Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6101-6104, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01259-8

A Convenient Synthesis of the (±)-Prelog-Djerassi Lactone from Cyclopentanone

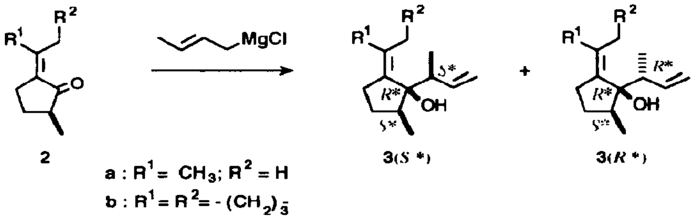
Christiane Santelli-Rouvier, Sophie Lefrère and Maurice Santelli

Laboratoire de Synthèse Organique associé au CNRS, Centre de St-Jérôme, 13397 Marseille Cedex 20 (France)

Abstract : The stereoselective addition of crotyl Grignard reagent to 2-alkylidene-5-methylcyclopentanones followed by dehydration, 1,4-reduction of the triene, ozonolysis and Baeyer-Villiger oxidation afforded a δ-lactone (28 % of overall yied), well-known precursor of the Prelog-Djerassi Lactone.

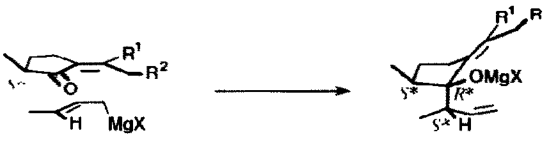
The Prelog-Djerassi lactone **1** (Scheme 3) is a degradation product of methymycin and narbomycin and a synthon for the preparation of several macrolide antibiotics.[1] Considering several strategies, the main difficulty is the elaboration of the side chain chirality (6*R*-stereogenic center).[1,2]

We have shown that unprecedented stereoselectivity is achieved in the addition of allylic Grignard reagents to 2-alkylidenecyclohexanones.[3] In the same way, a good selectivity is observed in the addition of crotylmagnesium to 2-alkylidenecyclopentanones.[3b] Thus, the addition of crotylmagnesium chloride to (±)-5-methyl-2-isopropylidenecyclopentanone **2a** and (±)-5-methyl-2-cyclopentylidenecyclopentanone **2b** [4] led respectively to the alcohols **3a** or **3b** in high yield (90 %) and good selectivity **3(*S**)** : **3(*R**)** = 85 : 15 (Scheme 1).[5]



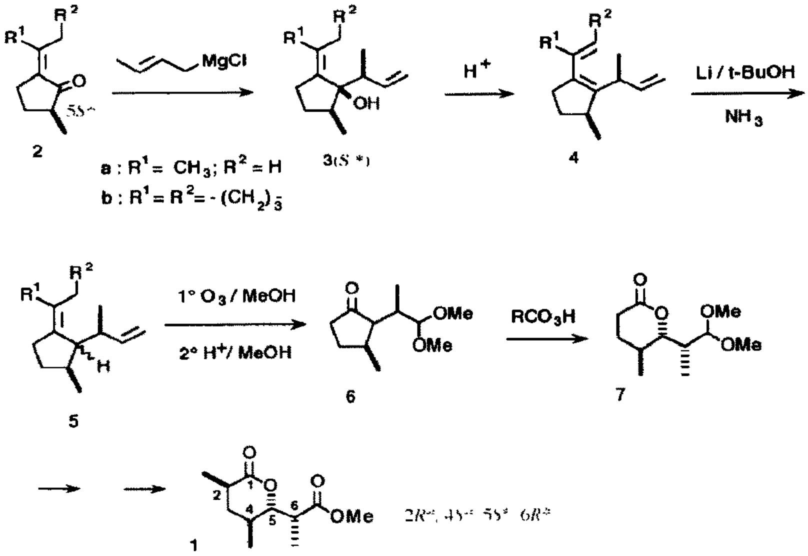
Scheme 1.

The stereo- and regioselectivity data can be nicely accommodated by assuming an open transition state with respect to the Grignard reagent and a boat-like conformation of the two reactants with respect to each other corresponding to a compact approach (Scheme 2). As the approach is solely *ul* demands that the addition takes place with the trans form of the allylic Grignard reagent.[3b]



Scheme 2.

From the inseparable mixture of alcohols **3a** or **3b**, the acetal **7** is obtained in four steps, the minor contaminant diastereomer could be conveniently removed during the synthetic stages. Dehydration (heating in acetic acid solution) led regioselectively to the trienes **4** (80 % yield).[6] The 1,3-diene moiety was 1,4-reduced by lithium (or sodium) in ammonia and gave rise to a 1 : 1 diastereomeric ratio of the dienes **5** (70 % yield).[7] Ozone was added to the methanol solution of **5** followed by addition of dimethylsulfide and acidic treatment of the crude product. The reaction was monitored by TLC to avoid the acetalization of the cyclopentanone moiety.[8] Only one diasteromer **6** (55 % yield) was obtained which is submitted to the action of *m*-chloroperbenzoic acid. The lactone **7** was obtained in 91 % yield.[9]



Scheme 3.

7 is a well known precursor of the Prelog-Djerassi lactone **1** (the following steps are the alkylation in 2-position and ozonolysis).[1,9] In summary, the Prelog-Djerassi lactone has been synthesized in a short and convenient route with good yields and excellent diastereoselectivity.

References :

1. for reviews, see : (a) Paterson, I.; Mansuri, M.M. *Tetrahedron* **1985**, *41*, 3569-3624.
   (b) Martin, S.F.; Guinn, D.E. *Synthesis* **1991**, 245-262.

2. (a) Grieco, P.A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749-4752.
   (b) Wovkulich, P.M.; Uskokovic, M.R. *J. Org. Chem.* **1982**, *47*, 1600-1602.

3. (a) El Idrissi, M.; Santelli, M. *J. Org. Chem.* **1988**, *53*, 1010-1016.
   (b) Zair, T.; Santelli-Rouvier, C.; Santelli, M. *J. Org. Chem.* **1993**, *58*, 2686-2693.

4. **2a** and **2b** were obtained respectively by alkylation (LDA/methyl iodide) of 2-isopropylidenecyclopentanone or 2-cyclopentylidenecyclopentanone according to the known procedure (for example see: 3b)(59 % yield). **2a** : ^{1}H NMR δ 2.4 (1, m), 1.97 (3, br. s), 1.55 (3, br. s), 0.78 (3, d *J* = 6.5 Hz); ^{13}C NMR δ 208.6 (s), 146.8 (s), 130.5 (s), 45.0 (d), 28.6 (t), 26.8 (t), 24.0 (q), 20.0 (q), 14.5 (q). **2b** : ^{1}H NMR δ 2.73 (1, m), 2.32 (8, m), 1.83 (4, m), 1.06 (3, d *J* = 6.7 Hz); ^{13}C NMR δ 207.4 (s), 157.6 (s), 127.1 (s), 44.0 (d), 33.4 (t), 31.8 (t), 28.6 (t), 26.7 (t), 26.3 (t), 24.6 (t), 14.1 (q).

5. The addition of crotylmagnesium chloride to **2a** or **2b** according to the Barbier procedure (see 3a) gave to an inseparable mixture of **3a** or **3b** (90 % yield, **3a,b(2*S**)** : **3a,b(2*R**)** = 85 : 15). **3a(2*S****)(major diastereomer) : ^{1}H NMR δ 5.69 (1, m), 4.97 (2, m), 2.68 (1, q *J* = 6.8 Hz), 1.87 (3, d *J* = 1.4 Hz), 1.62 (3, br s), 1.04 (3, d *J* = 6.8 Hz), 0.88 (3, d *J* = 6.8 Hz); ^{13}C NMR δ 140.9 (d), 139.3 (s), 127.0 (s), 114.1 (t), 83.8 (s), 45.5 (d), 39.3 (d), 30.4 (t), 29.4 (t), 23.0 (q), 20.1 (q), 15.5 (q), 13.7 (q). **3b(2*S****)(major diastereomer) :^{1}H NMR δ 5.75 (1, ddd *J* = 18.0, 9.8, 6.7 Hz),4.97 (2, m), 2.68 (1, quint *J* = 6.7 Hz), 1.04 (3, d *J* = 6.8 Hz), 0.9 (3, d *J* = 6.8 Hz); ^{13}C NMR δ 140.8 (d), 137.2 (s), 136.8 (s), 114.1 (t), 83.6 (s), 44.6 (d), 39.1 (d), 32.8 (t), 30.9 (t), 30.0 (t), 29.9 (t), 27.6 (t), 25.3 (t), 15.8 (q), 13.7 (q); **IR** 3500, 3083, 1640, 910 cm^{-1}.

6. Alcohols **3a** or **3b** (4.25 g) in acetic acid (40 mL) was refluxed for 1 h. After cooling, ether was added and the solution was washed with a solution of $NaHCO_3$ and dried over $MgSO_4$. **4a**: ^{1}H NMR δ 5.91 (1, ddd *J* = 16.7, 10.7, 6.2 Hz), 4.96 (2, m), 4.93 (1, br. s), 4.75 (1, br. s), 3.49 (1, qd *J* = 6.8, 6.2 Hz), 2.73 (1, m), 1.82 (3, s), 1.18 (3, d *J* = 6.4 Hz), 1.07 (3, d *J* = 6.8 Hz); ^{13}C NMR δ 144.4 (s), 142.7 (s), 142.3 (d), 138.5 (s), 112.8 (t), 112.6 (t), 41.4 (d), 36.9 (d), 34.3 (t), 32.5 (t), 22.7 (q), 20.9 (q), 20.0 (q); IR 3078, 1633, 910 cm^{-1}.**4b** (major diastereomer) shown : ^{1}H NMR δ 5.92 (1, ddd *J* = 16.7, 10.8, 6.8 Hz), 5.62 (1, t *J* = 2.0 Hz), 4.99 (1, dd *J* = 16.7, 5.8 Hz), 4.97 (1, dd *J* = 10.8, 5.8 Hz), 3.64 (1, qd *J* = 7.0, 6.8

Hz), 2.78 (1, m), 1.20 (3, d $J = 7.0$ Hz), 1.05 (3, d $J = 6.8$ Hz); ^{13}C NMR δ 145.5 (s), 140.7 (s), 132.5 (s), 142.1 (d), 128.2 (d), 112.9 (t), 41.9 (d), 36.9 (d), 34.8 (t), 34.3 (t), 32.3 (2C)(t), 23.9 (t), 21.1 (q), 19.9 (q); IR 3078, 1637, 909 cm^{-1}.

7. In a dry, three-necked reaction flask at -40 °C, equipped with a magnetic stirrer, a dry ice condenser and a dropping funnel, ammonia (160 mL) was condensed. Pieces of lithium were added (0.42 g, 0.06 g-atom) followed by a slow addition of **4a** (5.2 g, 30 mmol) or **4b** (6.0 g, 30 mmol) in *tert*-butyl alcohol (4.5 g, 60 mmol, 2 equiv.). After ammonia evaporation and anhydrous ether addition, the solution was washed to neutrality and the ethereal extract dried over $MgSO_4$.

8. Ozone in oxygen is bubbled through a methanolic solution (50 ml) of crude diene **5** (20 mmol) which contained a few drops of an ethanolic solution of "Soudan III" (Eastman Kodak)(1/10000)(ref. 10) at -60 °C until the solution turned yellow. While the solution was still at -60 °C, the system was flushed with nitrogen and dimethylsulfide (7 mL) was then added. At room temperature, a crystal of camphorsulfonic acid and methyl orthoformate (100 mmol) were added. Ketalization is followed by TLC. The solvent is eliminated under vacuo and the product chromatographed on silica gel. **6** : ^{1}H NMR δ 4.67 (1, d $J = 8.7$ Hz), 3.34 (3, s), 3.31 (3, s), 1.14 (3, d $J = 5.6$ Hz), 0.91 (3, d $J = 7.0$ Hz); ^{13}C NMR δ 219.7 (s), 105.7 (d), 57.3 (d), 53.5 (q), 52.8 (q), 38.8 (t), 34.3 (2C)(d), 29.9 (t), 19.6 (q), 11.9 (q); mass spectra *m/z* 183 (0.4), 169 (3), 137 (3.5), 109 (2.4), 102 (20), 75 (100), HRMS calcd for $C_{10}H_{17}O_2$ 169.12285, found 169.1223.

9. Hacini, S.; Santelli, M. *Tetrahedron* **1990**, *46*, 7787-7792.

10. Veysoglu, T.; Mitscher, L.A.; Swayze, J.K. *Synthesis* **1980**, 807-810.

(*Received in France* 16 *May* 1994; *accepted* 28 *June* 1994)