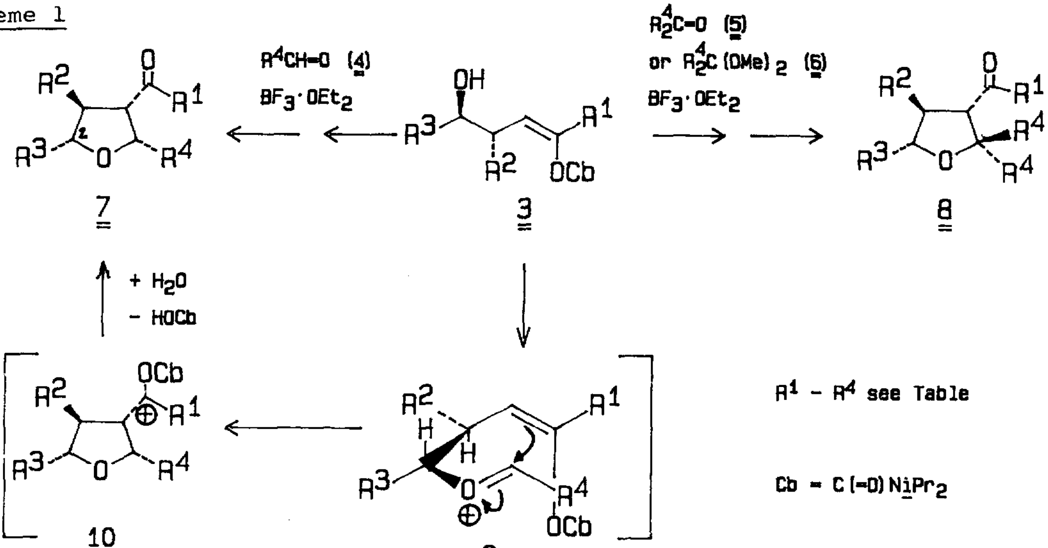
We now report on a very flexible method which utilizes (Z)-anti-4-hydroxy-1-alkenyl carbamates[5,6] **3** as enol equivalents. These masked homoaldols - stable under basic and acidic conditions - are obtained diastereomerically pure by addition of α-titanated (E)-2-alkenyl carbamates **1** to aldehydes **2** with high yield. Enantiomerically pure[7a,c] or enriched[7b,d] compounds **3** are also easily accessible by these methods.



On stirring **3** with an aldehyde **4** in the presence of 1.1 equiv. boron trifluoride etherate (CH_2Cl_2, 0 °C)[8] a condensation takes place with the formation of virtually one diastereomer **7**.[9] Analogously, penta-substituted tetrahydrofurans **8** are yielded by the use of ketones **5** or their dimethyl ketals **6** (Scheme 1 and Table 1).

The cis,trans,trans configuration of tetrahydrofurans **7** was established by an X-ray crystal structure analysis of the alcohol **11**[10] (Fig. 1), obtained by cleavage of the benzyl ether **7c** with hydrogen/Pd(0); yield 86%, mp 57 °C (ether/hexane).

Scheme 1



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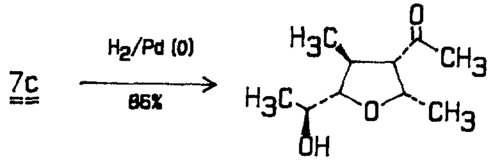


11

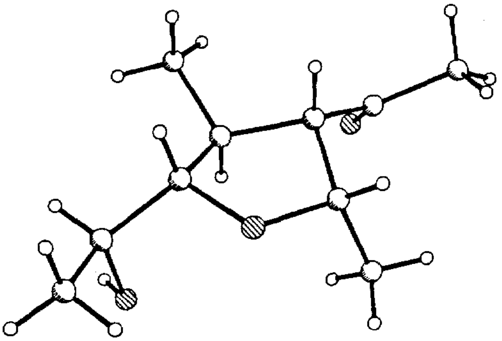


Fig. 1: Structure of **11** in the crystal (O atoms fully shaded)

The high double diastereofacial selection can be explained from the intermediate (*E*)-carbenium ion **9**, formed from the alcohol **3** and the aldehyde **4** by the action of boron trifluoride. For the ring-forming step, it is expected to occupy the least hindered transition state conformation, thus avoiding a pseudo-axial position of R^3. The carbamoyl group in the moderately stabilized intermediate **10** is removed either by fluoride or by hydrolysis during aqueous work-up.

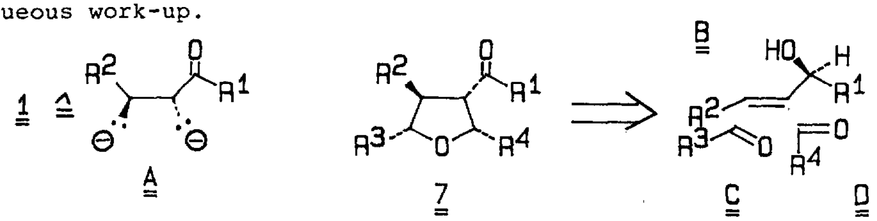
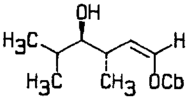
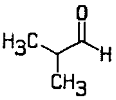
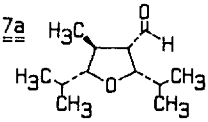
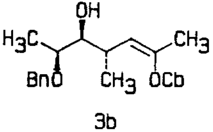
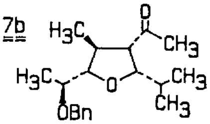
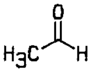
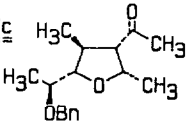
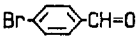
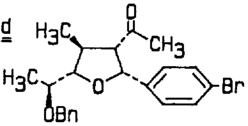
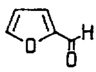
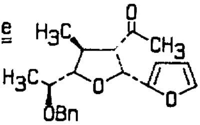
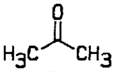
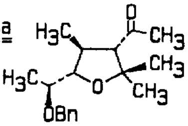
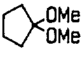
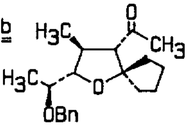
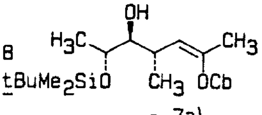
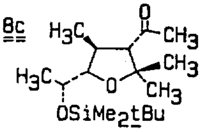
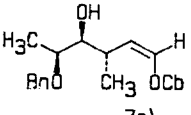
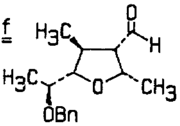


Table 1: 3-Acyl-tetrahydrofurans 7 and 8 Prepared [a]

Entry	Starting materials			Product [b]	Yield (%)	$[\alpha]_D^{20}$ [c]
1	 3a$^{5)}$ [d]	+	 4a	7a 	91	[d]
2	 3b	+	4a	7b 	80	-14.6
3	3b	+	 4b	7c 	82	-21.2
4	3b	+	 4c	7d 	72	+13.9
5	3b	+	 4d	7e 	49	-6.6
6	3b	+	 5a	8a 	80	+9.3
7	3b	+	 6a	8b 	70	+16.7
8	 3c$^{7a)}$	+	5a	8c 	71	-6.8
9	 3d$^{7c)}$	+	4b	7f 	61	+1.8

[a] Yield after LC purification. Satisfactory microanalyses obtained (C +0.20, H +0.14) with exception of **7a**, **7d**, and **7f**. **7f** was analyzed as alcohol after $NaBH_4$ reduction. [b] Diastereomeric purity >95%. [c] In $CHCl_3$, c = 1.15 - 4.5. [d] Racemate.

Altogether, the metallated (E)-allyl carbamates **1** act as equivalents for chiral ketone α,β dianions **A**. In conclusion, the method provides a versatile modul system for the rapid construction of diastereomerically and (if desired) enantiomerically pure tetrahydrofurans **7** by coupling an allylic alcohol **B** and two aldehydes **C** and **D** with only three synthetic steps.

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REFERENCES AND FOOTNOTES

1. Review: Boivin, T.L.B. Tetrahedron **1987**, 43, 3309-62.
2. Frauenrath, H., Runsink, J. J. Org. Chem. **1987**, 52, 2707-12.
3. Hopkins, M.H., Overman, L.E. J. Am. Chem. Soc. **1987**, 109, 4748-49.
4. Linderman, R.J., Godfrey, A. J. Am. Chem. Soc. **1988**, 110, 6249-51.
5. Hanko, R., Hoppe, D. Angew. Chem. **1982**, 94, 378-79; Angew. Chem. Int. Ed. Engl. **1982**, 21, 372-73.
6. Review: Hoppe, D. Angew. Chem. **1984**, 96, 930-46; Angew. Chem. Int. Ed. Engl. **1984**, 23, 932-48.
7. a) Krämer, T., Hoppe, D. Tetrahedron Lett. **1987**, 28, 5149-52. b) Hoppe, D., Krämer, T. Angew. Chem. **1986**, 98, 171-73; Angew. Chem. Int. Ed. Engl. **1986**, 25, 160-62. c) Hoppe, D., Tarara, G., Wilckens, M., Jones, P.G., Stezowski, J.J, ibid **1987**, 99, 1079-81; **1987**, 26, 1034-36. d) Hoppe, D., Zschage, O. Angew. Chem. **1989**, 102, in press.
8. Typical procedure: To a solution of **3** (0.65 mmol) and **4b** (0.72 mmol, 1.1 equiv.) in 2 mL CH_2Cl_2 at 0 °C, $BF_3 \cdot OEt_2$ (0.72 mmol, 1.1 equiv.) is introduced through a syringe within 1 min and stirring is continued for 30 min at 0 °C. Aqueous work-up and LC on silica gel (ether/pentane, 1:4) affords a single diastereomer **7c**.
   7c: 300 MHz-^{1}H-NMR (δ, $CDCl_3$) : 0.98 (d, 3-CH_3), 1.09 (d, 5-CH_3), 1.24 (d, $C\underline{H}_3CH$), 2.15 (d, $C\underline{H}_3C{=}O$), 2.54 (ddq, 3-H), 2.92 (ddq, 4-H), 3.47 (dd, 2-H), 3.61 (qd, $C\underline{H}OBn$), 4.37 (dq, 5-H), 4.58 und 4.67 (2 d, $OC\underline{H}_2Ph$), 7.2-7.4 (Ph-H); $J_{2,3}$ = 8.8 Hz, $J_{2,2'}$ = 4.9 Hz, $J_{3,4}$ = 8.4 Hz, $J_{3,3'}$ = 6.6 Hz, $J_{4,5}$ = 8.0 Hz, $J_{4,COCH3}$ = 0.5 Hz, $J_{5,5'}$ = 6.4 Hz, $J_{2',2''}$ = 6.4 Hz, J_{AB} = 12.1 Hz. 75-MHz-^{13}C-NMR (δ, $CDCl_3$): 15.99 (C-3'), 16.97 ($\underline{C}H_3CH$), 18.04 (C-5'), 31.07 ($\underline{C}H_3C{=}O$), 35.81 (C-3), 64.37 (C-4), 71.29 ($O\underline{C}H_2Ph$), 74.46 (C-5), 75.01 ($\underline{C}HOBn$), 88.49 (C-2), 127.24 (Ph-4), 127.59 (Ph-2, Ph-6), 128.11 (Ph-3, Ph-5), 138.84 (Ph-1), 206.84 (C=O).
9. Determined by ^{1}H and ^{13}C NMR and by capillary gas chromatography.
10. Crystal structure analysis of **11** ($C_{10}H_{18}O_3$): space group $P2_12_12_1$, a = 720.9(1), b = 742.0(1), c = 1957.2(7) pm, V = 1.047 nm^3, Z = 4; crystal dimensions: 0.7·0.7·0.6 mm^3, 1676 measured intensities, $2\theta_{max.}$ = 45° (Mo-Kα), T = 190 K; structure solved by direct methods (SHELXS-86), 1327 symmetry-independent reflections with $|F| > 4\sigma(F)$ used for anisotropic refinement (136 parameters), H atoms located by difference electron-density calculation and refinement with a riding model (r_{O-H} restrained), final R = 0.025 [$R_w = 0.035$, $w^{-1} = \sigma(F)^2 + 2\cdot10^{-4} F^2$]; crystal packing stabilized by intermolecular hydrogen bonds O-H...O=C. All relevant crystallographic data have been deposited with the Cambridge Crystallographic Database via the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2 (CSD-53605).

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