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Enantioselective Synthesis of the Prelog-Djerassi Lactonic Acid *via* Group-Selective Aldolization/Desymmetrization of a *Meso* Dialdehyde with a Chiral *N*-Propionylsultam.

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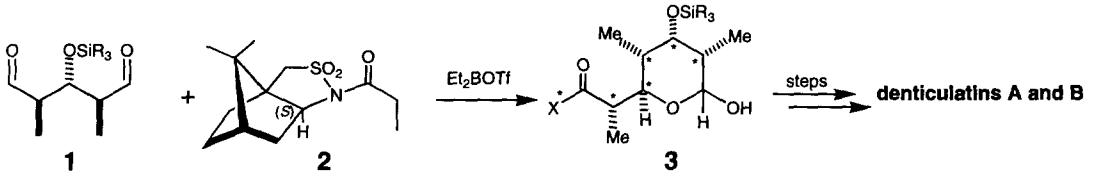
Abstract: The group-selective aldolization/desymmetrization of *meso* dialdehyde **5** with a borylenolate derived from *N*-propionylbornanesultam ***ent*-2** yields very efficiently lactols **6** with simultaneous generation of four stereogenic centers. Oxidation (**6** → **7**) followed by saponification of the sultam moiety (**7** → **4**) provided the Prelog-Djerassi lactonic acid **4** in a three step sequence in 61-71% overall yield. © 1997, Elsevier Science Ltd. All rights reserved.

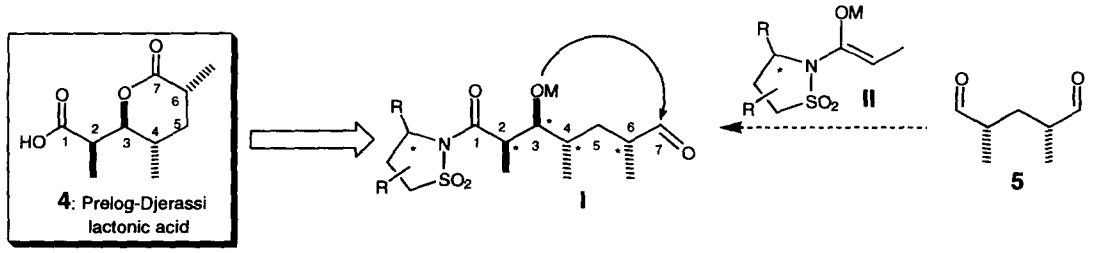
The architectural and stereochemical complexity of polyketide-derived natural products offers a unique platform for the development of new synthetic methods and concepts.[1] Among these, new versions of the aldol reaction constitute one of the most powerful ways for generating the contiguous stereogenic centers during the carbon-carbon bond forming steps.[2] In this context, we have described the preparation of crystalline, optically pure *syn*- or *anti*-aldols from sultam-derived enolates.[3] Furthermore, as part of a recent synthesis of the marine polypropionates (-)-denticulatins A and B, we presented, to the best of our knowledge, for the first time an enantiotopic group differentiation in a *meso* dialdehyde by an aldolization reaction (Scheme 1).[4,5]

Scheme 1



Thus, desymmetrization of *meso* dialdehyde **1** (SiR_3 = TBS or TIPS) by aldolization with the Z-(O)-borylenolate derived from *N*-propionylbornanesultam **2**, furnished a mixture of lactols **3** in 74-95% yield and with diastereomeric ratio's of 11.5-20 : 1. During the process, five contiguous stereogenic centers were generated. Herein we wish to report another application of this approach towards the synthesis of the Prelog-Djerassi lactonic acid **4** (Scheme 2).

Scheme 2

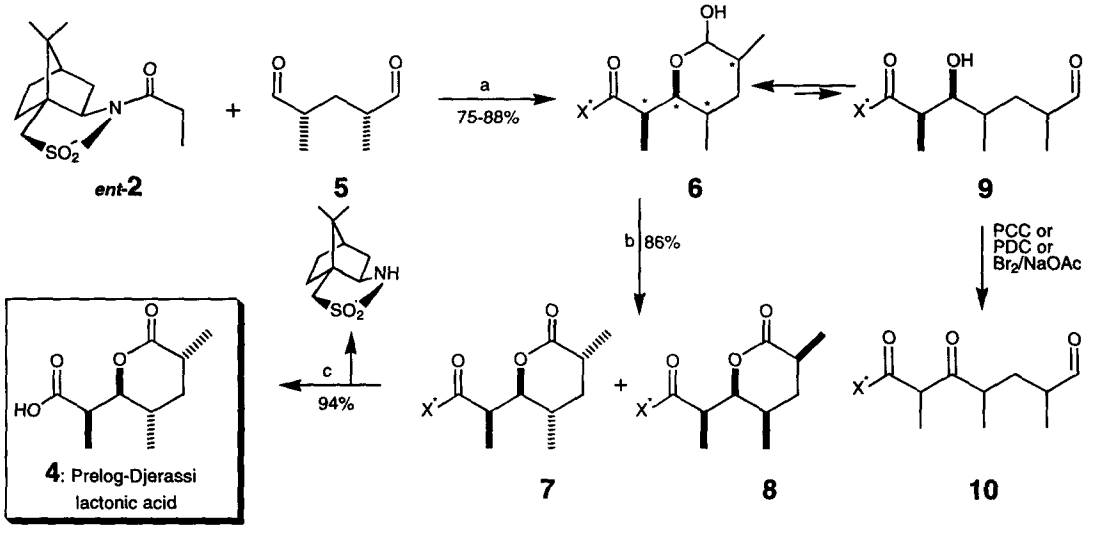


† Deceased March 15, 1996.

The Prelog-Djerassi lactonic acid **4** was isolated as an oxidative degradation product of neomethymycin, methymycin, narbomycin and picromycin.[6] It's full stereochemistry was established by Rickards and Smith in 1970.[7] Being the target for numerous synthetic investigations, the Prelog-Djerassi lactonic acid **4**, served both in the structural elucidation and the synthesis of macrolide antibiotics. Since substituents and stereochemical interrelationships present in **4** are also found in other oxygenated natural products, the synthesis of Prelog-Djerassi lactonic acid served as a probe for the invention and development of new methods and strategies for controling the stereoselective construction of cyclic and acyclic systems containing three or more contiguous and/or alternating stereocenters.[8] Our very different strategy forsees the desymmetrization of a *meso* dialdehyde with a chiral sultam-derived enolate (Scheme 2, **5** + **II** → **I**) with simultaneous generation of four stereogenic centers. Functional group transformation of aldol **I**, containing the complete carbon skeleton of **4**, would ultimately lead to the Prelog-Djerassi lactonic acid.

In Scheme 3 we outline our synthesis of the Prelog-Djerassi lactonic acid, which began with the crucial aldolization/desymmetrization as a key step.

Scheme 3



(a) ***ent*-2** (1 mol-equiv.), Et_2BOTf (1.15 mol-equiv.), *i*-Pr_2NEt (1.17 mol-equiv.), CH_2Cl_2, 0°C, 0.5 h; **5** (1.5 mol-equiv.), CH_2Cl_2, -78°C, 2 h. (b) TPAP (0.05 mol-equiv.), NMO (1.5 mol-equiv.), powdered 4 Å molec. sieves, CH_2Cl_2, r.t., 2 h. (c) $LiOH.H_2O$ (1.5 mol-equiv.), H_2O_2 (2 mol-equiv.), THF/H_2O (3:1), 0°C, 50 min.

Thus, when *N*-propionylbornanesultam ***ent*-2**[3a] (1 mol-equiv.) was successively treated with (freshly prepared and distilled) diethylboryl triflate[9] (1.15 mol-equiv.)/*i*-Pr_2NEt (1.17 mol-equiv.) and *meso* dialdehyde **5**[10] (1.5 mol-equiv.), we obtained after workup and flash chromatography (FC) a mixture of lactols **6** in 75-88% yield. It turned out to be impossible to determine the presence of other stereoisomers at this stage (analysis by ^1H NMR or GC).

We therefore decided to oxidize the mixture of lactols to the corresponding lactones **7** and **8**. Oxidation of the mixture of lactols **6** with either Br_2/NaOAc, PCC or PDC gave invariable a mixture of lactones **7** and **8**, together with tricarbonyl compound **10**, obtained *via* oxidation of the open chain alcohol **9** (ratio **7** + **8** : **10** = 1.3-2.6 : 1, 90% combined yield). However, when the oxidation was carried out with tetrapropylammoniumper-

ruthenate (TPAP)[11] in the presence of *N*-methylmorpholine-*N*-oxide and powdered 4 Å molecular sieves in CH_2Cl_2, the α,β-*syn*-β,γ-*anti* ("anti-Felkin")[2b] product **7** {m.p. 101-102°C, $[\alpha]_D$ = -68.8 (c=1.04, $CHCl_3$)} was isolated in 75% yield together with the α,β-*syn*-β,γ-*syn* ("Felkin") product **8** in 11% yield and no sign of the tricarbonyl compound **10** could be detected.[12] The "anti-Felkin" : "Felkin" selectivity (ratio **7** : **8**) was determined in every case by ^1H NMR analysis of the crude reaction mixture and proved to be invariable to the oxidation conditions (d.r = 7-8 :1). We can therefore conclude that the diastereomeric ratio determined for the lactones reflects the stereoselectivity for the aldol reaction/desymmetrization (***ent*-2** + **5** → **6**). Finally, hydrogen peroxide assisted saponification of lactone **7** with lithium hydroxide (1.5 mol-equiv.)/hydrogen peroxide (2 mol-equiv.) in a 3 : 1 mixture THF/H_2O, furnished the Prelog-Djerassi lactonic acid **4** {m.p. 124-125°C, $[\alpha]_D$ = +39.8 (c=0.71, $CHCl_3$)}[13] in 94% yield together with a nearly quantitative recovery of the bornanesultam auxiliary.

In summary, the enantioselective synthesis of the Prelog-Djerassi lactonic acid **4**, obtained from *meso* dialdehyde **5** *via* a 3 step sequence in 61-71% overall yield, demonstrates once more the power of the group selective aldolization/desymmetrization with bornanesultam-derived enolates as very efficient chirophores. This represents, to our knowledge, the shortest synthesis of the Prelog-Djerassi lactonic acid. Generalization of this concept with other types of *meso* dialdehydes and differently substituted bornanesultam-derived enolates will be reported in due course.

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10) *Meso* dialdehyde **5** was prepared from the corresponding known diol (J. C. Anderson, S. V. Ley, S. P. Marsden, *Tetrahedron Lett.* **1994**, *35*, 2087; Y.-F. Wang, C.-S. Chen, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1984**, *106*, 3695) *via* double Swern oxidation followed by a non-aqueous workup (precipitation of the ammoniumsalts with toluene and hexane and filtration over celite).

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12) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra. Experimental procedure and spectral data for compounds **7** and **8**: To a stirred solution of diethylboryl triflate (freshly prepared and distilled[9], 0.22 ml, 1.22 mmol) in dry CH_2Cl_2 (0.8 ml) was added at 0°C a solution of *N*-propionyl sultam ***ent*-2** (288 mg, 1.06 mmol) in dry CH_2Cl_2 (1 ml + 1 ml rince) followed by diisopropylethylamine (216 µl, 1.24 mmol). The mixture was stirred for 30 min at 0°C and then cooled to -78°C after which a solution of the *meso* dialdehyde **5** (204 mg, 1.59 mmol) in CH_2Cl_2 (2 ml + 1 ml rince) was added dropwise at -78°C. After stirring for 1-1.5 h at -78°C, the mixture was quenched by the addition of aq. phosphate buffer (pH 7, 2 ml), allowed to reach r.t., followed by extraction of the aq. phase with CH_2Cl_2 (3 X 10 ml). After drying ($MgSO_4$) and concentration, the residue was purified by flash chromatography (EtOAc/hexanes 1:4) to yield the corresponding lactols (373 mg, 88%). A Solution of a part of this mixture of lactols (140 mg, 0.35 mmol) in dry CH_2Cl_2 (1 ml) was added to a solution of *N*-methyl morpholine-*N*-oxide (63 mg, 0.54 mmol) and tetrapropylammoniumperruthenate (6.3 mg, 0.017 mmol) in dry CH_2Cl_2 (1 ml), containing 4Å powdered molecular sieves (200 mg). After stirring for 2 h at r.t., the mixture was filtered over a short path of silica gel, concentrated and purified by flash chromatography (silica gel, EtOAc/hexanes 1:5). The major diastereoisomer **7** was isolated in 75% yield (106 mg) and the minor isomer **8** in 11% yield (16 mg): **7**: m.p. 101-102°C IR: 2967, 2874, 1725, 1692, 1458, 1376, 1332, 1267 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 3 H), 1.01 (d, 3 H, *J* = 6.2 Hz), 1.15 (s, 3 H), 1.26 (d, 3 H, *J* = 6.6 Hz), 1.36 (d, 3 H, *J* = 7.1 Hz), 1.31-1.46 (m, 3 H), 1.84-2.02 (m, 5 H), 2.02-2.11 (m, 2 H), 2.45-2.57 (m, 1 H), 3.00-3.35 (dq, 1 H, *J* = 6.6, 7.1 Hz), 3.45 (d, 1 H, *J* = 14.1 Hz), 3.53 (d, 1 H, *J* = 14.1 Hz), 3.89 (t, 1 H, *J* = 6.4 Hz), 4.42 (dd, 1 H, *J* = 6.6, 8.1 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.6 (q), 17.1 (q), 19.1 (q), 19.9 (q), 20.8 (q), 26.4 (t), 32.7 (d), 32.8 (t), 35.5 (d), 36.9 (t), 38.3 (t), 44.4 (d), 44.5 (d), 47.8 (s), 48.4 (s), 53.2 (t), 65.3 (d), 84.8 (d), 172.8 (s), 174.2 (s). Exact mass calc. for $C_{20}H_{31}O_5NS^{+\cdot}$: 397.1923. Found: 397.1938; **8**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (d, 3 H, *J* = 7.1 Hz), 0.98 (s, 3 H), 1.15 (s, 3 H), 1.19 (d, 3 H, *J* = 6.6 Hz), 1.44 (d, 3 H, *J* = 6.6 Hz), 1.00-1.46 (m, 3 H), 1.84-1.94 (m, 3 H), 2.00-2.08 (m, 2 H), 2.25-2.47 (m, 2 H), 2.51-2.68 (m, 1 H), 3.38 (dq, 1 H, *J* = 7.1, 9.7 Hz), 3.45 (d, 1 H, *J* = 14.1 Hz), 3.52 (d, 1 H, *J* = 14.1 Hz), 3.88 (t, 1 H, *J* = 6.4 Hz), 4.52 (dd, 1 H, *J* = 2.7, 9.7 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 15.4 (q), 16.0 (q), 17.0 (q), 19.9 (q), 20.7 (q), 26.5 (t), 28.2 (d), 32.5 (d), 32.8 (t), 35.5 (t), 38.2 (t), 41.7 (d), 44.5 (d), 44.6 (s), 47.8 (s), 53.1 (t), 65.0 (d), 80.4 (d), 173.2 (s), 176.1 (s).

13) Compound **4** was identified by comparison (^{1}H-NMR, ^{13}C-NMR, IR, HRMS) with data of previous prepared samples.[8] See for example: D. A. Evans, J. Bartroli, *Tetrahedron Lett.* **1982**, *23*, 807. **4**: m.p. 122.5-123.5°C, $[\alpha]_D$ = +41.3 (c=2.1, $CHCl_3$).

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