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Article

A New Approach to the Synthesis of (±)-Methyl Jasmonate and (±)-Baclofen via Conjugated Addition of Oxazoline Cyanocuprate to Michael Acceptors.

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A introdução de um grupamento equivalente ao ânion carboximetil a enonas e nitroalquenos através da reação de adição 1,4 do cianocuprato da 2,4,4-trimetil-2-oxazolina **3**, resulta numa metodologia interessante para a síntese de produtos naturais como (±)-metil jasmonato (**1**) e (±)-baclofen (**2**).

Introduction of a synthon equivalent to a carboxymethyl anion to enones and nitroalkenes, through a 1,4-addition reaction of 2,4,4-trimethyl-2-oxazoline cyanocuprate **3**, proved to be an interesting methodology for the synthesis of natural products such as (±)-methyl jasmonate (**1**) and (±)-baclofen (**2**).

Keywords: 2-oxazoline cyanocuprate, 1,4-addition, tandem reaction, methyl jasmonate, baclofen.

Introduction

Conjugated addition of functionalized carbanions to the β position of a α,β-unsaturated systems have vast utility in synthetic organic chemistry, and several different variants have been developed for this purpose[1]. Among them, carboxymethyl anion equivalents such as silylketene acetals[2], were tacitly designed to depress the inherent nature of 1,2-carbonyl addition for naked ester enolates[3].

Recently, we developed the preparation and use of oxazoline cyanocuprate **3** in reactions with enones[4] and nitroalkenes[5], in which a nucleophilic addition allow the introduction of a carboxymethyl anion equivalent to those Michael acceptors. Application of this methodology in the synthesis of natural products is illustrated here, having (±)-methyl jasmonate (**1)** and (±)-baclofen (**2)** as target molecules. The retrosynthetic pathway that illustrate our approach to prepare both compounds is shown in Scheme 1, employing 2-cyclopenten-1-one and *p*-chloro-β-nitrostyrene as starting material.

Jasmonates induce genes encoding proteinase inhibitors, antifungal proteins, and enzymes involved in the biosynthesis of defensive secondary metabolites[6]. Thus, in addition to their well-established function as plant growth regulators and development[7], jasmonates play a key role as phytohormones or signal transducers in the defense signaling systems of plants. While there is a high degree of chemical diversity among the primary elicitors, defensive signaling in plants seems to rely on at least one common group of signal transducers. For a large number of species from different plant families, it has been shown that recognition of the primary elicitors eventually induces the biosynthesis of jasmonic acid or methyl jasmonate[8].

The γ-aminobutyric acid (GABA) is known as the major inhibitory neurotransmitter in the central nervous system, and its β-substituted derivatives play an important role in a number of central nervous system functions[9,10]. Baclofen (**2**)[11] (commercially available as Lioresal®, 3-(p- chlorophenyl)-γ-aminobutyric acid), a lipophilic derivative of GABA, is used in the treatment of spasticity caused by disease of the spinal cord[12], particularly traumatic lesions. While earlier studies were mainly concentrate on baclofen, recent literature indicate renewed interest in the biological activities of β-phenyl-GABA. These include anticonvulsant[13], antiepileptic[14], antistress[15], antiamnesic and antihypoxic[16], antihypertensive[17], and analgesic activities[18]. Because of its biological and pharmacological importance, several methodologies have been described focusing the total synthesis of baclofen[19,20].

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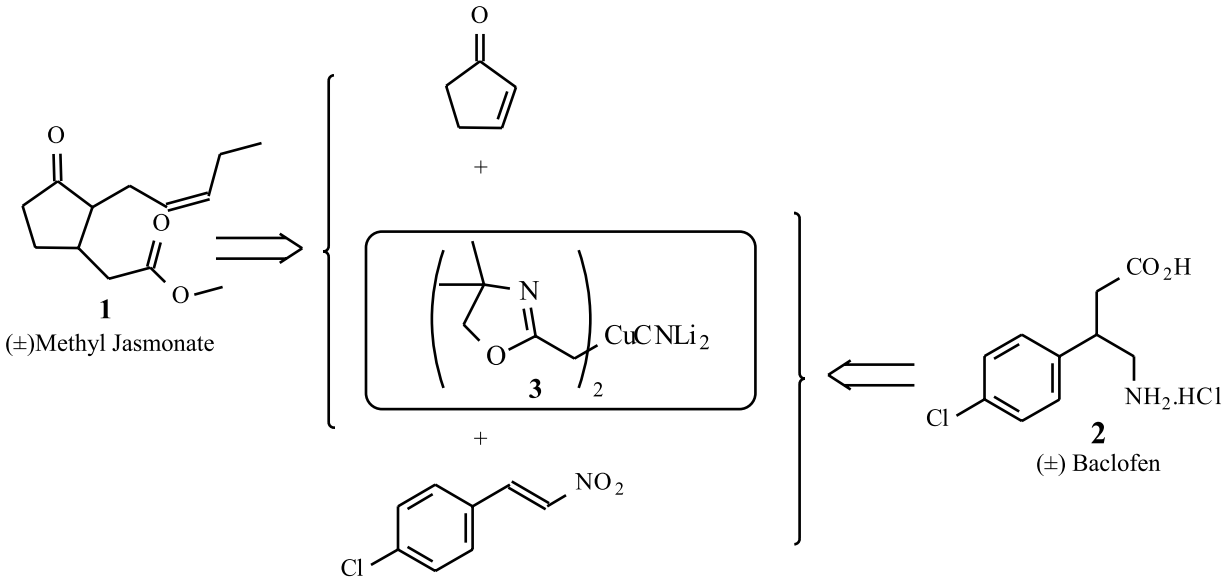


Scheme 1. Retrosynthetic analysis of (±)-methyl jasmonate and (±)-baclofen

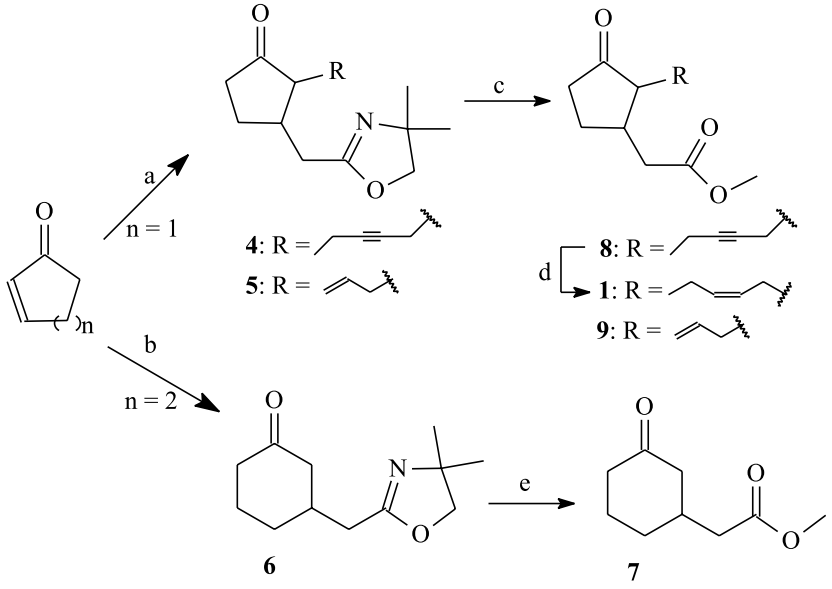
Results and Discussion

*Synthesis of (±)-methyl jasmonate (**1**)*

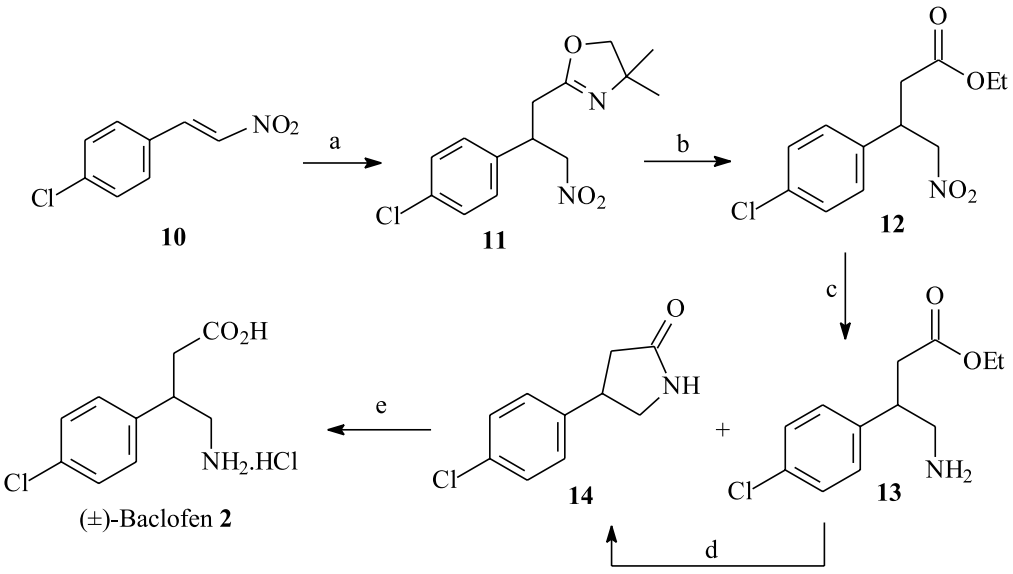
The keto-oxazolines **4** and **5** were prepared as shown in Scheme 2, employing sequential one-pot introduction of an oxazoline synthon at the β-position and an alkyl group (2-pent-2-ynyl and allyl groups respectively) at α-position of 2-cyclopenten-1-one.

We have previously established the one-pot conditions ($MeOH/H_2SO_4$) for the conversion of the oxazoline function to the respective methyl ester, which was carried out by using a mixture of compound **6** with propargyl alcohol, as a model system, to check the stability of the triple bond in this reaction. Under this condition, the keto-oxazolines **4** and **5** were converted to the desired esters **8** and **9**, respectively.

Final conversion of compound **8** into (±) methyl jasmonate (**1**) was accomplished by hydrogenation using



Scheme 2. Reaction conditions: (a) 2,4,4-trimethyl-2-oxazoline cyanocuprate, THF, -78 ºC, argon (40 min); tributyltin chloride, -78 ºC (30 min); warm to -45ºC, 1-iodo-2-pentyne (**4:** 42%) or allyl bromide (**5**: 41%) (5 eq.) in HMPA, -30ºC (30 h); (b) 2,4,4-trimethyl-2-oxazoline cyanocuprate, THF, -78ºC, argon (40 min) (**6**: 70%); (c) $MeOH/H_2SO_4$, reflux 8 h (**8**: 89%, **9**: 92%) ; (d) H_2/Lindlar/quinoline (**1**: 83%); (e) $MeOH/H_2SO_4$, propargyl alcohol, reflux 8 h (**7**: 92%)



Scheme 3. Reaction conditions: (a) 2,4,4-trimethyl-2-oxazoline cyanocuprate, THF, -78 ºC, argon (40 min) (**11**: 76%); (b) $EtOH/H_2SO_4$, reflux 52 h (**12**: 84%); (c) H_2/Raney-Ni, EtOH, rt, 24 h; (d) reflux in *o*-xylene, 1 h (**14**: 75%). ; (e) HCl (6 mol L^{-1}), reflux, 6 h (**2**: 82%).

Lindlar/quinoline catalyst, affording the desired product in 32% overall yield from 2-cyclopenten-1-one.

The success of this methodology relies on the exchange of the copper enolate by tin enolate, as described by Itoh *et al.*[21], using sequential vicinal double alkylation via stannyl enolate trapping in a *tandem* double addition on the 2-cyclopenten-1-one moiety. This methodology was employed to prevent the formation of C,O-dialkylation product, C,C-dialkylation product, O-alkylation product, among others, since the stannyl enolate trapping inhibits the equilibration of the enolates[22].

*Synthesis of (±)-baclofen (**2**)*

The Michael addition of oxazoline cyanocuprate **3** to the commercially available *p*-chloro-β-nitrostyrene **10** afforded γ-nitrooxazoline **11**, as shown in the Scheme 3.

The γ-nitrooxazoline **11** was submitted to several reduction conditions ($LiAlH_4$[23], $NiCl_2.6H_2O/NaBH_4$[24], [Al-Hg][25], H_2/Pd-C[26] and H_2/Raney-Ni[27]) aiming the selective reduction of the nitro group. All the attempts resulted in a mixture of several non-identified products, none of them holding the oxazoline ring.

An alternative approach to (±)-baclofen was then employed where the oxazoline group was first converted to the corresponding ester. The resulting nitroester **12** was submitted to reduction with H_2/Raney-Ni affording a mixture of aminoester **13** and the lactam **14**. This mixture was refluxed in *o*-xylene to provide lactam **14** as a single product. Hydrolysis of lactam **14** produced (±)-baclofen (**2**) as its hydrochloric salt in 39 % overall yield from *p*-chloro-β-nitrostyrene (Scheme 3).

Conclusion

The use of oxazoline cyanocuprate to introduce a carboxymethyl synthon to the β position of a α,β-unsaturated systems has shown to be a versatile methodology for the synthesis of natural products, and its chiral version is now been applied using optically active oxazolines.

Experimental

General

Reagents and solvents were purified and dried using standard methods. Reactions involving organometallic reagents were carried out under argon in oven-dried glassware. Hydrogenations were carried out using a Parr® apparatus or a balloon filled with hydrogen. Reactions were monitored by thin-layer chromatography (TLC; glass plates 7x21 cm) and gas chromatography (GC) using a Varian® model 3800 (flame ionization detector (FID, 30 m x 0.25 mm VA-5: 5%-phenyl-methylpolysiloxane) or (FID, 30 m x 0.25 mm VA-WAX: Polyethylene Glycol). GC-EIMS (70 eV) analysis were carried out on a Varian® Saturn 2000 GC-MS spectrometer in a split injector model with an Ion

Trap technology (30 m x 0.25 mm VA-5: 5%-phenyl-methylpolysiloxane). Conventional and flash column chromatographies were carried out with 70-230 and 230-400 mesh silica gel (E. Merck), respectively. IR spectra were recorded on a Bomem MB100 spectrometer with internal calibration. ^{1}H NMR were recorded on $CDCl_3$ solutions using Bruker AC-80, Bruker ARX-400, Bruker ARX-200 or Varian^{Ò} Gemini 300 spectrometer. Chemical shifts (d) are given in ppm and coupling constants (J) in Hz. Deuterated solvents were used as lock and reference signal (^{1}H NMR reference signal relative to the proton resonance resulting from TMS signal: d 0.00 ppm). ^{13}C NMR spectra were determined as solutions in $CDCl_3$ with the spectrometers described above. The chemical shifts (d) are reported in ppm relative to the center peak of $CDCl_3$ (d 77.0 ppm).

*General procedure for preparation of oxazoline cyanocuprate (**3**)*

To a solution of 2,4,4-trimethyl-2-oxazoline (0.452 g, 4.00 mmol) in THF (8.0 cm^3) at -78 °C was added ^{n}BuLi in hexanes (1.78 cm^3, 4.20 mmol). After stirring for 30 min at – 78 °C a solution of CuCN.2LiCl (0.348 g, 2.00 mmol) in THF (2.0 cm^3) was added and the resulting solution was stirred at -78 °C for additional 30 min., resulting in a pale red solution.

*3-(4,4-Dimethyl-4,5-Dihydro-oxazol-2-ylmethyl)-2-pent-2-ynyl-cyclopentanone (**4**)*

To a solution of oxazoline cyanocuprate **3** (2.00 mmol), prepared as described above, was added 2-cyclopenten-1-one (0.164 g, 2.00 mmol) in THF (2.0 cm^3). After 40 min at –78 °C tributyltin chloride (0.650 g, 2.00 mmol) in THF (2.0 cm^3) was added and the solution was stirred for 30 min at this temperature and then warmed to –45 °C. A solution of propargylic iodide (1.940 g, 10.00 mmol) in HMPA (10.0 cm^3) was added, and the solution was kept at -30 °C for 30 h. Ethyl ether (5.0 cm^3) and a 10% NH_4OH solution in a saturated NH_4Cl solution (3.0 cm^3) were added and this mixture was stirred for 30 min. After the addition of ethyl ether (10.0 cm^3), the phases were separated and the aqueous phase was extracted with ethyl ether (3 x 5.0 cm^3). The combined organic extracts were washed with saturated NaCl solution (1 x 5.0 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (ethyl ether/hexane 3:1 v/v) to give compound **4** (0.219g, 42%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, *J* 7.5 Hz, 3 H); 1.28 (s, 6 H); 1.50-1.66 (m, 1 H); 1.94 (dt, *J* 10.7 and 4.8 Hz, 1 H); 2.00-2.60 (m, 9 H); 2.71 (dd *J* 14.4 and 5.3 Hz, 1 H); 3.92 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.73, 14.54, 17.86, 27.34, 28.73, 28.86, 33.10, 38.15, 38.76, 53.70, 67.48, 76.22, 79.40, 83.99, 164.54, 218.18; MS *m/z* (relative intensity) 262 (M^++1, 51), 246 (17), 232 (25), 218 (21), 205 (38), 204 (30), 190 (30), 140 (24), 113 (100), 98 (37).

*3-(4,4-Dimethyl-4,5-dihydro-oxazol-2-ylmethyl)-cyclohexanone (**6**)*

To a solution of oxazoline cyanocuprate **3** (2.00 mmol) previously prepared at – 78 °C was added dropwise a solution of 2-ciclohexen-1-one (0.192g, 2.00 mmol) in THF (6.0 cm^3). After 2 h at –78 °C MeOH (1.0 cm^3) and 10% NH_4OH solution in a saturated NH_4Cl solution (2.0 cm^3) were added and the resulting mixture stirred from – 78 °C to room temperature (~ 1 h). After the addition of ethyl ether (10.0 cm^3), the phases were separated and the aqueous phase was extracted with ethyl ether (3 x 5.0 cm^3). The combined organic extracts were washed with saturated NaCl solution (2 x 3.0 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography (ethyl ether/hexane 6:1 v/v) affording keto-oxazoline **6** (0.292g, 70%) and 1,2 addition product (0.117g, 28%); IR ν_{max}/cm^{-1} 2965, 2921, 1704, 1666 (film); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 6 H), 1.36-1.45 (m, 1 H), 1.62-1.74 (m, 1 H), 1.92-2.48 (m, 9 H), 3.91 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.81, 28.39, 30.99, 34.83, 36.28, 41.08, 47.46, 66.98, 78.98, 163.83, 210.59; MS *m/z* (relative intensity) 210 (M^++1, 100), 166 (6), 153 (6), 113 (58), 98 (6), 70 (5).

*(3-Oxo-cyclohexyl)-acetic acid methyl ester (**7**)*

To a solution of keto-oxazoline **6** (0.209g, 1.00 mmol) and propargyl alcohol (0.056g, 1.00 mmol) in MeOH (5.0 cm^3) was added 5 drops of concentrated sulfuric acid and the solution refluxed for 8 h. The solution was concentrated under reduced pressure and the crude product was diluted with ethyl ether (5.0 cm^3). The resulting solution was washed with saturated NaCl solution (3 x 3.0 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (ethyl ether/hexane 1:1 v/v) affording **7** (0.158 g, 93%) and recovered propargyl alcohol; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 2 H); 1.98-2.48 (m, 9 H); 3.68 (s, 3 H); MS *m/z* (relative intensity) 171 (M^++1, 100), 139 (20), 127 (14), 110 (28), 97 (62), 82 (17), 67 (16), 55 (33), 39 (40).

*(3-Oxo-2-pent-2-ynyl-cyclpentyl)-acetic acid methyl ester (**8**)*

To a solution of keto-oxazoline **4** (0.200g, 0.766 mmol) in MeOH (5.0 cm^3) was added 3 drops of concentrated sulfuric acid and the solution refluxed for 8 h. The solution was concentrated under reduced pressure and the crude product was diluted with ethyl ether (5.0 cm^3). The resulting solution was washed with saturated NaCl solution (3 x 3.0 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (hexane/ethyl ether 2:1 v/v) to give **8** (0.170 g, 89%); IR ν_{max}/cm^{-1} 2972, 1736 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, *J* 7.2 Hz, 3H), 1.6 (s, 2 H); 1.85 (dt, *J* 10.4 and 5.2 Hz, 1 H), 2.00-2.60 (m, 7 H), 2.82 (dd, *J* 14.3 and 3.9 Hz, 2 H), 3.65 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.21, 14.00, 17.34, 27.06, 37.61, 37.81, 38.48, 51.57, 52.83, 75.75, 83.70, 172.24, 217.85; MS *m/z* (relative intensity) 223 (M^++1, 11), 193 (49), 161 (12), 147 (14), 133 (20), 122 (100), 107 (62), 91 (22), 79 (18), 38 (19).

*(3-Oxo-2pent-2-enyl-cyclopentyl)-acetic acid methyl ester [(±)-methyl jasmonate (**1**)]*

Methyl ester **8** (0.170 g, 0.75 mmol) was dissolved in hexanes/ethyl acetate 2:1 v/v (3.0 cm^3) and hydrogenated (balloon) over Lindlar/quinoline (0.010 g) at 0 °C for 2 h. The mixture was filtered through Celite® and the filtrate was evaporated at reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl ether 2:1 v/v), to afford (±) methyl jasmonate-**1** (0.139 g, 0.622 mmol, 83%).; IR ν_{max}/cm^{-1} 2955, 1736, 1452, 1160 (film); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, *J* 7.5 Hz, 3H), 1.88-2.45 (m, 11 H); 2.71 (dt, *J* 10.9 and 3.8 Hz, 1 H), 3.69 (s, 3 H), 5.25 (dtt, *J* 10.8, 7.4 and 1.6 Hz, 1 H), 5.45 (dtt, *J* 10.8, 7.2 and 1.6 Hz, 1 H); MS *m/z* (relative intensity) 225 (M^++1, 100), 224 (M^+, 72), 207 (18), 193 (18), 197 (17), 151 (51), 133 (36), 93 (29), 83 (39), 38.

*(2-Allyl-3-Oxo-cyclopentyl)-acetic acid methyl ester (**9**)*

To a solution of oxazoline cyanocuprate **3** (2.00 mmol) prepared as above, was added 2-cyclopenten-1-one (0.164 g, 2.00 mmol) in THF (2.0 cm^3). After 40 min at –78 °C tributyltin chloride (0.650 g, 2.00 mmol) in THF (2.0 cm^3) was added and the solution was stirred for 30 min at this temperature and then warmed to –45 °C. A solution of allyl bromide (1.209 g, 10.00 mmol) in HMPA (10.0 cm^3) was added, and the solution was kept at –30 °C for 30 h. Ethyl ether (5.0 cm^3) and a 10% NH_4OH solution in a saturated NH_4Cl solution (3.0 cm^3) were added and this mixture was stirred for 30 min. After the addition of ethyl ether (10.0 cm^3), the phases were separated and the aqueous phase was extracted with ethyl ether (3 x 5.0 cm^3). The combined organic extracts was washed with saturated NaCl solution (1 x 5.0 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was taken up in methanol (7.0 cm^3). Four drops of concentrated sulfuric acid was added and the solution refluxed for 8 h. The solution was concentrated under reduced pressure and the crude product was diluted with ethyl ether (10.0 cm^3). The organic extract were washed with saturated NaCl solution (3 x 5.0 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (ethyl ether/hexane 3:1 v/v) to give compound **9** (0.178g, 38 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22-2.70 (m, 10 H); 3.71 (s, 3 H); 5.04-5.11 (m, 2 H); 5.70-5.77 (m 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.55, 32.59, 38.00, 38.15, 39.03, 51.97, 54.08, 117.77, 135.39, 172.85, 218.87; MS *m/z* (relative intensity) 197 (M^++1, 52), 196 (M^+, 49), 179 (13), 167 (11), 123 (100), 107 (11), 95 (24), 81 (15).

*2-[2-(4-Chloro-phenyl)-3-nitro-propyl]-4,4-dimethyl-4,5-dihydro-oxazole (**11**)*

To a solution of oxazoline cyanocuprate **3** (2.00 mmol) previously prepared at –78 °C was added 1-chloro-4-(2-nitro-vinyl)-benzene solution (0.367 g, 2.00 mmol) in dry THF (2 cm^3). After stirring 2 h at –78 °C, the reaction mixture was quenched with 10 % concentrated NH_4OH in saturated NH_4Cl (2.0 cm^3). After the addition of ethyl ether (8.0 cm^3), the phases were separated and the aqueous phase was extracted with ether (3 x 20.0 cm^3). The combined organic extracts were dried over anhydrous Na_2SO_4. The product was isolated by filtration, followed by solvent removal over vacuum and them purified by flash chromatography (ethyl ether/hexane, 6:1 v/v) affording **11** (0.451 g, 76%).; IR ν_{max}/cm^{-1} 2962, 1733, 1664, 1547, 1369, 1245, 819 cm^{-1} (film); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.19 (s, 3 H), 2.68 (dd, *J* 7.5 and 4.2 Hz, 2 H), 3.84 (s, 1 H), 3.85 (s, 1 H), 3.81-4.01 (m, 1 H), 4.63 (dd, *J* 12.9 and 8.5 Hz, 1 H), 4.77 (dd, *J* 12.9 and 6.3 Hz, 1 H), 7.15-7.22 (m, 2 H), 7.27-7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.21, 28.27, 31.96, 40.56, 67.34, 79.34, 129.06, 129.35, 130.38, 134.08, 137.06, 162.59; MS *m/z* (relative intensity) 297 (M^++1, 11), 281 (3), 250 (100), 178 (9), 138 (7), 103 (8), 41 (6).

*3-(4-Chloro-phenyl)-4-nitro-butyric acid methyl ester (**12**)*

To a solution of nitrooxazoline **11** (0.507 g, 1.81 mmol) in ethyl alcohol (5.0 cm^3) was added a catalytic amount of

concentrated H_2SO_4 (~ 5 drops) and refluxed for 52 hours. This solution was concentrated and percolated in a silica-gel column with ethyl alcohol. The mixture was concentrated again and ethyl ether (20.0 cm^3) was added. After washing with water (2 x 15.0 cm^3) and saturated $NaHCO_3$ solution (2 x 15.0 cm^3), the organic layer was dried under Na_2SO_4 and evaporated under reduced pressure. The product was purified by flash chromatography (hexane: ethyl acetate, 2:1 v/v) affording **12** in (0.412 g, 84%) yield.; IR ν_{max}/cm $^{-1}$ 2981, 1724, 1548, 1364, 1089, 1010, 983 cm^{-1} (film); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1,18 (t, *J* 7.2 Hz, 3 H);), 2.70 (dd, *J* 16.2 and 7.8 Hz, 1 H), 2.76 (dd, *J* 16.2 and 6.9 Hz, 1 H), 3.97 (m, 1 H), 4.08 (q, *J* 7.2 Hz, 2 H), 4.6 (dd, *J* 12.6 and 7,8 Hz, 1 H), 4/72 (dd, *J* 12.6 and 6.2 Hz, 1 H), 7.15-7.20 (m, 2 H); 7.29-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.09, 37.69, 39.7, 61.16, 79.34, 134.19, 137.06, 170.64.

*4-(4-Chloro-phenyl)-pyrrolidin-2-one (**14**)*

The nitroester **12** (0.150 g, 0.55 mmol) was dissolved in EtOH (7.5 cm^3) and a suspension of methanol wet Raney-Ni (0.037 g) was added at room temperature and stirred for 8 h under (50 psi) of H_2 pressure in a Parr® apparatus. The mixture was suction filtered on Celite, and the residue was washed several times with ethanol. The solvent was evaporated and the residue, purified by flash chromatography using AcOEt, affording 0.045 g of lactam **14** and 0.056 g of the corresponding ethyl 3-(4-chlorophenyl)-4-aminobutanoate **13**. This mixture was refluxed in *o*-xylene affording **14** (0.081g, 75%) as a single product.; IR ν_{max}/cm^{-1} 3428, 3188, 2955, 1670, 1485, 1294, 1093, 827 cm^{-1} (film); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (dd, *J* 16.8 and 8.4 Hz, 1 H), 2.76 (dd, *J* 16.8 and 9.0 Hz, 1 H), 3.38-3.43 (m, 1 H), 3.69 (quint., *J* 8,4 Hz, 1 H), 3.78-3.83 (m, 1 H), 6.3 (bs, 1 H, NH), 7.19 (d, *J* 8.1 Hz, 1 H), 7.32 (d, *J* 8,4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.98, 39.71, 49.79, 128.37, 129.32, 133.29, 140.62, 177.73.

*(±)-Baclofen, hydrochloride (**2**)*

A mixture of 4-(4-Chlorophenyl) pyrrolidin-2-one **15** (0.070 g, 0.35 mmol) in HCl aqueous solution (6 mol L^{-1}, 1.5 cm^3) was heated at 100 °C for 6 h. The solvent was removed under reduced pressure and the residue was triturated in isopropanol yielding a crystalline (±)-baclofen hydrochloride **2** (0.071 g, 82%).; IR ν_{max}/cm $^{-1}$: 3415, 3006, 1713, 1562, 1492, 1407, 1251, 1186, 815 cm^{-1} (KBr, neat); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (dd, *J* 16.5 and 8.7 Hz, 1 H); 2.82 (dd, *J* 16.5 and 5.7 Hz, 1 H); 2.93-3.50 (m, 3 H); 7.34 (d, *J* 8.7 Hz, 2 H), 7.40 (d, *J* 8.7 Hz, 2 H), 7.94 (bs, 3H, NH3$^+$), 12.23 (bs, 1 H, COOH), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.94, 39.70, 43.28, 128.89, 130.27, 132.20, 139.56, 172.71.

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