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A three-step and enantioselective synthesis of (−)-(*S*)- or (+)-(*R*)-2-(furan-3-yl)-3,6-dihydro-2*H*-pyrans

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Abstract

Enantiomerically enriched (3-furyl)-2-pyran derivatives, key-intermediates in the synthesis of the pharmacophoric pyranofuranone system of the bioactive natural products manoalide and cacospongionolide B, are easily accessible by a rapid sequence involving a chiral allylation and a ring closing metathesis reaction.

Keywords: furyl-dihydropyranes; asymmetric allylation; ring-closing metathesis.

Recent investigations on structure–activity relationships have confirmed that the pyranofuranone system **3** is the pharmacophoric group[1] of cacospongionolide B (**1**), a sesterterpene isolated from soft sponge *Fasciospongia cavernosa.* Compound **1**, structurally related to manoalide,[2] exhibits a potent anti-inflammatory activity. Furthermore, the pharmacological properties of some synthetic analogs of **1** have been well established.[3,4]

During work devoted to the development of short and efficient syntheses of type **3** compounds we have already designed a synthesis of carbonyl-analogues of compound **2**[5a] (eight steps from acetyl acetic acid).

Previous results[5b,c] having pointed out that 2-(3-furyl)-dihydropyranes **2** could be easily converted into pyranofuranones **3** by a regioselective photo-oxidation (Scheme 1), we came up with the following three-step synthesis of (−)-(*S*)-**2a** and (−)-(*S*)-**2b** which involves, as key-step, a chiral allylation[6] followed by a ring closing metathesis reaction.[7]

Allylation of a 3-furaldehyde using salt-free Brown's reagent provided the desired alcohol **4**[8] in 88% isolated yield (Scheme 2). The enantiomeric ratios were determined by ^{1}H NMR using Eu(hfc)$_3$ and the furyl–proton signals.

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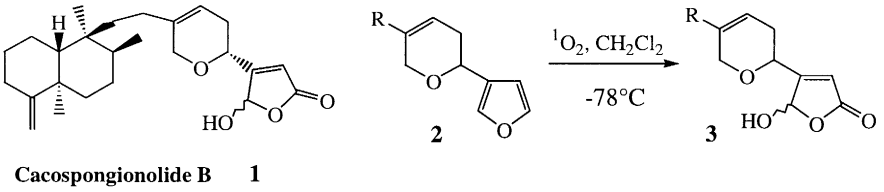
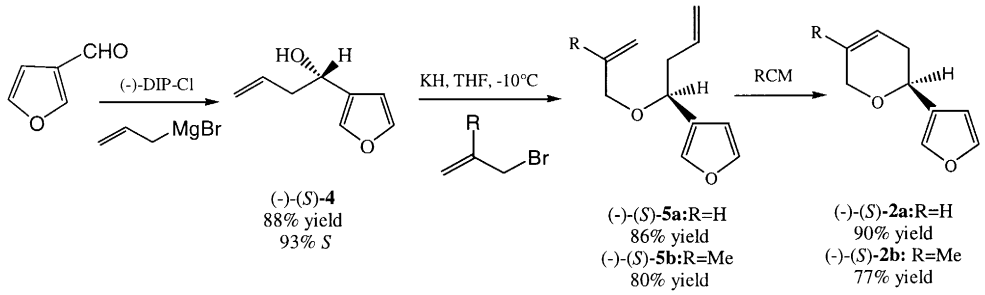


Scheme 1.



Scheme 2.

In accord with literature results, the (−)-alcohol having the *S*-configuration[6] was obtained with allyldiisopinocamphenylborane prepared from (−)-DIP-chloride or (−)-DIP-OMe, while the (+)-(*R*)-alcohol was obtained when the reagent was prepared from (+)-DIP-OMe. However, it is worth noting that the enantiomeric ratios were lower when the reagent was prepared from (−)-DIP-chloride and (−)-DIP-OMe (93:7 and 92:8)[9] than when it was prepared from (+)-DIP-OMe (96:4)[9] which is probably due to the lower enantiomeric purity of the (+)-(*R*)-α-pinene used for the synthesis of (−)-DIP-chloride and (–)-DIP-OMe.

Although non-linear effects[10] might be troublesome, the use of 97% e.e. (+)-α-pinene, now available, should solve this problem.

The desired α,ω-diene (−)-(*S*)-**5a**[11] was prepared in 86% isolated yield by treatment of the potassium alkoxide of (−)-(*S*)-**4** with allyl bromide. The target compound (−)-(*S*)-**2a**[12] was then obtained in 90% yield by using 2% of $Cl_2(PCy_3)RuCHPh$ as catalyst in benzene and at room temperature.

In the same way, (+)-(*R*)-**2a** was obtained in 77% isolated yield from (+)-(*R*)-**4**.

However, the enantioselective synthesis of the 5-methyl derivative **2b**[13] required careful optimization of the experimental conditions for the last step, the RCM reaction is indeed particularly sensitive to steric factors. The results are shown in Table 1. By changing the solvent (CH_2Cl_2 instead of benzene), the temperature (~40°C instead of 20°C) and the percentage of catalyst (8% instead of 2%) it has been possible to increase the yield from 10 to 77%.

As it is reasonable to postulate that no isomerization occurred during the last two steps, the enantiomeric purities of **2a** and **2b** were postulated to be the same as those of the alcohol **4** from which they were derived.

In a typical experiment, allylmagnesium bromide 1 M in Et_2O (10 mmol) was added dropwise to a stirred solution of DIP-OMe (10 mmol) in anhydrous Et_2O (10 mL) at 0°C. After stirring for 1 h at 25°C, Et_2O was evaporated under vacuum and the residue rinsed with pentane (20 mL×2) under N_2 (through a Kramer filter). After evaporation of the pentane under vacuum, anhydrous Et_2O (20 mL) was added to allyldiisopinocamphenylborane free of Mg^{+2} salt and the solution cooled to −100°C. A solution of 3-furaldehyde (10 mmol) in anhydrous Et_2O (10 mL), cooled at about −78°C, was then added dropwise

Table 1
RCM on α,ω-diene **5b** to give **2b**

entry	catalyst (%)	reac.time/h	T/°C	solvent	yield (%)[a]
1	2	24	rt	C_6H_6	10
2	14	120	rt	C_6H_6	10
3	2	48	50	C_6H_6	17
4	2	24	80	C_6H_6	23
5	8	3	refl.	CH_2Cl_2	60
6	**8**	**24**	**refl.**	**CH_2Cl_2**	**77**

[a] Yields were determined on isolated product by chromatography

and the mixture stirred at −100°C for 2 h. After quenching with MeOH and evaporation under vacuum, Et_2O (65 mL) was added again followed by a 3N solution of NaOH in water (16 mL) at 0°C and then 30% aqueous H_2O_2 (10 mL). The organic phase was recovered, joined with Et_2O extractions of the aqueous phase and the final product **4** recovered as usual. After a classical Williamson reaction affording compound **5a** (and/or **5b**), the RCM was conducted in the following way: a solution of **5a** (0.88 mmol) in benzene was added to a homogeneous violet solution of Grubbs' catalyst (0.019 mmol) in benzene (28 ml) under argon. The reaction was prolonged for 4 h at room temperature, and then was quenched by exposure to air. After removal of the solvent, a chromatographic purification afforded pure **2a**.

Therefore (−)-(*S*)-**2a**, (−)-(*S*)-**2b** and (+)-(*R*)-**2a** were obtained in a three-step sequence and in, respectively, 68, 54 and 66% overall yields which are, by far, the highest obtained until now.

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8. Compound (−)-**4**: $[\alpha]_D$=−8 (*c* 1.54, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 2H), 6.41 (s, 1H), 5.82 (ddt, 1H, J=16, 12, 6, 6), 5.15 (bd, 1H, J=12), 5.21 (bd, 1H, J=16), 4.73 (bm, 1H), 2.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.1, 134.9, 125.8, 118.5, 69.1, 40.9. Anal. calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found C, 69.47; H, 7.39.
9. The enantiomeric purities of the different badges of alcohol **4** have been determined by ^{1}H NMR using $Eu(hfc)_3$. The specific rotations are, by far, less precise either being measured from small quantities of compounds (weight <50 mg) or because of non-linear effects.
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11. Compound (−)-**5a**: $[\alpha]_D$=−36 (*c* 1.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.35 (s, 1H), 6.39 (s, 1H), 5.88 (2 superimposed ddt, 2H), 5.24 (bd, 1H, J=18), 5.13 (bd, 1H, J=12), 5.06 (bd, 1H, J=18), 5.03 (bd, 1H, J=12), 4.34 (t,

1H, J=6.5), 3.88 (AB part of an ABX system, 2H, ^{2}J=13, ^{3}J~5, 5, $\Delta\nu_{AB}$=15 Hz), 2.50 (AB part of an ABMX system, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.1, 134.9, 134.5, 125.8, 117.0, 116.8, 108.7, 72.9, 69.1, 40.9. Compound (+)-**5a**: $[\alpha]_D$=+39 (*c* 1.16, $CHCl_3$).

12. Compound (−)-**2a**: $[\alpha]_D$=−63 (*c* 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.39 (s, 1H), 6.43 (s, 1H), 5.87 (AB part of an X_2ABM_2 system with small $^{3}J_{AX}$ and $^{3}J_{BM}$, 2H, $^{3}J_{AB}$=11, $\Delta\nu_{AB}$~15 Hz), 4.57 (dd, 1H, J=3.5, 9), 4.29 (AB part of an ABX system with long-range J, 2H, ^{2}J=13, $\Delta\nu_{AB}$~15 Hz), 2.32 (AB of an ABXM system, 2H, $^{2}J_{AB}$=13, $\Delta\nu_{AB}$~13 Hz). ^{13}C NMR (100MHz, $CDCl_3$) δ 143.2, 139.3, 126.9, 126.4, 123.9, 108.9, 68.5, 65.8, 31.3. Compound (+)-**2a**: $[\alpha]_D$=+64 (*c* 1.10, $CHCl_3$).
13. Compound (−)-**2b**: $[\alpha]_D$=−87 (*c* 1.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.39 (s, 1H), 6.43 (s, 1H), 5.56 (m, 1H), 4.50 (dd, 1H, J=3.5, 10), 4.20 (d, 1H, J=16), 4.07 (d, 1H, J=16), 2.32 (m, 1H), 2.21 (m, 1H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 139.2, 133.1, 126.7, 118.2, 108.9, 69.1, 68.4, 31.2, 18.6. Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found C, 73.06; H, 7.43.