An Efficient Synthesis of Enantiomerically Pure (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-Rosaprostol Methyl Esters

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Abstract: We report a concise synthesis of the enantiomerically pure 1,2-*trans*-1,5-*cis*-methyl esters of rosaprostol, a prostaglandin derivative used for the treatment of gastric and duodenal ulcers, using as key step the chemo- and stereoselective Michael addition of a Grignard reagent to an unprotected hydroxycyclopentenone.

Key words: cyclopentenones, Grignard reactions, Michael additions, stereoselective synthesis, prostanoids

Rosaprostol, a trade name for 7-(2-hexyl-5-hydroxycyclopentyl)heptanoic acid, is a prostaglandin derivative used for the treatment of gastric and duodenal ulcers which is devoid of many undesirable side effects common to other prostanoids such as diarrhoea, hypotension, and uterine contraction.[1] Rosaprostol has been commercialized as Rosal, the sodium salt of a racemic mixture of the 1,2-*trans*-1,5-*cis* and 1,2-*trans*-1,5-*trans* diastereoisomers of 7-(2-hexyl-5-hydroxycyclopentyl)heptanoic acid (Figure 1). Various syntheses of this racemic mixture of epimers have been reported by several groups.[2]

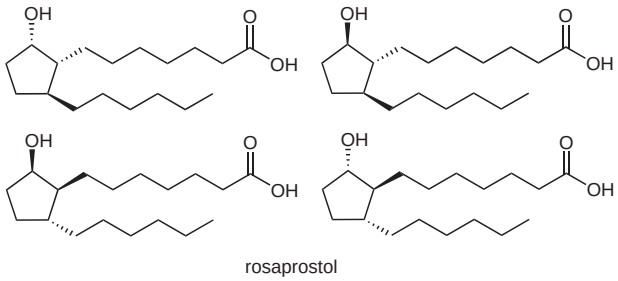
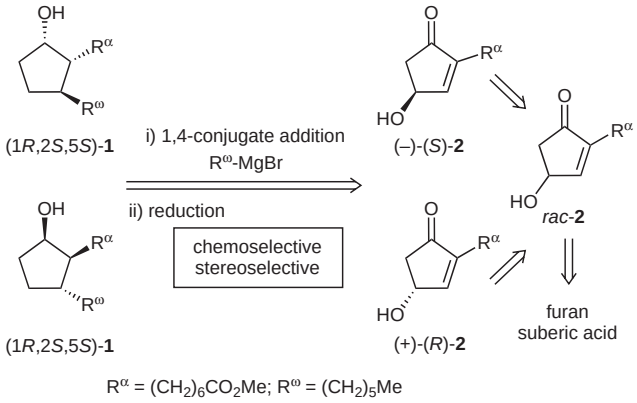


Figure 1

The introduction of enantiopure active pharmaceutical ingredients in the market has been enforced since 1992 by the US Food and Drug Administration (FDA) and the European Committee for Proprietary Medicinal Products, which demand that the physiological action of each enantiomer of a pharmaceutical product must be individually characterized. This may allow for lower dosages and improved efficacy of pharmaceuticals.[3]

We report herein the first synthesis of enantiomerically pure (1*R*,2*S*,5*S*)-**1** and (1*S*,2*R*,5*R*)-**1** (Scheme 1). It was our goal to develop a concise synthesis using readily available chemicals and simple transformations, avoiding the use of protection–deprotection steps, which may be useful for the large-scale preparation of these compounds. The key steps of our synthetic approach consisted in: i) the chemo- and stereoselective hydroxyl-directed 1,4-addition of an organomagnesium reagent to the α,β-unsaturated moiety of the 2-alkyl-4-hydroxycyclopent-2-enones **2**, which will determine the absolute stereochemistry of the stereogenic centers in the target molecules; and ii) the stereoselective reduction of an α,β-unsaturated ketone to saturated alcohol.



Scheme 1

2-Alkyl-4-hydroxycyclopent-2-enones have been widely used as intermediates for the two-component synthesis of prostaglandins[4] and other types of natural or bioactive compounds.[5] It is well known that the addition of organocuprates to their TBS-protected derivatives takes place *anti* with respect to the bulky OTBS group (Scheme 2). On the other hand, the conjugate addition of Grignard reagents to unprotected 4-hydroxycyclopent-2-enones takes place under chelation control and is *cis* with respect to the OH group. This second alternative has the advantage of not requiring protection of the OH group, and the use of simple organomagnesium reagents instead of organocuprates in the conjugate-addition step.[6] However, to date this strategy had only been applied to the functionalization of simple α-alkyl or α-aryl-substituted derivatives, and the compatibility with labile functional groups, such as esters, had not been validated.

The synthesis of optically pure compounds **1** started with the preparation of racemic 2-alkyl-4-hydroxy-2-cyclopent-2-enone **2** as a common precursor for both optically

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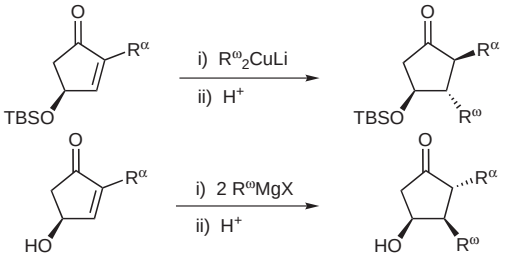
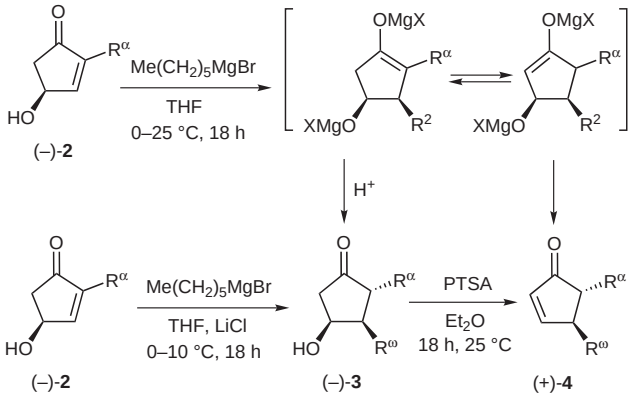


Scheme 2

pure targets by slight modifications of previously reported procedures.[7,8] Kinetic resolution[9] of *rac*-**1** with PPL, using vinyl acetate as solvent and reagent, afforded (–)-(*S*)-**2** (41% yield, 98% ee) and the acetate of (+)-(*R*)-**2** (46% yield, 98% ee), which is converted into (+)-(*R*)-**2** (98% ee) by deprotection with guanidine.[10] It is worth mentioning that compounds (–)-(*S*)-**2** and (+)-(*R*)-**2** can be interconverted by inversion of the stereogenic center with the aid of a Mitsunobu reaction.[7] This operation allows for a maximum yield of either of the optically pure enantiomers of **2**.[11]

For the synthesis of (1*R*,2*S*,5*S*)-**1**, compound (–)-(*S*)-**2** was treated with hexylmagnesium bromide (2 equiv, THF, 0–25 °C, 18 h, Scheme 3). Under these reaction conditions we observed the formation of hydroxycyclopentanone (–)-**3**[12] together with cyclopentenone (+)-**4**[13] in 1:1 ratio and 80% overall yield. The reaction was completely chemoselective, as the presence of an ester group in the R$^{\alpha}$-chain was found to be compatible with the 1,4-conjugate-addition reaction of the organomagnesium reagent to the α,β-unsaturated ketone moiety of (–)-(*S*)-**2**.

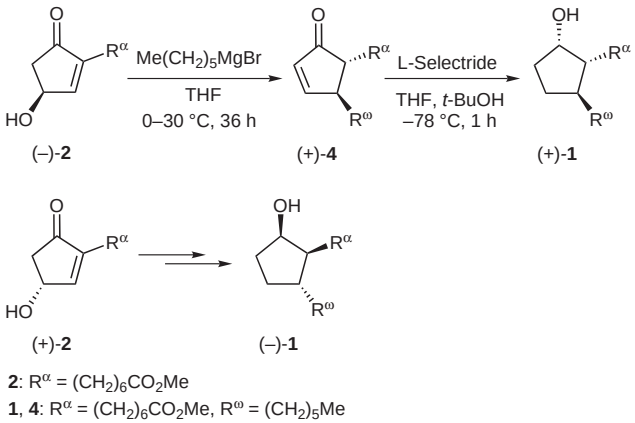


Scheme 3

The formation of compound (+)-**4** prior to the hydrolytic workup of the reaction mixture may be understood by enolate equilibration followed by β-elimination.[14] This was prevented when the conjugate-addition reaction of the organomagnesium reagent was carried out at lower temperature (0–10 °C, 18 h) in the presence of LiCl (2 equiv).[15] Under these reaction conditions, **3** was obtained in 75% yield.

Independent dehydration (Scheme 3) of (–)-**3** (PTSA, Et_2O) gave rise to (+)-**4** in 90% yield.[16] Once it had been confirmed that the enantiomeric purity of (+)-**4** obtained by this two-step procedure was the same as that of (+)-**4** directly isolated from the initial reaction of hexylmagnesium bromide with (–)-(*S*)-**2** in the absence of LiCl, we optimized (Scheme 4) the single-step transformation from (–)-**2** to (+)-**4** (2 equiv hexylmagnesium bromide, THF, 0–30 °C, 36 h), which was obtained in 80% yield.[17] This saves one reaction step in the overall synthesis of the target molecules.

In order to make the reaction sequence as short as possible, the reduction of the C=C double bond and the C=O bond in (+)-**4** was optimized as a one-step stereoselective transformation. Thus, treatment of (+)-**4** with L-Selectride (THF–*t*-BuOH, –78 °C, 1 h)[18,19] gave rise to ester (+)-**1**[20,21] in 75% yield.



Scheme 4

The synthesis of the (1*S*,2*R*,5*R*)-**1** was carried out starting from (+)-(*R*)-**2** following the same reaction sequence (Scheme 4).

In conclusion, we have developed the first synthesis of enantiomerically pure (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-Rosaprostol methyl esters **1**. All the transformations are relatively simple, and make use of readily available chemicals, do not require protection–deprotection steps, and are compatible with the presence of an ester group. This may be of use for the large-scale preparation of these and related prostanoids.

Acknowledgment

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References and Notes

(1) (a) Valcavi, U.; Caponi, R.; Brambilla, A.; Palmira, M.; Minoja, F.; Bernini, F.; Musanti, R.; Fumagalli, R. *Arzneim.-Forsch.* **1982**, *32*, 657. (b) Adami, M.; Scarpignato, C.; Signorini, G.; Coruzzi, G.; Bertaccini, G. *Farmaco Ed. Prat.* **1984**, *39*, 409. (c) Fumagalli, R.; Caponi, R.; Corsini, A.; Brambilla, A.; Palmira, M.; Bernini, F.; Valcavi, U. *Prostaglandins* **1985**, *29*, 467. (d) Tincani, G. P.; Maniscalco, G.; Gunelli, M.; Ciarrocchi, V. *Minerva Medica* **1987**, *78*, 847. (e) Aly, A. *Scand. J. Gastroenterol.* **1987**, *Suppl. 137*, 43. (f) Canonica, G. W.; Ciprandi, G.; Scordamaglia, A.; Ruffoni, S.; Pizzorno, G.; Caria, M.; Cheli, R. *Ann. Allerg.* **1988**, *60*, 541. (g) Di Murro, R.; Camarri, E.; Ciani, D.; Mariotti, L.; Nencioni, C.; Romagnoli, A. M. *Int. J. Clin. Pharm. Res.* **1988**, *8*, 345. (h) Foschi, D.; Trabucchi, E.; Galeone, M.; Ferrante, F.; Toti, G. L.; Castoldi, L.; Musazzi, M.; Centenero, A.; Montorsi, W. *Int. J. Tissue React.* **1988**, *10*, 53. (i) Ciprandi, G.; Ruffoni, S.; Ciani, D.; Tosca, M. A.; Canonica, G. W. *Int. J. Immunol.* **1989**, *5*, 81. (j) Calcamuggi, G.; Babini, G.; Arduino, C.; Lanzio, M.; Anfossi, G.; Ciani, D.; Emanuelli, G. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1991**, *21B*, 789.

(2) (a) Valcavi, U. DE 2535343, **1976**. (b) Valcavi, U.; Innocenti, S.; Bosone, E.; Farina, P.; Marotta, V.; Zabban, G. B. EP 155392, **1985**. (c) Shono, T.; Kise, N. *Tetrahedron Lett.* **1990**, *31*, 1303. (d) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175. (e) Tanimori, S.; Kainuki, T.; Nakayama, M. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 1807. (f) Mikolajczyk, M.; Zurawinski, R. *J. Org. Chem.* **1998**, *63*, 8894. (g) Mikolajczyk, M.; Mikina, M.; Zurawinski, R. *Pure Appl. Chem.* **1999**, *71*, 473. (h) Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601. (i) Mikolajczyk, M.; Mikina, M.; Jankowiak, A.; Mphahlele, M. J. *Synthesis* **2000**, 1075. (j) Trost, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, *66*, 7714. (k) Mikolajczyk, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1839. (l) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (m) List, B.; Castello, C. *Synlett* **2001**, 1687.

(3) See for example: Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788; and references cited therein.

(4) See for example: (a) West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 2402. (b) West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 5043. (c) Johnson, C. R.; Golebiowski, A.; Braun, M. P.; Sundram, H. *Tetrahedron Lett.* **1994**, *35*, 1833. (d) Pudukulathan, Z.; Manna, S.; Hwang, S.-W.; Khnapure, S. P.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *J. Am. Chem. Soc.* **1998**, *120*, 11953. (e) Usami, Y.; Numata, A. *Synthesis* **1999**, 723. (f) Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328. (g) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2002**, *43*, 4575.

(5) (a) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeld, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480. (b) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

(6) (a) Csaky, A. G.; Mba, M.; Plumet, J. *J. Org. Chem.* **2001**, *66*, 9026. (b) Csaky, A. G.; Contreras, C.; Mba, M.; Plumet, J. *Synlett* **2002**, 1451. (c) Csaky, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092.

(7) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Eur. J. Org. Chem.* **1999**, 2655.

(8) According to ref. 7, condensation of furan with suberic acid monomethyl ester afforded the corresponding furylketone, which was reduced to methyl-8-(2-furyl)-8-hydroxy-octanoate. This was transformed into methyl 7-(2-hydroxy-5-oxocyclopent-3-enyl)heptanoate by a Nazarov cyclization. Isomerization to *rac*-**2** was best performed upon treatment with an aqueous phosphate buffer solution: To a solution of methyl 7-(2-hydroxy-5-oxocyclopent-3-enyl)heptanoate (1.28 g, 5.33 mmoL) in 1,4-dioxane (50 mL) was added a phosphate buffer solution (pH 8, 37 mL) and the mixture was heated at reflux for 30 h. Concentration under reduced pressure followed by extraction with EtOAc afforded an oil which was purified by chromatography (hexane–EOtAc, 8:2) to give *rac*-**2** in 80% yield.

(9) Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L. *J. Org. Chem.* **1990**, *55*, 3377.

(10) Enzymatic resolution of **2** was carried out according to ref. 9. For a more recent report of the resolution of **2**, see ref. 7. Compounds (+)-**2** and (–)-**2** are commercially available (Aldrich).

(11) For a recent preparation of (+)-**2** from methyl oleate and 2,3-*O*-isopropylidene-D-glyceraldehyde, see: Muhammad Nor, O.; Hamilton, R. J. *J. Palm Oil Res.* **2004**, *16*, 37.

(12) **(–)-Methyl 7-[(1*R*,2*R*,3*S*)-2-Hexyl-3-hydroxy-5-oxocyclopentyl]heptanoate [(–)-3]**
$[\alpha]_D^{25}$ –22 (*c* 3.5, $CHCl_3$). R_f = 0.22 (CH_2Cl_2–EtOAc, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.48 (m, 1 H), 3.67 (s, 3 H), 2.36–2.28 (m, 4 H), 2.13–2.05 (m, 1 H), 1.90–1.80 (m, 1 H), 1.66–1.50 (m, 8 H), 1.38–1.25 (m, 12 H), 0.93 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.8 (s), 175.0 (s), 75.2 (d), 51.8 (q), 50.6 (d), 48.6 (d), 47.0 (t), 39.7 (t), 32.5 (t), 30.5 (t), 30.0 (t), 28.6 (t), 28.3 (t), 27.6 (t), 27.02 (t), 26.8 (t), 23.8 (t), 23.1 (t), 14.5 (q) ppm.

(13) **(+)-Methyl 7-[(1*R*,2*S*)-2-Hexyl-5-oxocyclopent-3-enyl)heptanoate [(+)-4]**
$[\alpha]_D^{25}$ +34 (*c* 2.7, $CHCl_3$). R_f = 0.89 (CH_2Cl_2–EtOAc, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (dd, ^3J = 1.59 Hz, ^3J = 5.67 Hz, 1 H), 6.1 (dd, ^3J = 1.68 Hz, ^3J = 5.70 Hz, 1 H), 3.67 (s, 3 H), 2.62–2.53 (m, 1 H), 2.30 (t, *J* = 7.35 Hz, 2 H), 1.98–1.89 (m, 1 H), 1.65–1.56 (m, 2 H), 1.37–1.23 (m, 18 H), 0.91–0.86 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.9 (s), 174.6 (s), 167.7 (d), 133.2 (d), 52.2 (d), 51.8 (q), 48.6 (d), 35.0 (t), 34.4 (t), 32.2 (t), 32.1 (t), 31.6 (t), 29.8 (t), 29.3 (t), 27.2 (t), 25.3 (t), 23.1 (t), 22.9 (t), 14.5 (q) ppm.

(14) Csaky, A. G.; Mba, M.; Plumet, J. *Tetrahedron: Asymmetry* **2004**, *15*, 647.

(15) To a suspension of LiCl (0.52 mmol) in THF (0.75 mL) at 0 °C was added hexylmagnesium bromide (2 M solution in Et_2O, 0.26 mL) and the mixture was stirred for 5 min. A solution of (–)-**2** (0.23 mmol) in THF (0.75 mL) was added dropwise. The mixture was stirred at 0–10 °C for 18 h, and hydrolyzed with sat. NH_4Cl. The organic layer was decanted and the aqueous layer extracted with Et_2O. The combined organic layers were dried on $MgSO_4$. Filtration and elimination of the solvent under reduced pressure afforded an oil that was purified by chromatography (CH_2Cl_2–EtOAc, 8:2).

(16) To a solution of (–)-**3** (0.14 mmol) in Et_2O (2.2 mL) was added PTSA (0.035 mmol) and the solution was stirred at 25 °C for 18 h. The mixture was diluted with Et_2O and washed with sat. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The resulting oil was purified by chromatography (CH_2Cl_2–EtOAc, 8:2).

(17) To a solution of (–)-**2** (0.23 mmol) in THF (0.75 mL) at 0 °C was added dropwise a 2 M solution of hexylmagnesium bromide in Et_2O (0.26 mL). The mixture was stirred from 0 °C to 30 °C for 36 h, and hydrolyzed with sat. NH_4Cl solution. The organic layer was decanted and the aqueous layer extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. Filtration and elimination of the solvent

under reduced pressure afforded an oil that was purified by chromatography (CH_2Cl_2–EtOAc, 8:2).

(18) To a solution of L-Selectride (0.3 mL) in THF (0.3 mL) at –78 °C was added dropwise a solution of **3** (0.1 mmol) in *t*-BuOH (20 μL) and THF (0.5 mL) and the mixture was stirred at –78 °C for 1 h. The mixture was hydrolyzed with sat. NH_4Cl solution at –78 °C. The organic layer was decanted and the aqueous layer extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. Filtration and elimination of the solvent under reduced pressure afforded an oil that was purified by chromatography (hexane–EtOAc, 8:2).

(19) For a previous use of L-Selectride with KH_2PO_4 as proton source to convert an enone into an alcohol, see: Bell, R. A.; Turner, J. V. *Tetrahedron Lett.* **1981**, *22*, 4871.

(20) **(+)-Methyl 7-[(1*R*,2*S*,5*S*)-2-Hexyl-5-hydroxycyclopentyl]heptanoate [(+)-1]**
$[\alpha]_D^{25}$ +13 (*c* 0.6, $CHCl_3$). R_f = 0.43 (hexane–EtOAc, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.25–4.18 (m,1 H), 3.68 (s, 3 H), 2.31 (t, *J* = 7.35 Hz, 2 H), 2.07–1.91 (m, 1 H), 1.91–1.77 (m, 1 H), 1.67–1.54 (m, 4 H), 1.37–1.22 (m, 20 H), 0.91–0.87 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8 (s), 74.8 (d), 51.9 (q), 42.3 (d), 39.6 (d), 35.5 (t), 34.5 (t), 33.9 (t), 32.3 (t), 32.3 (t), 30.1 (t), 29.5 (t), 29.4 (t), 28.7 (t), 28.6 (t), 28.0 (t), 25.3 (t), 23.1 (t), 14.5 (q) ppm.

(21) The *cis* relative stereochemistry of the OH and R^1 groups in (+)-**1** was unambiguously determined by COSY and NOE measurements. Saturation of the H5 signal (δ = 4.25–4.18 ppm, m, 1 H) afforded a 4% increase of the H2 signal (δ = 1.91–1.77 ppm, m, 1 H).