Pergamon

Tetrahedron Letters 39 (1998) 7097–7100

TETRAHEDRON
LETTERS

Synthesis of (±)-Nephromopsinic Acid

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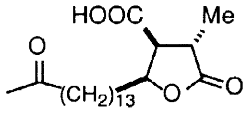
Received 17 June 1998; accepted 21 July 1998

Abstract

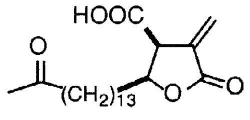
The preparation of (±)-nephromopsinic acid form 7-oxabicyclo[2.2.1]hept-5-en-2-one is reported. The synthesis takes advantage of a previously reported radical acyl migration. A remarkable iodide mediated cleavage of the bicyclic systems followed by the introduction of the γ-chain via a mixed Kolbe electrolysis are the key features of this approach. This strategy is expected to be of interest for the preparation of all kinds of paraconic acids with excellent control of the stereochemistry. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: natural products; lactones; electrochemistry; radical reactions.

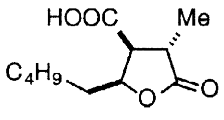
Paraconic acids are a class of trisubstituted γ-butyrolactones possessing attractive biological activities [1]. They have attracted considerable attention of organic chemists and several different strategies for their synthesis have been used. Efficient preparation of β,γ-*trans*-γ-butyrolactones has been developed [1-18]. However, β,γ-*cis* disubstituted systems such as pertusarinic, phaseolinic, allo-pertusaric and nephromopsinic acids appear to be more difficult to prepare [1,19-26]. Interestingly, these compounds possess a very similar substitution pattern at the α-position (methyl or methylene) and β-position (carboxyl). However, they differ by the carbon residue at the γ-position. Therefore, it would be highly attractive to elaborate a synthesis that allows the introduction of any kind of γ-substituent at a later stage during the synthesis. In this communication, we describe the synthesis of nephromopsinic acid with a late introduction of the γ-chain. This approach is expected to be general for any type of paraconic acids in both enantiomeric forms.



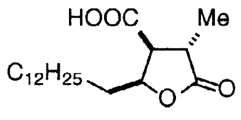
pertusarinic acid



allo-perturasic acid



phaseolinic acid



nephromopsinic acid

Recently, we have demonstrated that the bicyclic selenoacetal **1**, easily obtained via radical addition of dimethyl phenylselenomalonate to racemic 7-oxabicyclo[2.2.1]hept-5-en-2-one, was a highly versatile building block for the synthesis of 12-*epi*-prostaglandins and all-*cis* thromboxanes [27-29]. The same compound was chosen as starting material for the synthesis of nephromopsinic acid (Scheme 1). Reductive deselanylation (Bu_3SnH, AIBN) of **1** furnished

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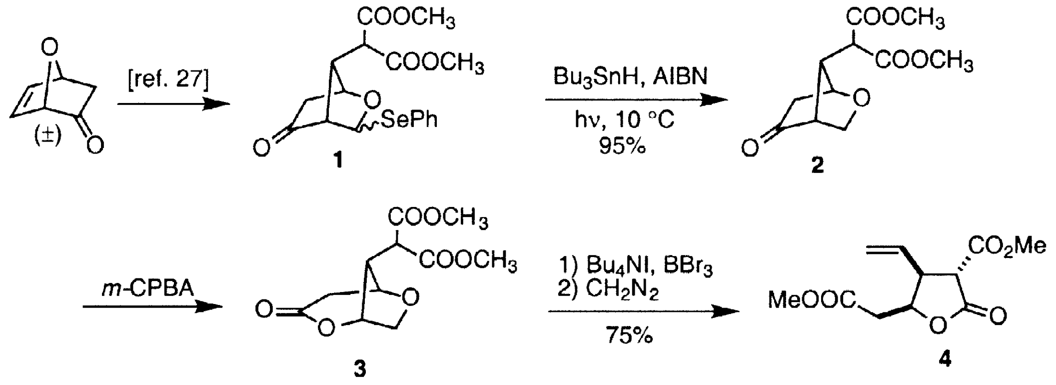
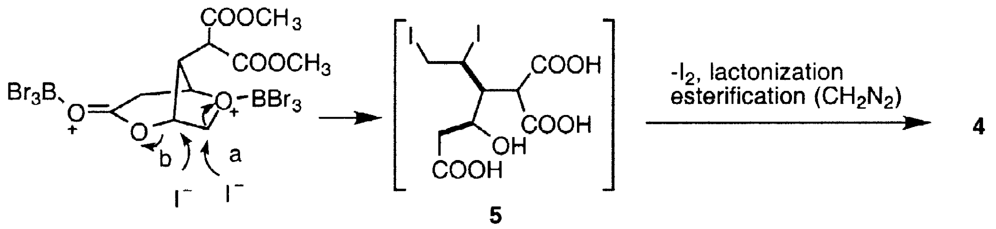
PII: S0040-4039(98)01550-0

the bicyclic compound **2** in 95% yield. Baeyer-Villiger oxidation with *m*-CPBA gave the desired lactone **3** (50%) together with its regioisomer. The key step of the transformation is the iodide mediated double ring opening of the lactone-ether **3** in the presence of BBr_3. Treatment of the crude product with diazomethane before flash-chromatography furnished the butyrolactone **4**[1] with the desired β,γ-*cis* disubstitution[2] in 75% yield.



Scheme 1

A tentative mechanism of this remarkable rearrangement is depicted in Scheme 2. It consists in the simultaneous acid catalyzed opening of the bicyclic ether (a) and of the lactone (b). The methyl ester moieties are also presumably cleaved under these conditions. The vicinal diodide **5** loses spontaneously I_2 to afford the vinyl group. The final product **4** results from the lactonization and esterification with diazomethane.



Scheme 2

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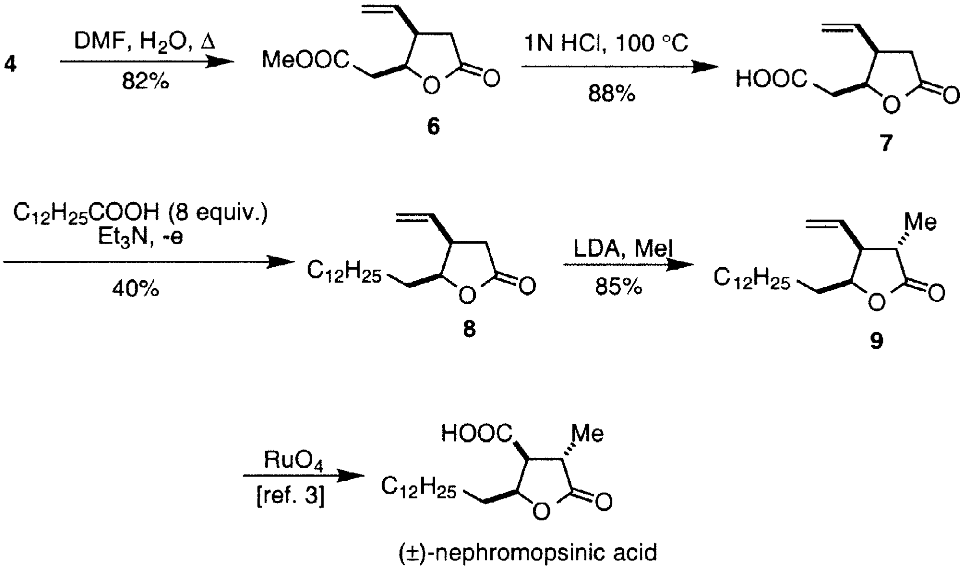
1) Methyl (3*RS*,4*SR*,5*SR*)-5-methyloxycarbonylmethyl-2-oxo-4-vinyltetrahydrofurane-3-carboxylate (**4**). A solution of **3** (1.75 g, 6.5 mmol) and tetrabutylammoniumiodide (12.05 g, 32.6 mmol) in dry CH_2Cl_2 under N_2 was cooled to -30 °C and BBr_3 (3.14 ml, 32.6 mmol) was added. The reaction mixture was stirred at -30 °C during 15 min and then allowed to warm to r.t. After addition of H_2O, extraction with CH_2Cl_2 followed by drying (Na_2SO_4) and evaporation of the solvent afforded a residue which was treated with diazomethane in Et_2O until N_2 evolution stopped. The solvent was removed and the crude product was purified by flash-chromatography (AcOEt/hexane 1:2) to give **4** (1.18 g, 75%). ^{1}H-NMR (360 MHz, $CDCl_3$): 5.70 (*ddd*, J_{trans} = 16.8, J_{cis} = 10.2, *J* = 18.6, C*H*=CH$_2$); 5.31 (*dd*, *J* = 6.4, 0.8, 1 H, CH*H*=CH); 5.26 (*dd*, *J* = 13.1, 0.8, 1 H, C*H*H=CH, trans); 5.16 (*m*, H-C(3)), 3.82 (*s*, COOMe); 3.75-3.70 (*m*, H-C(4)); 3.71 (*s*, COOMe); 3.58 (*d*, *J* = 7.5, H-C(5)); 2.66 (*dd*, *J* = 16.6, 7.3, C*H*$_2$COOMe). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 170.20 (*s*), 169.74 (*s*), 167.17 (*s*), 131.36 (*d*), 120.57 (*t*), 77.64 (*d*), 53.26 (*q*), 52.13 (*q*); 51.20 (*d*), 46.29 (*d*), 35.74 (*t*). IR (film): 2957, 2360, 2342, 1787, 1742, 1439, 1355, 1317, 1287, 1199, 1166, 1126. EI-MS: 243 ($M^{\cdot+}$, 100), 211 (80); 193 (32), 165 (36), 138 (11), 112 (20), 81 (8). Anal. calc. for $C_{11}H_{14}O_6$ (242.23): C 54.54, H 5.83; found: 54.44, H 5.64.

2) The *cis* stereochemistry of **7** has been assessed by measurement of NOE difference spectra.

The conversion of **4** to nephromopsinic acid is depicted in Scheme 3. Decarboxylation in refluxing DMF/H_2O afforded lactone **6**. The γ-chain was introduced by a mixed Kolbe electrolysis[3] between the carboxylic acid **7**, obtained by treatment of **6** with 1 M HCl at 100 °C, and tridecanoic acid (8 equivalents) in 40% yield.[4] The Kolbe electrolysis approach [30], even if not high yielding presents some advantages over classical chemical methods since it furnishes the desired compound in one single step and many different alkanoic acids can be used for the coupling reaction. Moreover, the reaction conditions are very mild so that the lactone and the vinyl group are preserved during the electrolysis. Lactone **8** was methylated in 85% yield, as expected, the methyl group is exclusively introduced *trans* to the β- and γ-substituents. The last step, i.e. the oxidation of **9** to (±)-nephromopsinic acid with RuO_4 was performed according to Mulzer procedure [23].[5]



Scheme 3

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3) (4*RS*,5*SR*)-5-Tridecyl-4-vinyltetrahydrofuran-2-one (**8**). A solution of the acid **7** (24 mg, 141 μmol), tridecanoic acid (242 mg, 1.13 mmol) and Et_3N (10 μl, 71 μmol) in MeOH (1.5 ml) was electrolyzed in a undivided cell with a platinum foil electrode (current density 100 mA/cm^2). The solvent was evaporated. The residue was dissolved in AcOEt and washed with 1 M NaOH. The organic layer was dried (Na_2SO_4), evaporated and purified by flash-chromatography (AcOEt/hexane 1:3) to give **8** (16 mg, 40%). ^{1}H-NMR (500 MHz, $CDCl_3$): 5.76 (*ddd*, *J* = 17.0, 10.3, 8.7, C*H*=CH_2); 5.19 (*dt*, *J* = 10.3, 1.2, 1 H, CH*H*=CH); 5.15 (*dt*, *J* = 17.0, 1.2, 1 H, C*H*H=CH); 4.49 (*ddd*, *J* = 9.2, 6.4, 4.2, H-C(5)); 3.19-3.11 (*m*, H-C(4)); 2.70 (*dd*, *J* = 17.3, 8.1, 1 H, H-C(3)); 2.43 (*dd*, *J* = 17.3, 5.7, 1 H, H-C(3)); 1.60-1.40 (*m*, 4 H, CH_2 tridecyl); 1.25 (*s*, 20 H, CH_2 tridecyl), 0.88 (*t*, *J* = 6.8, CH_3). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 176.25 (*s*); 134.05 (*d*), 118.04 (*t*), 83.28 (*d*), 43.13 (*d*), 34.73 (*t*), 31.91 (*t*), 30.86(*t*), 29.67-29.34 (*t*), 25.68 (*t*), 22.68 (*t*), 14.10 (*q*). IR (film): 2990, 2974, 2928, 2856, 2361, 1774, 1295, 1237, 902. CI-MS (CH_4): 296 (M^+, 16), 295 (M, 59), 278 (19), 277 (41), 236 (28), 235 (100), 233 (28), 137 (17), 111 (16). MS (high resolution): calc. 295.2659, found: 295.2631.

4) Unreacted acid **7** was still present but not recovered. Dimerization of **7** could be almost suppressed (<5%) by using 8 equivalents of tridecanoic acid. No other side-product was identified.

5) The spectral data of **9** and of (±)-nephromopsinic acid are identical with the one reported in the literature [23].

In conclusion, our synthesis of (±)-nephromopsinic acid is expected to be general for all kind of β,γ-*cis* paraconic acids. Since the epimerization of the β-position has already been reported [1], access to the ***trans*** **substituted** paraconic acids should also be possible. Moreover, the 7-oxabicyclo[2.2.1]hept-5-en-2-one is easily prepared in both enantiomeric forms; therefore access to optically active paraconic acids is possible. Preparation of other paraconic acids using the same strategy is under investigation in our laboratory.

Acknowledgments

We are very grateful to the Swiss National Science Foundation for financial support.

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