Tetrahedron Letters, Vol. 33, No. 26, pp. 3809-3812, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

The First Asymmetric Synthesis of Polyfunctionalized 4H-Pyrans via Michael Addition of Malononitrile to 2-Acyl Acrylates

Rafael González[a], Nazario Martín[a]*, Carlos Seoane[a]*, José L.Marco[b]*, Armando Albert[c] and Félix H. Cano[c]+

[a]Departamento de Química Orgánica. Facultad de Química. Universidad Complutense. 28040-Madrid. Spain.

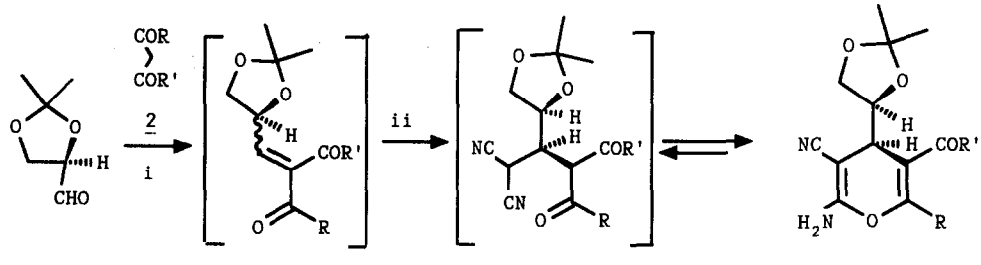
[b]Instituto de Química Orgánica. C.S.I.C. Juan de la Cierva, 3. 28006-Madrid. Spain.

[c]U.E.I. Cristalografía. Instituto " Rocasolano". C.S.I.C. Serrano, 119. 28006-Madrid. Spain.

Abstract: *Starting from (R)-2,3-O-isopropylideneglyceraldehyde, the first asymmetric synthesis of 4H-pyrans (4) has been developed; a detailed X-ray structural and stereochemical study has established as R the absolute configuration at the new stereocenter in compounds 4.*

Polyfunctionalized 4*H*-pyrans are a common structural unit in a number of natural products.[1] Asymmetric synthesis of these type of compounds are scarce and a general approach is still lacking.[2] During the last few years we have developed synthetic methods for the elusive 2-amino-4*H*-pyran ring and studied its ring transformation into pyridine systems related to pharmacologically important calcium antagonists of the DHP type.[3] Now we have embarked in a project directed to the synthesis of enantiomerically pure 4H-pyrans and in this communication we report our first results in this area.

Taking into account that monosaccharides and their derivatives are versatile substrates for the synthesis of optically active target molecules,[4] we have selected (*R*)-2,3-O-isopropylideneglyceraldehyde (**1**) as starting material. This compound is readily available from D-mannitol and



1 **3** **4**

i: Toluene/piperidine; ii: NC-CH_2-CN, EtOH, piperidine.

Scheme

the presence of the free aldehyde functionality is needed in the planned strategy to build the 4*H*-pyran ring. The synthetic route is shown in the Scheme(*R*)-2,3-*O*-Isopropylideneglyceraldehyde (**1**)[5] gave, after condensation with the appropriate β-ketoester (**2**)[6] in toluene-piperidine,[7] the chiral 2-acyl acrylates (**3**). Without further purification, these intermediates were treated with malononitrile following the standard method.[3,7] The desired 4*H*-pyrans [8] were finally obtained after flash chromatography as unseparable mixtures of isomers in good overall yield from **1** (Table); other more polar by-products were detected by t.l.c., but could not be identified. Fortunatelly, recrystallization provided pure major **4b** ($[\alpha]_D^{25}$ +40° (*c* 0.9, $CHCl_3$))and **4c** ($[\alpha]_D^{25}$ +19° (*c* 1.1, $CHCl_3$)) isomers, or in an improved diastereomeric excess (**4a**: 80% see Table); minor isomers remained in the mother liquors and we were not able to isolate them in a pure state. Diastereomeric excesses depend strongly upon the nature of R and OR' and we could not improve them conducting the Michael addition at -78 °C.

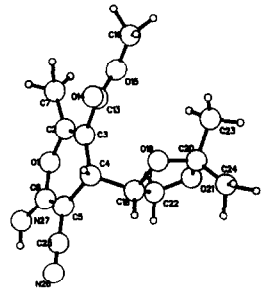
Table

Compound	R	R'	Ratio (R:S)	Yield (%)
4a	Me	OEt	70:30[a] (90:10)[b]	36[c] (25)[d]
4b	Me	OMe	80:20[a] (100:0)[b]	45[c] (35)[d]
4c	Ph	OEt	55:45[a] (100:0)[b]	51[c] (26)[d]

[a] *Determined in crude reaction mixtures by* ^1H *nmr.*
[b] *Determined after chromatography and recrystallization.*
[c] *Overall yield of* **4** *(R+S) from compound* **1** *after chromatography.*
[d] *Overall yield of* **4** *(R) after chromatography and recrystallization.*

In the ^1H nmr spectra of compounds **4**, H(4) appears at 3.6-3.8 ppm, showing characteristic vicinal coupling constants with the contiguous hydrogen (*J*= 3.0-3.6 Hz)

The absolute stereochemistry at the new stereocenter C(4) in major isomers **4** has been assigned as *R* by X-ray analysis of compound **4b**;[9] it has been assumed on the basis of the configuration of compound **1**. From a structural standpoint, the conformation of the pyran ring corresponds to a 1,4-boat. C(4) Is farther above the plane formed by C(2), C(3), C(5) and C(6) than O(1), probably due to the steric hindrance of the acetal ring. In compound **4b** (Figure) the acetal and pyran rings are *cisoid* with respect to the C(4)-C(18) bond. A second X-ray analysis carried out on compound **4c** supports these data.



At this point and in view of the reported racemization of compound **1** under Knoevenagel condensation conditions (pyridine-piperidine, -10 °C),[10] experiments were performed in order to control the optical purity of our substrates. Thus, we have observed that *compound 1 under our reaction conditions*[7] *showed no or very little racemization*[11] {**1**: $[\alpha]_D^{25}$ +51° (*c* 1.6, toluene-piperidine; after 1 h, when the reaction with **2** was completed, **1**: $[\alpha]_D^{25}$ +46° (*c* 1.6, toluene-piperidine)}. Aliquots taken from the reaction **1** + **2**, after 1 h or a more extended period of time (18 h), showed that the optical rotation did not fall to 0°. This discardes also the possibility that compound **3** could be racemized in the medium. In addition, it has been proved[12] that analogous Knoevenagel adducts obtained from aldehyde **1** and monoethyl methylmalonate or α-methylacetoacetic acid are stable enough and racemization was only observed after an extended period of time.

We can conclude that the mild basic Knoevenagel conditions used in this work, besides the high reactivity of the β-ketoesters, prevents any racemization and secures the optical purity of our substrates.

It is important to point out that although the diastereomeric excesses during the Michael addition[13] have been only moderate, to our knowledge this is the first time that chiral 2-acyl acrylates of type **3** have been studied as acceptors.

In conclusion, we have described a general method for the synthesis of enantiomerically pure 4*H*-pyrans from (*R*)-2,3-O-isopropylideneglyceraldehyde by following chemical protocols well established previously in our laboratory in racemic series. Work is in progress to increase the asymmetric induction by using other aldehydes derived from monosaccharides and study their transformations into other carbocyclic and heterocyclic rings. This should eventually lead to a theoretical model on this kind of addition-heterocyclization processes.

Acknowledgments

Support of this work by grants from the Comisión Interministerial de Ciencia y Tecnología of Spain (Grants PB 89-0495, PB 90-0078 and PB 87-0291) is gratefully acknowledged.

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+ To whom correspondence about X-ray analysis should be addressed.

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7. Compounds **4** were obtained as follows: To a solution of compound **1** (4 mmol) recently distilled, cooled in an ice bath and dissolved in toluene (10 mL)-piperidine (4 drops), the β-ketoester (1 equiv.) was added dropwise and the reaction was warmed at room temperature. After 1 h the reaction was completed (t.l.c. analysis). The organic layer was separated, dried, evaporated and the crude residue (**3**) dissolved in ethanol (15 mL) and the malononitrile (1 equiv.) and piperidine (2-3 drops) were added. The reaction mixture was kept with stirring at room temperature for 1 h and then evaporated. The residue was submitted to crhomatography, eluting with hexane/ethyl acetate mixtures. The products were finally recrystallized from *n*-butanol.
8. All new compounds showed correct analytical and spectroscopic data.
9. **Crystal data:** **4b**: $C_{14}H_{18}N_2O_5$, Mr = 294.307, orthorhombic, $P2_12_12_1$, a= 14.107(1) A, b = 13.350(1) A, c = 7.8634(3) A, V = 1480.9(1) A^3, Dc = 1.32 gr/cm^3, Z = 4, F(000) = 624, μ = 8.07 cm^{-1}, refined cell parameters were obtained from setting angles of 65 reflections. Prismatic colorless (0.4x0.37x0.05 mm.) sample was used for the analysis. **4b**: M.p. 180-182 °C (from n-butanol); i.r. (KBr) 3400, 3320, 3200, 2180, 1715, 1680, 1630, 1610, 1405, 1255, 1060 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.30 (s, 3H, $C\underline{H}_3$-C=), 3.60 (d, 1H, J= 3.0 Hz, C_4-H), 3.76 (s, 3H, CH_3O), 3.86-3.91 (dd, 1H, CH_2), 3.96-4.01 (dd, 1H, CH_2), 4.14-4.20 (m, 1H, CH), 4.77 (s, 2H, NH_2); ^{13}C n.m.r. ($CDCl_3$, 75 MHz) δ 18.47 (CH_3), 24.97, 25.90 (2 CH_3), 35.44 (C_4), 51.76 ($CO_2\underline{C}H_3$), 54.90 ($\underline{C}$-CN), 65.88 ($\underline{C}H_2$-CH), 78.23 ($\underline{C}H$-CH_2), 105.59 ($\underline{C}$-CO_2Me), 109.57 ($Me_2\underline{C}$), 119.68 (CN), 159.02 (=$\underline{C}$-CH_3), 160.81 (C-NH_2), 166.64 (CO); *m/z* 294 (M^+,2), 279 (3), 219 (5), 193 (100), 176 (10), 161 (22), 133 (8), 101 (8).
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(Received in UK 7 April 1992)