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HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF DI- AND TRISUBSTITUTED 4-BUTANOLIDES FROM ALDEHYDES AND KETONES VIA THREE-CARBON-EXTENSION BY ALLYLIC HOMOENOLATE REAGENTS

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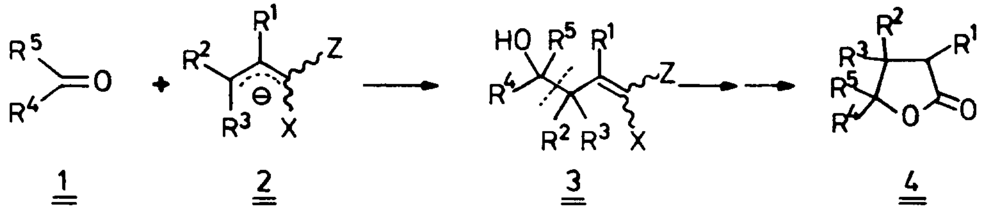
Summary: *Lithiated or titanated O-allyl carbamates* ***7*** *or* ***8*** *add to aldehydes and ketones regio- and diastereoselectively to yield O-(4-hydroxy-1-alkenyl) carbamates* ***9****, which are converted to γ-lactones* ***12*** *with an one-pot procedure.*

4-Butanolides (γ-lactones) **4** are structural features of numerous natural products and versatile synthetic intermediates[1]. Frequently, three-carbon-extensions of carbonyl compounds by homoenolate equivalents were employed for their synthesis[2-4]:



However, these approaches based on 1-hetero-substituted allyl anions[2,3] **2** suffer from severe limitations

Only anions of type **2**, bearing none or at most one alkyl group R^1 - R^3 are readily accessible by simple deprotonation[2,3,5].

γ-Regioselectivity of carbonyl addition to substituted anions **2** is often poorly controlled.

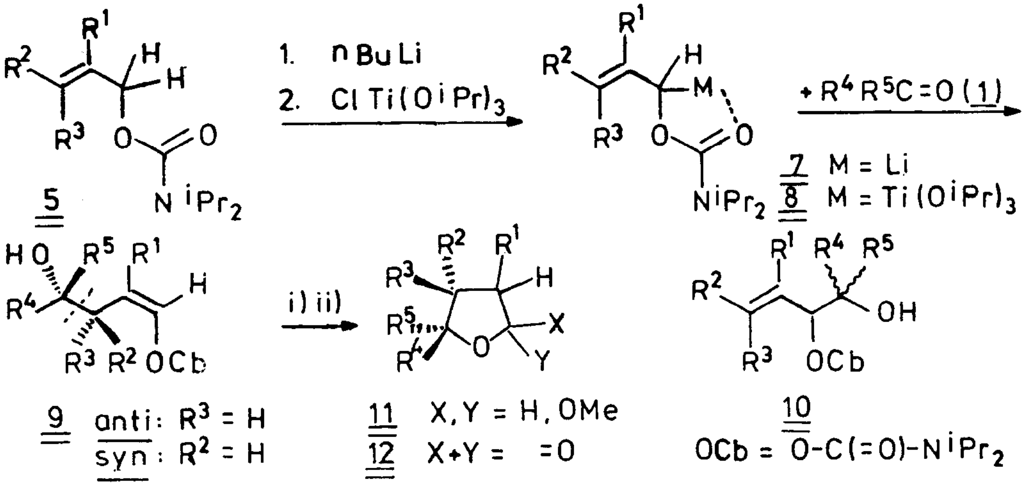
Methods which provide diastereoselective connection of C-3 - C-4 bond in **3** are rare[6-10], of which only one[7b] has been applied for γ-lactone synthesis very recently.

We now report on a flexible approach to γ-lactones via homoaldol reaction[8], utilizing metalated N,N-diisopropyl 2-alkenyl carbamates[8-10] **7** or **8**. Carbamate esters **5** (prepared by heating the appropriate allylic alcohol with N,N-diisopropyl carbamoyl chloride in pyridine[8]) are lithiated by n-butyllithium at -78 °C to give etheral solutions of anions **7**, stable at this temperature. Due to the complexing ability of the carbamoyloxy group[11] even di- or trialkylated esters **5** are smoothly deprotonated[8a]. The lithium compounds[12] **7** add to aldehydes **1** to form preferentially 4-hydroxyalkenyl carbamates[8a] **9** eventually accompanied by small amounts of α-adducts **10** (see **9a** and **9d**, table 1). The γ-selectivity observed is contrary to the reaction pattern of most 1-oxyallyl metal species, where α-addition predominates[13].

After exchange of the counter ion in **7** for titanium[14] by chloro tri(isopropoxy)titanium[14] (**6**), the intermediates **8b** or **8d** add to aldehydes or to acetophenone (**1d**) with high *lk*-diastereoselectivity[15] to form *anti*-adducts **9** with greater than 96 % *ds* (see table 1).

For conversion to γ-lactones **12**, carbamates **9** were methanolized [methanesulfonic acid (1.00 equiv.)/ mercuric acetate (0.01 equiv.)] to yield crude lactol methyl esters **11**, which were oxidized by the Grieco procedure[16] (m-chloroperbenzoic acid/boron trifluoride etherate); see table 1. Direct transformation of **9** to 12 by a modified Wacker oxidation[17] (Pd_2Cl_4, CuCl, CH_3SO_3H, O_2) proofed less effective.

Racemic Quercus lactone A[18] (**12b**), a constituent of oak wood, was prepared from **5b** by this two-step procedure in 87 % overall yield.



5,7,8	a	b	c	d	1	a	b	c	d
R^1	H	H	H	$-(CH_2)_3-$	R^4	n-C_4H_9	$(CH_3)_2CH$	C_6H_5	C_6H_5
R^2	H	CH_3	CH_3		R^5	H	H	H	CH_3
R^3	H	H	CH_3	H					

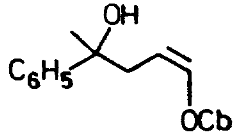
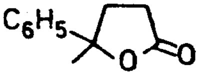
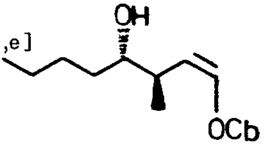
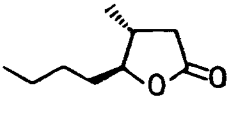
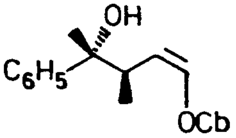
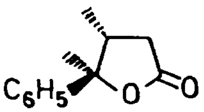
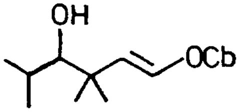
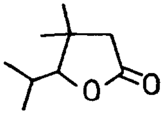
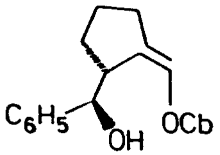
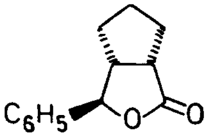
9 – 12: see table 1

i) CH_3OH, CH_3SO_3H, 1 mol-% $Hg(OAc)_2$. ii) MCPBA, 20 mol-% $BF_3 \cdot OEt_2$

General Procedure: All reactions were carried out with exclusion of air and moisture. For intermediate formation of **8**, chloro tri(isopropoxy)titanium[14] (**6**) (1.10 equiv.) is injected to the etheral solution of lithium compound[12] **7** prior addition of **1** (1.10 equiv.), and the reaction mixture is continued to stirr at -78 °C until decolorization (3 hrs; with **1d** at -30 °C and 4 hrs at 20 °C). The mixture is allowed to warm to -10 °C and is poured to icy-cold 2N hydrochloric acid/ether (50 + 50 ml). Usual work-up followed by flash chromatography (silica gel; ether/ hexanes) affords pure O-(4-hydroxy-1-alkenyl)carbamate **9**.

For conversion to 4-alkanolide **12** carbamate **9** (1.00 mmol) and dry methanol (5 ml) are stirred at 25 °C with methanesulfonic acid (1.00 equiv.) and mercuric acetate[10] or palladium dichloride (0.01 equiv.) for 2 – 4 hrs (3 hrs at 60 °C for **9e**; tlc analysis). The solvent ist evaporated, the crude lactol ether **11** in dry dichloromethane (7 ml) is stirred with m-chloroperbenzoic acid (1.10 equiv.), and boron trifluoride etherate (0.20 equiv.)[16] for 3 hrs at 25 °C (12 hrs for formation of **12e**). Before workup (ether/aqueous sodium bicarbonate), dimethyl sulfide (0.25 equiv.) is added for removal of excess peracid. Lactones **12** are purified by flash chromatography on neutral with ether/hexanes.

Table 1. Synthesis of Enolcarbamates **9** and Butanolides **12**

Educts	Enolcarbamates 9[a]		Yield[b] [%]	*anti/syn* γ / α	Lactones 12[a]		Yield[b] [%]
7a + **1d**	**9a**[c]		80	– (85 : 15[d])		**12a**	90
8b + **1a**	**9b**[c,e]		97 [m]	98 : < 2[f] 97 : < 3[f]		**12b**	90
8b + **1d**	**9c**[c]		75 [m]	97 : < 3[g] 85 : 15		**12c**[h]	91
7c + **1b**	**9d**[i]		87	– 97 : < 3[d]		**12d**	93
8d + **1c**	**9e**[k]		88 [n]	96 : 4[g] 97 : <3[g]		**12e**[l]	67

[a] All compounds gave satisfactory combustion analysis (C,H $\mp$0.3 %). [b] Yields refer to chromatographically homogeneous products. [c] Z-Configuration is deducted from $J_{1,2}$ = 6 - 7 Hz in ^{1}H-nmr spectra ($CDCl_3$). [d] Determined by ^{1}H-nmr. [e] ^{1}H-nmr ($CDCl_3$): δ = 3.43 and 2.75 ppm, $J_{3,4}$ = 3.6 Hz; H-4 and H-3. [f] Determined by capillary gas chromatography. [g] Determined by ^{13}C-nmr. [h] No up-field shift of 3-CH_3 is observed in ^{1}H-nmr (δ = 1.23 ppm) compared to **12d** (1.10 and 1.22 ppm). [i] 5 % Z-**9d** was detected besides E-**9d** ($J_{1,2}$ = 13 Hz) [8a]. [k] ^{1}H-nmr ($CDCl_3$): δ = 4.60 ppm, d, $J_{3,4}$ = 8.5 Hz, H-4. The minor diastereomer (4 %) (δ = 4.91, $J_{3,4}$ = 4.5 Hz) failed to cyclize under standard conditions and was assigned to be syn-E-**9e**. [l] ^{1}H-nmr ($CDCl_3$): δ = 5.10 ppm, d, $J_{4,5}$ = 3.6 Hz, H-4. [m] Same results were obtained with tetra(isopropoxy)titanium instead of **6**. [n] The use of tetra(isopropoxy)titanium resulted in decreased diastereoselectivity.

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