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A general synthesis of (2*Z*)-terpenoic acids

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Abstract

A three-step synthesis of (2*Z*), (4*E*)-polyenic acids **6** is described. Condensation of aldehydes **1** with potassium prenal enolate led to dihydropyranols **3** which were oxidized into dihydropyrones **5**, precursors of (2*Z*), (4*E*)-polyenic acids **6**. The procedure was applied to a synthesis of 13-*cis*-retinoic acids from β-ionylidene acetaldehydes. © 2000 Elsevier Science Ltd. All rights reserved.

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We reported that lithium or potassium prenal enolates **2** react with aldehydes **1** yielding to cyclic adducts **3** by a γ; 1,4-addition and a subsequent intramolecular attack of the alkoxide on the carbonyl group.[1–3] Hydroxydihydropyranes **3** were easily transformed into polyenals **4** with a predominant (2*Z*) (kinetic product)[4] or (2*E*) (thermodynamic product)[1–3] configuration, according to the experimental conditions. In this note, we report a synthesis of (2*Z*), (4*E*)-dienic acids **6** via oxidation of dihydropyranols **3** followed by ring-opening of the resulting dihydropyrones **5** (Scheme 1).

We prepared dihydropyranols **3** by condensation of aldehydes **1** with potassium dienolate **2** easily obtained by reaction of potassium *tert*-butoxide with the trimethylsilyl enol ether of prenal.[2–5]

The oxidation of dihydropyranols **3** was performed using two procedures, either Jones' reagent[6] (CrO_3 in acidic medium, method A) or Corey's reagent[7] (PCC, method B).[8] Finally, dihydropyrones **5** were transformed into (2*Z*), (4*E*)-dienic acids **6** by means of *t*-BuOK according to the procedure described by Cainelli and Cardillo.[9,10] Acids **6a**–**j** were isolated as single stereoisomers as evidenced by NMR analyses. Results are reported in Table 1.

We applied this method to a synthesis of 13-*cis*-retinoic acids **6k** (Scheme 2) used in dermatology and for the treatment of some cancers.[11] As the starting β-ionylidene acetaldehyde **1k** was constituted by (2*E*) and (2*Z*) isomers ((2*E*)/(2*Z*)=70/30), a mixture of 9-*trans*, 13-*cis*- and 9-*cis*, 13-*cis*-retinoic acids **6k** was obtained.[12,13]

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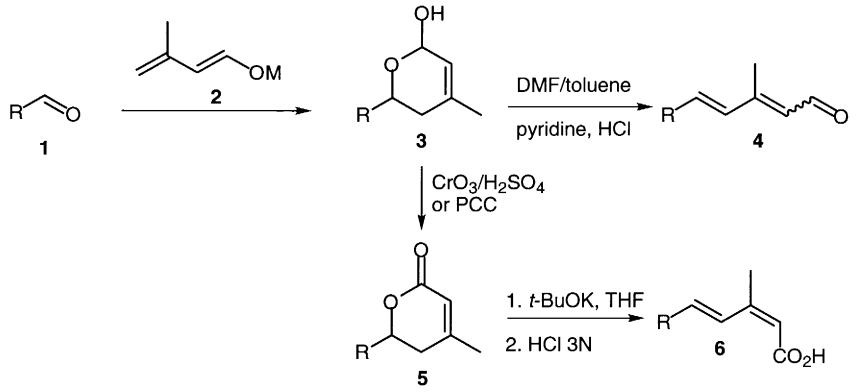
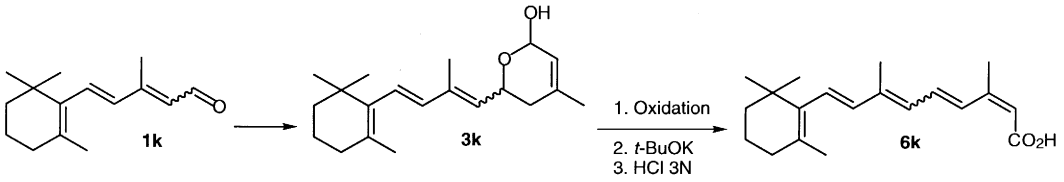


Scheme 1.

Table 1

R	3 yield % (**1** → **3**)	5 yield % (**3** → **5**) (mp°C)			6 yield % (**5** → **6**) (mp°C)	
		A[a]	B[a]			
X = H (a)	86	98	71	(61)[b]	63	(154)[c]
p-Me (b)	65		83	(96-97)	83	(180)
p-F (c)	76		95	(89-91)	50	(160-162)
p-Cl (d)	75	94	90	(85-86)	59	(212-214)
p-Br (e)	76	94	97	(78-79)	51	(172-175)
o-NO_2 (f)	75	94		(106-108)	65	(208-210)
(g)	84	98			71	(195-197)
(h)	86		73		77	(139-140)
(i)	63	90			75	(188-190)
(j)	58	52			79	(208)
(k)	66	90	65	(92)[d]	89[e]	

a) Method A : CrO_3/H_2SO_4/acetone ; Method B : PCC/CH_2Cl_2 or CH_2Cl-CH_2Cl. b) (lit : 60-61°C) ref 14. c) (lit : 153°C) ref 13c. d) (lit : 93.5-95°C) for **5k** obtained from *all trans* **1k**, ref 15 (see text). e) crude oily product.



Scheme 2.

In the literature, dihydropyrones **5** are classically obtained by condensation of aldehydes with lithium or potassium dienolates prepared from senecioic acid and LDA or *t*-BuOK/*n*BuLi[9,13d–f,14] or from lithium enolate of methylsenecioate in controlled conditions[15] or from the zinc derivative of γ-bromosenecioic acid.[16] In some cases, the desired lactones **5** are contaminated by by-products.

In summary, our three-step procedure to (2*Z*)-dienic acids **6** presents the advantages to give good yields, high regio-, and stereoselectivities as well as to use very cheap reagents and mild conditions.

Acknowledgements

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5. Compound **3** was obtained as a single *cis* diastereomer. In the synthesis of **3** from **1** and prenal trimethylsilyl enol ether, it is to be noted that a catalytic quantity of *t*-BuOK can be used.[4]
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8. Method A: To **3** (1.4 mmol) in acetone (5 mL) was added at room temperature a solution of CrO_3 (0.4 g, 4 mmol) in water (3 mL) and concentrated H_2SO_4 (1 mL) until fading. After adding saturated solution of $NaHCO_3$ (25 mL), the mixture was extracted with ether. Method B: A solution of **3** (5 mmol) and PCC (12.5 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 1.5 to 5 h (**3c**–**e**,**k**) or at reflux for 30 min (**3a**,**b**,**h**). After adding 1,2-dichloroethane (100 mL), the mixture was filtered on florisil. Dihydropyrones **5b**,**d** and **j** were chromatographed on silica gel.
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10. To a solution of dihydropyrone **5** (5 mmol) in THF (5 mL) was added potassium *tert*-butoxide (5 mmol) in THF (5 mL) at 0°C. The solution was stirred for 30 min and then diethyl ether (10 mL) and HCl 3N (10 mL) was added. The mixture was extracted with diethyl ether, washed with water and dried over $MgSO_4$. Compounds **6a**,**b** and **h** were purified by crystallization in ethanol, **6c**,**f**,**g** and **j** by washing with pentane, **6d**,**e** and **i** after treatment with a basic then an acidic solution. The (2*Z*) configuration of **6** was established by NOE experiments.
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12. HPLC analysis of **6k** showed three signals (area ratios: 47:46:7). The first and third signals were identified to 9-*trans*, 13-*cis*- and all *trans* retinoic acids (commercial samples). Thus, the second signal was attributed to 9-*cis*, 13-*cis*-retinoic acid. We were unable to determine the 9-*trans*, 13-*cis*/9-*cis*, 13-*cis* ratio by NMR and we do not know the molecular extinction coefficient of the three detected stereoisomers. Moreover, we observed a slight isomerization of commercial 9-*trans*, 13-*cis* acid into the all *trans* isomer in MeOH, solvent used for HPLC analyses.
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