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Asymmetric Synthesis of 4-Alkyl-3,5-dialkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines

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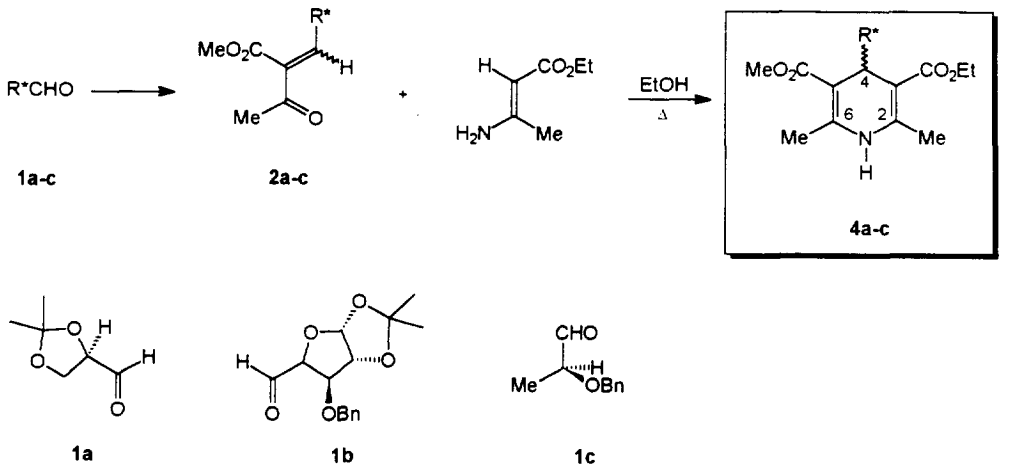
Abstract: The first asymmetric synthesis of some novel substituted 1,4-dihydropyridines (1,4-DHPs) is reported. The synthetic methodology used is based on the Michael addition of β-aminocrotonates to chiral α-acetylacrylates, readily available from chiral aldehydes, leading to the 1,4-DHPs in excellent diastereoselectivity. A Felkin-Ahn model is proposed for the generation of the new stereocenter (C-4) whose absolute configuration has been established as *S* by X-Ray analysis.

4-Arylsubstituted 1,4-dihydropyridines (1,4-DHPs) are well-known compounds used in the treatment of hypertension and other circulatory disorders[1] due to their calcium antagonist effect. The dihydropyridine chemistry has been widely developed[2] and, more recently, much interest has been focused on the effects of chirality on the calcium antagonist or agonist activities[3]. On the other hand, substitution on C-4 of the 1,4-DHP ring has proved to be critical for the pharmacological effect.[4] Thus, replacement of the aromatic moiety required for the calcium antagonist activity by an alkyl chain leads to an interesting platelet antiagregatory activity.[5]

In previous papers we have reported for the first time the asymmetric synthesis of enantiomerically pure polyfunctionalized 2-amino-4*H*-pyrans by following two different stereocontrolled routes[6]. Taking into account that the 4*H*-pyran ring can be considered as the oxa-analogue of the 1,4-dihydropyridine (1,4-DHP) system, in this communication we describe our preliminary results on the application of the synthetic methodology used for the 4*H*-pyrans to the synthesis of enantiomerically pure 1,4-DHPs. Thus, the first asymmetric synthesis of 4-alkyl-3,5-dialkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines (**4a-c**), in enantiomerically pure form, by means of Michael addition of ethyl aminocrotonate (**3**) to chiral α-acetylacrylates (**2**) is now reported (Scheme). The titled compounds have never been prepared in enantiomerically pure form.

The synthesis of α-acetylacrylates (**2a-c**) was carried out by Knoevenagel condensation of methyl acetylacetate and the appropriate readily available chiral aldehyde **1a-c** [**a**: (*R*)-2,3-O-isopropylideneglyceraldehyde[7], **b**: 3-O-benzyl-1,2-isopropylidene-α-D-xylopentodialdo-1,4-furanose[8] and **c**: (*S*)-2-(benzyloxy)propanal[9]]. Further reaction of α-acetylacrylates (**2a-c**) with ethyl aminocrotonate (**3**) in

refluxing alcohol solution for 4 hours led to the respective 1,4-DHP in good overall yield and excellent diastereoselectivity (Table).



Scheme

All the new compounds showed spectroscopic and analytical data in good agreement with the proposed structures .

The reaction mixture of compounds **4b** and **4c** showed the presence of both diastereomers in the ^1H NMR spectra of the crude product. However, for compound **4a** solely a diastereomer was detected in the ^1H NMR spectrum of the crude reaction mixture. All attempts to separate the diastereomeric mixture in compounds **4b** and **4c**, either by crystallization or chromatographic techniques were unsuccessful.

Table. 1,4-Dihydropyridines (1,4-DHPs) **4a-c**.

Compound	Yield (%)[a]	Ratio S:R (d.e.)[b]
4a	75	> 99
4b	79	90:10
4c	50	95:5

[a] After flash chromatography.

[b] Determined from the OCH_3 signal in the ^1H NMR spectra (300 MHz) of the crude reaction mixture.

The assignments in the ^1H NMR spectra ($CDCl_3$ as solvent) were ascertained by selective proton-proton decoupling experiments. The ^1H NMR spectrum for **4a** showed H-4 at δ 4.33 as a doublet (J= 5.1 Hz). The diastereomeric excesses have been determined from the ^1H NMR spectra of the crude product by integrating the observed signal for OCH_3 in compounds **4a-c** (see Table). Major diastereomer in the 1,4-DHP **4b** showed H-4 as a doublet at δ 4.77 (J= 8.4 Hz). The minor diastereomer presented H-4 at δ 4.69

with a slighly lower coupling constant (J= 7.8 Hz). Compound **4c** showed the H-4 signal together with the methylene of the OBn group as a multiplet integrating for three protons at δ 4.51.

Finally, we could isolate compound **4a** $[\alpha]_D^{25}$ +5.6 (*c*.1.0, $CHCl_3$) as suitable crystals for X-Ray diffraction analysis[10]. This allowed us to establish as *S* the absolute configuration at C-4 in **4a** and, by analogy, to major isomers of **4b-c** (Figure 1).

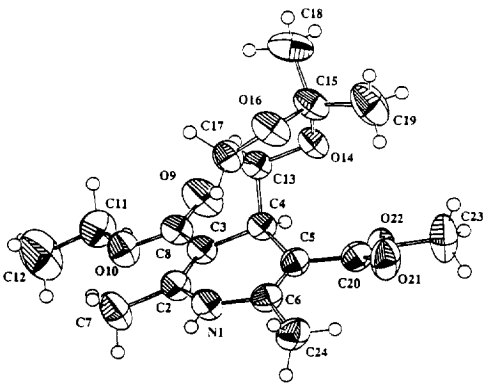


Figure 1. Molecular structure of **4a** showing the atomic numbering.

The geometry and the planarity found in **4a** are similar to those previously reported for other anologous dihydropyridines exhibiting calcium antagonist.[11] Thus, the 1,4-dihydropyridine ring shows a boat conformation with C-4 and N-1 out of the plane formed by C-4, C-3, C-5 and C-6 atoms 0.12 (1) and 0.27 (1) Å respectively.

Taking into account the experimental conditions used for the preparation of these 1,4-DHPs (**4**) we can rationalize the stereochemical result obtained as shown in Figure 2 in which a Felkin-Ahn model is proposed. In this model we assume the similarity of the $C{=}C(COR^1)CO_2R^2$ and C=O groups[12] and that the γ-alkoxy group is perpendicular to the carbonyl plane.[13] The attacking nucleophile approaches from the face of the α-acylacrylate opposite to the electronegative oxygen. This model is similar to that previously reported by us for the synthesis of structurally related 4*H*-pyrans.[14]

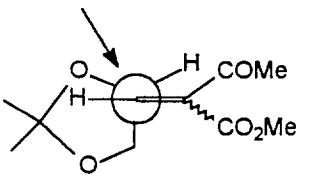


Figure 2

In summary, the results obtained show that the well-known methodology previously established in our laboratory for the asymmetric synthesis of 4*H*-pyrans can be successfully applied to the preparation of novel 1,4-DHPs in good yields and high diastereomeric excesses by Michael addition of aminocrotonates to chiral acetylacrylates. This approach opens up a new route to the synthesis of chiral dihydropyridines bearing different substituents derived of monosaccharides on C-4 with potential effects on the calcium channels.

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REFERENCES AND NOTES

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1. Bossert, F. and Vater, W. *Medicinal Research Reviews* **1989**, *9*, 291.
2. For a review see: Kuthan, J. and Kurfürst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191-261.
3. For a recent review see: Goldmann, S. and Stoltefuss, J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1559-1578.
4. Goldmann, S.; Born, L.; Kazda, S.; Pittel, B.; Schramm, M. *J. Med. Chem.*, **1990**, *33*, 1413-1418.
5. Sunkel, C. E.; Fau de Casa-Juana, M.; Cillero, F. J.; Priego, J. G.; Ortega, M. P. *J. Med. Chem.*, **1988**, *31*, 1886-1890.
6. Martín, N.; Martínez-Grau, A.; Seoane, C.; Marco, J. L. *Tetrahedron: Asymmetry* **1995**, *6*, 255 and references cited therein.
7. Jurczak, J.; Pikul, S; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
8. Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.
9. Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3248.
10. The authors have deposited atomic coordinates for this structure in the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, XB2 1EZ, UK.
11. Fosshein, R.; Suarteng, K.; Mostad, A.; Romming, E. S.; Triggle, D. J. *J. Med. Chem.* **1982**, *25*, 126.
12. Wallenfels, K.; Friedrich, K.; Rieser, J.; Estel W.: Thieme, H.K. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 261.
13. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
14. Marco J. L.; Martín, N.; Martínez-Grau, M. A.; Seoane, C.; Albert, A.; Cano, F. H. *Tetrahedron* **1993**, *49*, 7133.

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