First Enantioselective Synthesis of (–)-(2*S*,6*S*)-(6-Ethyltetrahydropyran-2-yl)formic Acid

Leandro S. M. Miranda,[a] Bruno A. Meireles,[a] Jerônimo S. Costa,[a] Vera. L. P. Pereira,[a]
Mário L. A. A. Vasconcellos*[b]

[a] Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Bloco H, CCS, Ilha do Fundão, Rio de Janeiro, RJ, 21941-590, Brasil

[b] Departamento de Química, Universidade Federal da Paraíba, Campus I, João Pessoa, PB, 58059-900, Brasil
Fax +55(83)2167413; E-mail: mlaav@quimica.ufpb.br

Received 22 December 2004

Abstract: We describe in this letter the first enantioselective synthesis of (–)-(2*S*,6*S*)-(6-ethyltetrahydropyran-2-yl)formic acid (**2**) in five steps (30% overall yield, 87% ee), from the commercial chiral template (*R*)-2,3-isopropylideneglyceraldehyde (**4**). The two stereogenic centers in **2** were controlled by diastereoselective Barbier allylation of **4** in aqueous media and an efficient Prins cyclization reaction between **5** with propanal.

Key words: enantioselective synthesis, antinociceptive activity, tetrahydropyran, Prins cyclization, Barbier reaction, (*R*)-2,3-*O*-isopropylideneglyceraldehyde

Six-membered ring saturated oxygen heterocycles are an integral part of many biologically active compounds.[1] The Prins cyclization of homoallylic alcohols with aldehydes under strongly protic acidic conditions is an old reaction,[2] that is now emerging as an efficient methodology for the preparation of substituted tetrahydropyran.[3] In general, 2,4,6-*cis* all equatorial substituted are obtained in high diastereoselectity.[4,5] In a recent paper, Rychnovsky developed the first axial-selective Prins cyclization methodology to the heteroatom at the 4-position, expanding the synthetic scope of this reaction.[6]

In our search for bioactive substances[7] we have detected a very active one, the (±)-*cis*-(6-ethyltetrahydropyran-2-yl)formic acid (**1**), as a novel class of non-steroidal analgesic compound.[8] In our previous paper, **1** was efficiently prepared in the racemic form and showed important analgesic properties in the tail flick model.[8] In order to provide this compound as a pure enantiomer for further pharmacological assays, we decided to create a fast enantioselective synthesis of **2** which could be also appropriate to prepare **3**. In this letter we described the first total enantioselective synthesis of **2** (Figure 1), based on the strategy of constructing the tetrahydropyran ring through an efficient diastereoselective Prins cyclization.

In our retro-synthetic analysis of 2 (Scheme 1) the ketal **A** can be easily transformed to the carboxylic acid moiety of **2**, trough a oxidative cleavage.[9] The stereogenic carbon on C_6(*S*) present in **A** could be controlled through a diastereoselective Prins reaction, between homoallylic alcohol **5** and propanal, through intermediate **B**, furnishing the *cis*-configuration between C_2-C_6.[3–5] To the best of our knowledge the homoallylic alcohol **5** has never been used as substrate on the Prins cyclization, probably due the presence of a ketal moiety, which could lead to side reactions in such an acidic media. However, the use the homoallylic alcohol **5** in this synthesis leads to a few steps procedure, avoiding deprotection–protection steps. Finally the *anti*-**5** could be prepared through a diastereoselective Barbier reaction between the synthon **4** and allylbromide.[10]

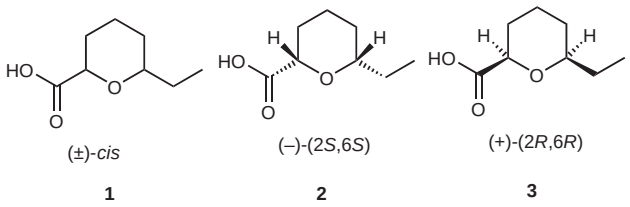
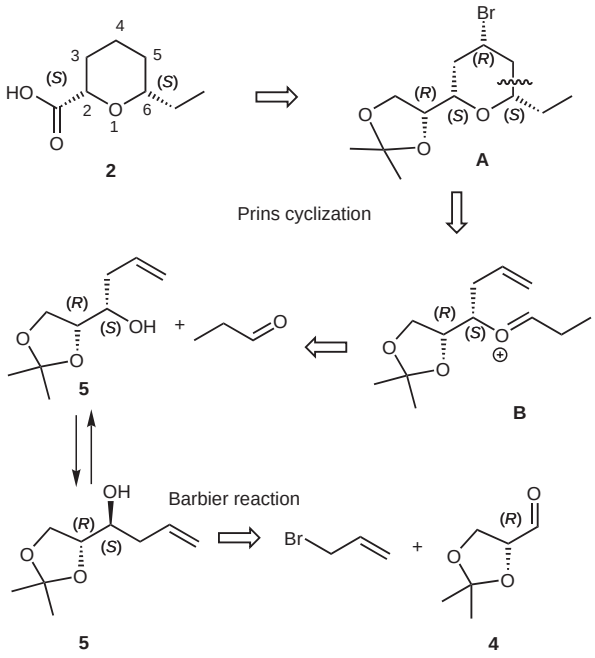


Figure 1 *Cis*-(6-ethyl-tetrahydropyran-2-yl)formic acids.



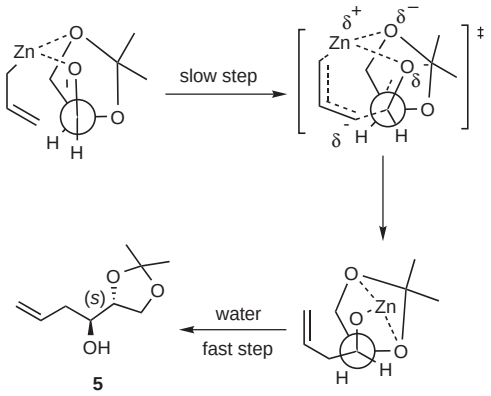
Scheme 1 Retro-synthetic analysis of **2**.

SYNLETT 2005, No. 5, pp 0869–0871
Advanced online publication: 09.03.2005
DOI: 10.1055/s-2005-863744; Art ID: S11704ST

The (*R*)-2,3-isopropylideneglyceraldehyde (**4**) and its enantiomer are commercially available and can be efficiently prepared from D-mannitol and L-ascorbic acid, respectively. Both have been extensively used as starting materials in enantioselective synthesis.[11]

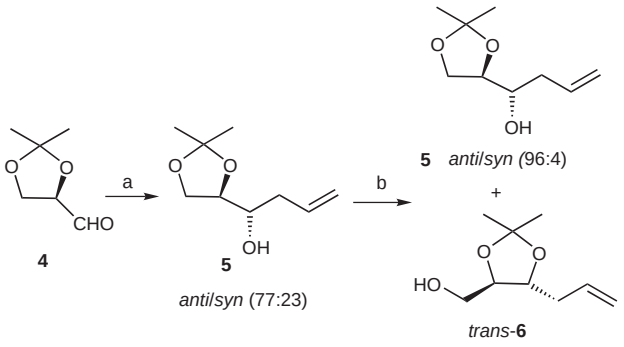
The present synthesis of **2** starts with the allylation of the non-distilled aldehyde **4** with allyl bromide under zinc-mediated Barbier protocol in aqueous media, leading to the formation of homoallylic alcohol **5** in 74% yield,[12] as an epimeric mixture (77:23, *anti*:*syn*, Scheme 2). It is important to note that the stereoselectivity using our protocol was similar to that obtained in the literature, in which the very expensive metallic indium in non-catalytic amounts is used as promoter.[9]

We believe that the major *anti*-epimer could be obtained through a chelated six-membered ring transition state, where the allylzinc attacks the less hindered *Si* face of the chiral aldehyde **4** (Scheme 2).[11]



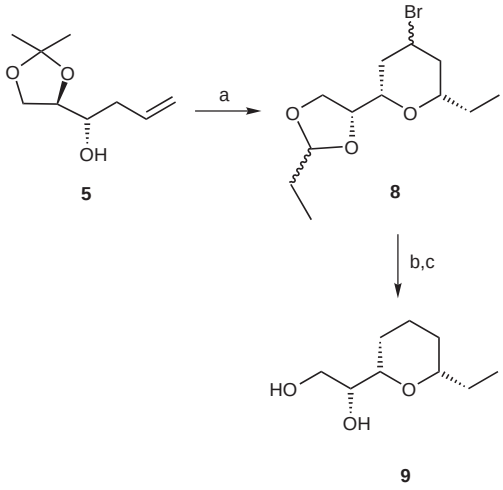
Scheme 2

The separation of the *anti*-diastereoisomer of **5** from the diastereoisomeric mixture was difficult to accomplish by chromatographic methods. Thus, a selective transketalization of the *syn*-isomer led to *trans*-ketal **6**, which was easily separated by column chromatography, yielding the desired *anti*-isomer in 92% de (Scheme 3).[13]



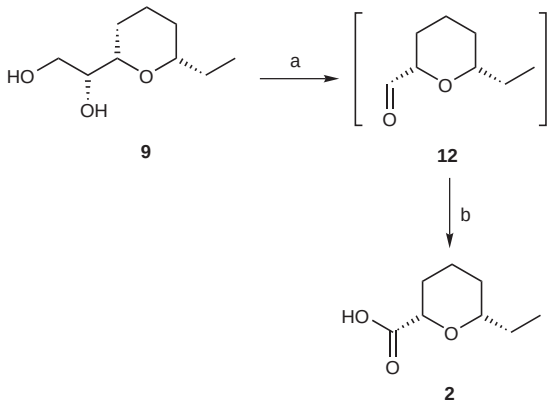
Scheme 3 *Reagents and conditions*: a) Zn, allyl bromide; THF–NH_4Cl (1:5), 74%; b) acetone, *p*-TSA, 71%.

Then, compound **5** was treated with propanal and $SnBr_4$, and ethyl-ketal **8** was obtained subsequently in 66% yield as a mixture of 4 diastereoisomers (Scheme 4).[14]



Scheme 4 *Reagents and conditions*: a) $SnBr_4$, propanal; CH_2Cl_2, 0 °C, 66%; b) $NaBH_4$, DMSO, 80 °C; c) HCl, MeOH, 24 h, r.t., 88% (two steps).

Compound **8** was converted in the diol **9** (Scheme 5) in a sequence concerning of debromination with sodium borohydride followed by acidic ketal opening in 88% yield for the two steps and 96% de measured by GC/MS.[15] Finally, the oxidative cleavage of **9** with $NaIO_4$ led to aldehyde **12** which was immediately converted to de desired (*S*,*S*)-*cis*-acid **2** through oxidation using $NaClO_2$–H_2O_2 in 90% yield and 87% ee (measured through chiral capillary gas chromatography).[16]



Scheme 5 *Reagents and conditions*: a) $NaIO_4$, MeOH–H_2O (1:3), 93%; b) $NaClO_2$, H_2O_2, 90%.

In conclusion, we present in this letter the following results: (1) the first example using the (*R*)-2,3-isopropylidene glyceraldehyde (**4**) as an efficient chiron template in an enantioselective strategy of construction of the tetrahydropyran ring through the Prins cyclization; (2) a fast and efficient first total enantioselective synthesis to the tetrahydropyran derivative (*S*,*S*)-**2**, a novel class of analgesic

compound; (3) an efficient methodology to purify an epimeric mixture of **5** through a selective transketalization of the *syn*-isomer vs. the *trans*-isomer. Once the enantiomer (*S*)-2,3-isopropylidene glyceraldehyde is commercial or easily prepared from L-ascorbic acid, our approach also allows a fast and efficient synthesis of the enantiomer (*R*,*R*)-**3**. Detailed pharmacological assays, comparing the racemic (±)-**1** with the enantiopure (*S*,*S*)-**2** and (*R*,*R*)-**3** is now under investigation.

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(12) (a) The diastereoisomeric purity of **5** was determined through ^{13}C NMR spectroscopy (ref.[9]), and its enantiomeric purity through comparison of its optical rotation with literature reference data: $[\alpha]_D$ 15.0 (92% de and 87% ee). See: Roush, W. H.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Spectroscopical data of *anti*-**5**: ^1H NMR (200 MHz, $CDCl_3$): δ = 5.92–5.75 (m, 1 H), 5.20 (m, 1 H), 5.10 (m, 1 H), 4.05–3.87 (m, 3 H), 3.77 (dq, *J* = 8.8, 4.4 Hz, 1 H), 2.43–2.10 (m, 2 H), 2.00 (d, *J* = 3.4 Hz, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 133.8, 118.1, 108.9, 77.9, 70.2, 65.0, 37.4, 26.3, 25.0. MS (70 eV): *m*/*z* (%) = 59 (100), 73 (35), 101 (72), 114 (2.5), 131 (7), 157 (45). IR (KBr, neat): 3444, 3078, 2987, 2936, 2899, 1642, 1456, 1435, 1381, 1254, 1215, 1066, 917, 854 cm^{-1}.

(13) **Experimental Procedure for Diastereoisomeric Enrichment of *anti*-5.**
To a stirred solution of the diastereoisomeric mixture of **5** (3.0 g, 17.4 mmol) in 45 mL of dry acetone, under Ar atmosphere, is added in one portion 0.2 g of *p*-TSA (1.04 mmol). The reaction is left stirring at –15 °C for 48 h, then the solvent is evaporated under reduced pressure and the residue submitted to flash column chromatography yielding 1.6 g (71%) of diastereoisomeric enriched **5** (92% de).

(14) To a stirred solution of **5** (0.5 g, 2.9 mmol) in dry CH_2Cl_2 (5 mL), under an Ar atmosphere, is added propanal (0.5 mL, 6 mmol). The reaction mixture is cooled in an ice bath and then a solution of $SnBr_4$ (1.25 g in 3 mL of dry CH_2Cl_2) is slowly added. The reaction is monitored through TLC and then quenched with 4 mL of a sat. solution of $NaHCO_3$ followed by 5 mL of EtOAc. The mixture is left stirring for more 40 min. The aqueous phase is then extracted with EtOAc (3 × 5 mL). The combined organic phases are dried with anhyd $NaSO_4$ and then concentrated. The crude product is filtered through silica (eluted with 20% EtOAc–hexanes) furnishing 0.55 g of **8** as a mixture of four diastereomers.

(15) Spectroscopical data of **9**: $[\alpha]_D$ –5.5 (*c* 2.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.8 (m, 2 H), 3.6 (m, 1 H), 3.4 (dq, 1 H, *J* = 11.09, 5.12, 1.83 Hz), 3.20 (m, 2 H), 2.40 (br s, 1 H), 1.90 (m, 1 H), 1.20–1.70 (m, 7 H), 0.90 (t, 3 H, *J* = 7.33 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 79.9, 79.5, 73.5, 63.7, 30.9, 29.1, 27.2, 23.0, 9.7. MS (70 eV): *m*/*z* (%) = 143 (9), 131 (4), 113 (57), 95 (98), 69 (61), 55 (100). IR (KBr, neat): 3390, 2934, 2856, 1460, 1441, 1085, 1045 cm^{-1}.

(16) Spectroscopical data of **2** $[\alpha]_D$ –45.2 (*c* 0.53, $CHCl_3$, 87% ee). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.0 (dd, 1 H, *J* = 9.1, 2.7 Hz), 3.4 (m, 1 H), 2.40 (m, 1 H), 2.00 (m, 2 H), 1.00–1.80 (m, 6 H), 0.99 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.3, 79.5 75.8, 29.9, 28.7, 28.3, 23.0, 9.6. MS (70 eV): *m*/*z* (%) = 129 (10), 113 (77), 101 (33), 95 (100). IR (KBr, neat): 3412, 2961, 2938, 2877, 2861, 1732, 1651, 1441, 1383, 1203, 1105, 918 cm^{-1}.