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On the diastereocontrol in the formation of (2*R*,3*S*)-3-(3′-furyl)-1,2-*O*-isopropylidenedioxy-3-pentanol and its (2*R*,3*R*)-diastereomer†

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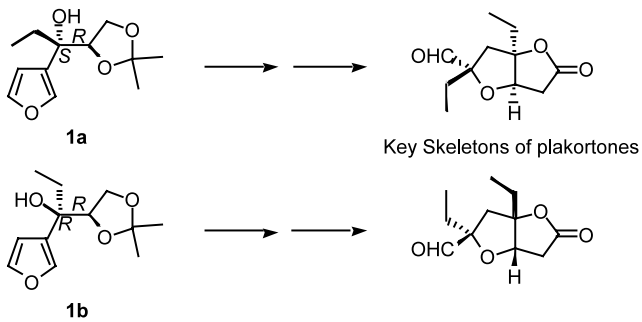
Abstract—The two enantiomeric bicyclic lactone skeletons of the marine natural products plakortones, whose absolute configuration are yet unknown, are approachable from (2*R*,3*S*)-3-(3′-furyl)-1,2-*O*-isopropylidenedioxy-3-pentanol **1a** and its (2*R*,3*R*)-diastereomer **1b**. To obtain these optically pure diastereomers, two pathways were studied, in which different solvents, additives and nucleophilic reagents were employed. The stereochemistry was successfully controlled in the reaction of (2*R*)-1,2-*O*-isopropylidenedioxy-3-pentanone **3** with 3-furyllithium, which gave high *syn*-selectivity in Et_2O, but excellent *anti*-selectivity in toluene.

Plakortones are a class of marine natural products isolated from the sponge *Plakortis halichondriodes* in 1996,[1] and were found to exhibit a unique calcium-pumping effect in *sarcoplasmic reticulum* ATP synthase.[2] In our independent total synthesis[3] of these intriguing molecules whose absolute configuration is as yet unknown,[4] we needed to prepare two enantiomeric precursors starting from (2*R*,3*S*)-3-(3′-furyl)-1,2-*O*-isopropylidenedioxy-3-pentanol **1a** as well as its (2*R*,3*R*)-diastereomer **1b**. The recent reports from Honda[5] and Nakai[6] also prompted us to disclose our own results on the preparation of **1a** and **1b**, employing (2*R*)-3-(3′-furyl)-1,2-*O*-isopropylidenedioxy-3-propanone (**2**)[3a,7] and (2*R*)-1,2-*O*-isopropylidenedioxy-3-pentanone (**3**)[3a,6] as precursors. We report herein our routes towards **1a** and **1b** via a series of reactions involving change of solvents, additives and organometallic nucleophiles that are known[8] to affect the operation of the Cram's chelation model[9] and the Felkin–Anh model.[10]



The ethylation of the known compound **2**[7] under various reaction conditions was first examined and the results are shown in Table 1. As can be seen, entries 1–8 depict the use of several commonly used solvents (THF, Et_2O, C_6H_{14} and C_6H_5Me). All reactions were carried out at −78°C except for entries 7 and 8. The experiments involved the slow addition of a solution of 2–3 equivalents of EtM. The products were obtained after normal work-up procedures. It is noteworthy that the two diastereomeric products were separable chromatographically. From Table 1, all the results demonstrate a preference for the formation of a five-membered chelate transition state,[5,6,9] leading to *anti*-alcohol **1a**, especially for those reactions involving Et_2O (>85% de). Moreover, the change of the reaction temperature did not seem to influence the ratio (entries 6–8). For entries 9, 10 and 12, the trend was not too obvious when $CaCl_2$,

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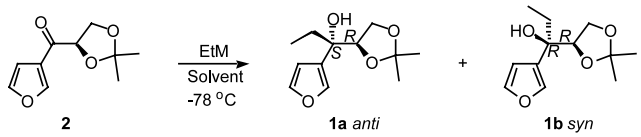
Table 1. Ethylation of (2*R*)-3-(3′-furyl)-1,2-*O*-isopropylidenedioxy-3-propanone (**2**)



2 **1a** *anti* **1b** *syn*

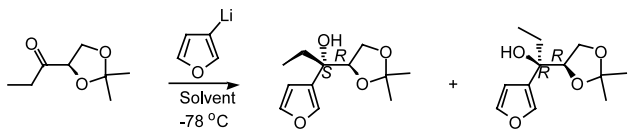
Entry	EtM	Solvent (additive)	Yield (%)	*anti*	*syn*
1	EtMgBr	THF	73	3.5	1
2	EtMgBr	C_6H_{14}:Et_2O = 3:2	70	4	1
3	EtMgBr	C_6H_{14}	68	6.5	1
4	EtMgBr	C_6H_5Me:Et_2O = 3:2	85	5.5	1
5	EtMgBr	C_6H_5Me	82	6.5	1
6	EtMgBr	Et_2O	78	10	1
7[a]	EtMgBr	Et_2O	78	15	1
8[b]	EtMgBr	Et_2O	83	7	1
9	EtMgBr	Et_2O ($CaCl_2$)	75	7.5	1
10	EtMgBr	THF ($ZnCl_2$)	87	1	1.5
11	EtMgBr	Et_2O (TMEDA)	75	39	1
12	EtMgBr	THF (HMPT)	40	1	1
13	EtLi	Et_2O	84	4	1
14	EtCu	Et_2O	74	34	1

[a] Reaction temperature = 0°C.
[b] Reaction temperature = 25°C.

$ZnCl_2$ and HMPT were added. However, the addition of a Lewis base TMEDA led dramatically to an increase of the *anti*-selection to 39:1 (entry 11).[11] This result was unexpected because TMEDA was thought to compete with **2** for lithium chelation.[12] Moreover, addition of a metal salt was also expected to increase the chelation model but the results were unsatisfactory. For entries 13 and 14, EtCu[13] seemed to exhibit the best ability towards the formation of the five-membered chelate, thereby providing excellent *anti*-selection (34:1). The selectivity shown by EtLi was not very pronounced when compared with the use of EtMgBr.

To search for a good diastereocontrol for the formation of **1a** as well as **1b**, we also investigated the nucleophilic addition of a furyl group to ketone **3**.[14] Table 2 illustrates our results involving the use of **3**. It is worthy of note that a procedure involving 3-lithiofuran at –78°C was used because furan-3-magnesium bromide is prone to rearrange to its 2-isomer.[15] For ethereal solvents (entries 1–4), the *syn*-isomer was preferred which again was due to the formation of a five-membered chelate.[5,6,9,14] Ethereal solvents are known to be able to break down the aggregates of organolithium reagents,[16] thus releasing the lithium ion to take part in the chelation. Furthermore, coordination of lithium with the solvent oxygen atom would increase the polarity of the lithium–carbon bond of the organolithium reagent and as a result the energy requirement for reaching the transition state would be lowered.[17] Despite this notion, THF, a strong Lewis base, competed for the chelation with **3** and decreased the selectivity for the *syn*-isomer (entry 4). Hydrocarbon solvents are unable to deaggregate organolithium reagents, neither are they able to polarize the lithium–carbon bond for an effective nucleophilic attack. For these reasons, desirable *anti*-selection was observed in hydrocarbon solvents (entries 5–7).

Table 2. Nucleophilic addition to (2*R*)-1,2-*O*-isopropylidenedioxy-3-pentanone (**3**)



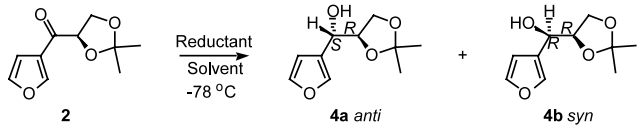
3 **1a** *anti* **1b** *syn*

Entry	Solvent	Yield (%)	*anti*	*syn*
1	Et_2O	83	1	9
2	DME	68	1	2.5
3	$PhCH_2OMe$	49	1	2
4	THF	73	2	1
5	Dioxane:C_6H_{14} = 1:10	92	5.5	1
6	C_6H_{14}	80	7.5	1
7	C_6H_5Me	74	27	1

Reduction of ketone **2** was also investigated employing $LiAlH_4$ and $LiBEt_3H$ (Table 3). Not surprisingly, all reduction reactions favored the formation of the Felkin–Anh product[10] because chelation was not likely, affording the *syn*-isomer[18] as the major product. This outcome is due to the large size of the metal ions, which were unable to form an efficient chelate with **2**. In addition, solvents and addition sequences did not appear to play crucial roles in these reduction reactions.

In conclusion, a change of solvents successfully controlled the diastereomeric ratio for the formation of **1a** and **1b** from ketone **3** when 3-lithiofuran was chosen as the nucleophile. When Cram's chelation model was in operation, *syn*-isomer **1b** was preferentially formed. However, in the cases where chelation was not likely, the size of the attacking furyl ring may render its addition much more selective towards the formation of the Felkin–Anh product **1a**.[19]

Table 3. Reduction of (2*R*)-3-(3′-furyl)-1,2-*O*-isopropylidenedioxy-3-propanone (**2**)



2 **4a** *anti* **4b** *syn*

Entry	Method[a]	Reductant[b]	Solvent	Yield (%)	*anti*	*syn*
1	A	$LiAlH_4$	THF	73	1	25
2	B	$LiAlH_4$	THF	78	1	14
3	A	$LiAlH_4$	Et_2O	66	1	2
4	B	$LiAlH_4$	Et_2O	71	1	4.5
5	A	$LiAlH_4$	DME	43[c]	1	9
6	B	$LiAlH_4$	DME	45[c]	1	12
7	A	$LiBEt_3H$[d]	THF	61[c]	1	23
8	B	$LiBEt_3H$[e]	THF	100	<1	>99
9	A	$LiBEt_3H$	THF	77	1	27
10	B	$LiBEt_3H$	THF	90	1	33
11	A	$LiBEt_3H$	Et_2O	64	1	9.5
12	B	$LiBEt_3H$	Et_2O	57	1	10
13	A	$LiBEt_3H$	C_6H_5Me	78	1	13
14	B	$LiBEt_3H$	C_6H_5Me	76	1	117

[a] Method A: Reductant was added to ketone; method B: ketone was added to reductant.
[b] Entries 1–6: an excess of $LiAlH_4$ was used; entries 9–14: 3 equivalents of $LiBEt_3H$ were used.
[c] Recovered yield.
[d] $LiBEt_3H$:ketone = 1.2:1.
[e] $LiBEt_3H$:ketone = 4.8:1.

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11. To a stirred solution of ketone **2** (97 mg, 0.50 mmol) in Et_2O (2 mL) was added a solution of EtMgBr (3 equiv.) and TMEDA (1.5 equiv.) in Et_2O (3 mL) at −78°C. The mixture was stirred for 30 min and then quenched with a saturated aqueous NH_4Cl solution (3 mL). After extraction with Et_2O (3×10 mL), the organic layer was dried ($MgSO_4$) and removed under reduced pressure. Flash chromatography on silica gel (hexanes–ethyl acetate, 7:1) gave *anti*-alcohol **1a** (82 mg, 73%) as a less polar colorless oil and *syn*-alcohol **1b** (2 mg, 2%) as a more polar colorless oil. Compound **1a**: $[\alpha]_D^{20} = +22.6$ (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (t, $J = 7.5$ Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.69 (m, 1H), 1.93 (m, 1H), 2.06 (s, 1H), 3.69 (t, $J = 7.5$ Hz, 1H), 3.78 (t, $J = 7.5$ Hz, 1H), 4.19 (t, $J = 7.1$ Hz, 1H), 6.24 (m, 1H), 7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 7.35, 25.16, 26.22, 32.54, 65.24, 72.94, 80.90, 108.06, 109.71, 126.53, 139.47, 143.06; MS *m*/*z* 226 (M^+); anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.50; H, 7.91. Compound **1b**: $[\alpha]_D^{20} = +16$ (*c* 2.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (d, $J = 7.5$ Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.67 (m, 2H), 2.36 (s, 1H), 3.89 (t, $J = 8$ Hz, 1H), 4.01 (t, $J = 7.3$ Hz, 1H), 4.27 (t, $J = 7.1$ Hz, 1H), 6.33 (m, 1H), 7.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 7.45, 25.34, 26.14, 30.31, 64.77, 73.10, 80.63, 108.94, 109.35, 128.60, 139.87, 142.93; MS *m*/*z* 226 (M^+); anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.99; H, 8.12.
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14. General procedure: To a solution of freshly distilled 3-bromofuran (1.31 g, 8.9 mmol) in anhydrous solvent (10 mL) was added dropwise 1.6 M *n*-BuLi in hexane solution (5.6 mL, 9.0 mmol). The solution was stirred at −78°C for 0.5 h then a ketone **3** (1.1 g, 7.0 mmol) solution in solvent (5 mL) was added slowly. After stirring for a further 0.5 h at −78°C, the reaction was quenched with saturated aqueous NH_4Cl (15 mL). The mixture was extracted with Et_2O (3×20 mL) and dried over $MgSO_4$ and evaporated. The physical and spectroscopic data of both isomers were identical to those of the authentic samples prepared previously.
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