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Bioorganic & Medicinal Chemistry Letters
ELSEVIER
Bioorganic & Medicinal Chemistry Letters 14 (2004) 1573–1575

(±)-*cis*-(6-Ethyl-tetrahydropyran-2-yl)-formic acid: a novel substance with antinociceptive properties

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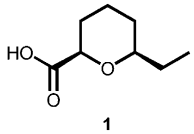
Received 7 August 2003; revised 13 December 2003; accepted 18 December 2003

Abstract—We described in this paper the first synthesis to the (±) *cis* (6-ethyl-tetrahydropyran-2-yl) formic acid (**1**) using the very efficient Prins cyclization reaction as strategy to construction of its tetrahydropyran skeleton. This new compound presented a significant antinociceptive property by the tail-flick model.

1. Introduction

In our continuing search for bioactive substances from natural sources, we have detected a very active one, from the barks of a Brazilian medicinal plant of the genus *Vitex,* with analgesic properties by the tail-flick model.[1] Further, the substance responsible for the major activity of this extract was isolated, and its structure was tentatively assigned as *cis*-(6-ethyl-tetrahydropyran-2-yl) formic acid, **1**.[2] In order to confirm its structure, and also to provide large amounts of this substance for further pharmacological assays, a fast and efficient synthetic route was proposed. In this work, we describe the first diastereoselective synthesis of **1**, which when compared with the spectroscopic data of the natural product proved to have a different, although very similar, structure. However, pharmacological assays with the synthetic product **1** showed that it is also an analgesic, by the tail-flick model.



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2. Chemistry

Preparation of **1**, was based on the strategy of construction of the tetrahydropyran ring through the Prins cyclisation reaction.[3] The Prins cyclisation is an old reaction that is now emerging as an efficient and high diastereoselective methodology for the preparation of tetrahydropyran skeletons, leading to tetrahydropyrans 2,4,6 all *cis* substituted. It has already been successfully used in the synthesis of natural products.[4]

The synthesis of **1** starts with the allylation of the commercial aldehyde **2**, with allyl bromide, under zinc mediated Barbier protocol,[5] leading to the formation of homoallylic alcohol **3** in 72% yield, after 3 h at rt. The racemic homoallylic alcohol **3** was then employed as the substrate for the Prins cyclization reaction with Propanal, mediated by aluminum chloride as the Lewis acid,[6,7] to furnish **4** in 67% yield as the only diastereoisomer (Scheme 1).

For the dechlorination reaction of C4 in compound **4** energetic conditions were necessary, using lithium aluminum hydride in refluxing THF for 6 h.[8] This protocol led to alcohol **5** in 75% yield (Scheme 2).[9]

Finally the alcohol **5** was oxidized by the Jones reagent,[10] furnishing the carboxylic acid **1** in 91% yield. The relative *cis* configuration of the groups present in

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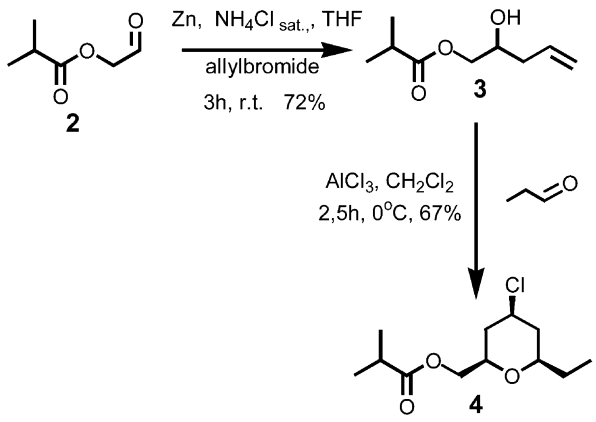
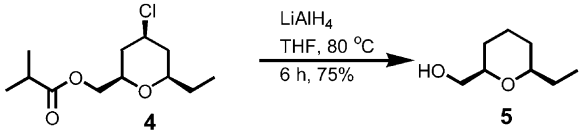
doi:10.1016/j.bmcl.2003.12.075



Scheme 1.



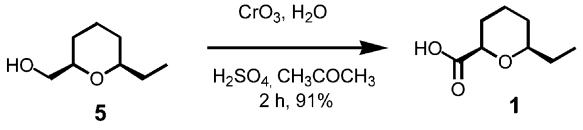
Scheme 2.

the C2 and C6 positions of **1** were determinated by ^{13}C NMR spectroscopy through the characteristic down field shift of the C2, C6 carbons[11,12] for *cis* substituted tetrahydropyran skeletons. The acid **1** was prepared from **2** in 33% global yield (Scheme 3).

3. Sample of the Prins cyclization

3.1. Isobutiric acid (*cis*-4-chloro-*cis*-6-ethyl-tetrahydropyran-2-yl) methyl ester (4)

In a typical procedure for the Prins cyclization reaction, 2.70 g of aluminum chloride (20.2 mmol) is added to a flame-dried flask, where 10 mL of dichloromethane (dried under calcium hydride), is added. To this flask, a solution containing 3.5 g (20.2 mmol) of homoallylic alcohol **3**, 1.5 mL (20.2 mmol) of propanal, in 6 mL of dichloromethane is slowly added at 0 °C. The reaction mixture is left stirring at this temperature for 2.5 h. After this time, 5 mL of a saturated sodium bicarbonate solution is slowly added until pH 7. The organic phase is then separated washed with brine, dried with sodium sulphate and the evaporated under reduced pressure. This crude product is then submitted to column flash chromatography, yielding a colorless liquid in 67% yield (3.03 g). ^1H NMR ($CDCl_3$ 200 MHz) δ 4.0 (m, 3H), 3.6 (m, 1H), 3.2 (m, 1H), 2.6 (sp, 7.1 Hz, 1H), 2.1 (m, 2H), 1.55 (m, 5H), 1.18 (d, 7.1 Hz, 6H) 0.93 (t, 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$ 50 MHz), δ 176.4, 77.8, 74.1, 55.0, 41.6, 38.5, 33.6, 28.3, 18.6, 9.5. IR (neat, cm^{-1}) 2972, 2937, 1737, 1470, 1387, 1197, 1150, 757.



Scheme 3.

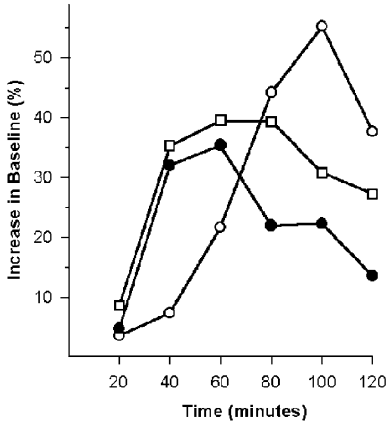


Figure 1. Effect of **1**, dipyrone and morphine on tail flick model. Substances were administered by oral application at the doses of 1 mg/kg for **1** (□), morphine (○), dipyrone (•). At different time the reaction time was recorded as described in materials and methods. Results are expressed as increase in baseline (in%) from 10 animals.

4. Pharmacology

4.1. Tail flick test

Mice were tested according to Eddy and Leimback.[13] The animals tail were placed on a water bath set at 55 ± 1 °C and the reaction time was recorded when the animals withdraw their tail. The reaction time (s) was measured 40 and 20 min before and 20, 40, 80, 100, and 120 min after oral treatment with 1 mg/kg of **1**. In order to compare with commercially avaiable analgesic drugs groups were composed by animals that received oral administration 1 mg/kg of morphine or dipyrone.

Figure 1 shows the results obtained after oral administration of **1** at the dose of 1 mg/kg. This substance developed a maximal effect increasing the antinociceptive activity in 40% after 1 h decreasing thereafter. When **1** was compared with analgesic drugs dipyrone and morphine at doses corresponding to its IC_{50} values (in our model) we observed that the effects of **1** was almost the same of dipyrone with curves with similar patterns. When **1** was compared with morphine administered orally the results showed that maximal effects from morphine was reached only after 100 min and maximal response was 55% increase in analgesic activity. Results indicates that substance **1** develops analgesic activity similar to dipyrone and more rapidly than morphine in this case in half of time necessary to reached tmaximal effects.

5. Conclusion

The present work showed the first preparation of **1**. The methodology employed was highly diastereoselective through the Prins cyclization reaction for the construction of the tetrahydropyran ring. This compound showed significative antinocioceptive properties in the preliminary tests by the tail flick model.

Detailed pharmacological and toxicological essays are under investigation.

Acknowledgements

CNPq, CAPES, FUJB and FAPERJ.

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9. Spectroscopic data of **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.6–3.42 (m, 3H), 3.29–3.19 (m, 1H), 1.88 (m, 1H), 1.69–1.42 (m, 5H), 1.28–1.14 (m, 3H), 0.95 (t, 7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.1, 77.9, 66.5, 31.1, 29.3, 27.3, 23.1, 10.1; IR (neat, cm^{-1}): 3520, 2954, 2923, 2853, 1458, 1375, 1227, 1178, 874.
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11. Spectroscopic data of **1**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.0 (dd, 2.7, 9.1, 1H), 3.4 (m, 1H), 2.4 (m, 1H), 2.0 (m, 2H), 1–1.8 (m, 6H), 0.99 (t, 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.3, 79.5, 75.8, 29.9, 28.7, 28.3, 23.0, 9.6; IR (neat, cm^{-1}): 3412, 2938, 2877, 1732, 1441, 1383, 1203, 1105, 918; MS (70 eV): 158 (M^+, 0.5%), 129 (10%), 113 (77%), 101 (33%), 95 (100%).
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