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RING ENLARGEMENT BY FRAGMENTATION REACTION: TRANSFORMATION OF 2-AMINOMETHYL-2-(3-HYDROXYPROPYL)CYCLODODECANONE TO 12-METHYLENE-15-PENTADECANOLIDE

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Summary: A fragmentation reaction was used to transform 2-aminomethyl-2-(3-hydroxypropyl)cyclododecanone to 12-methylene-15-pentadecanolide by ring enlargement.

In preceeding papers we have reported on ring enlargement reactions in which an intramolecular anion (carbanion[1], R-$\bar{\underline{O}}|^{\ominus}$[2], $R^1R^2\bar{N}|^{\ominus}$[3]) attacked an internal ketone group by formation of an alkoholate, a half acetal anion, and an amino half acetal anion, respectively. In the second step the ring enlargement takes place by charge delocalization from R-$\bar{\underline{O}}|^{\ominus}$ to an electron withdrawing group (e.g. $-NO_2$[1], $-SO_2R^4$[4], -CN[5]):

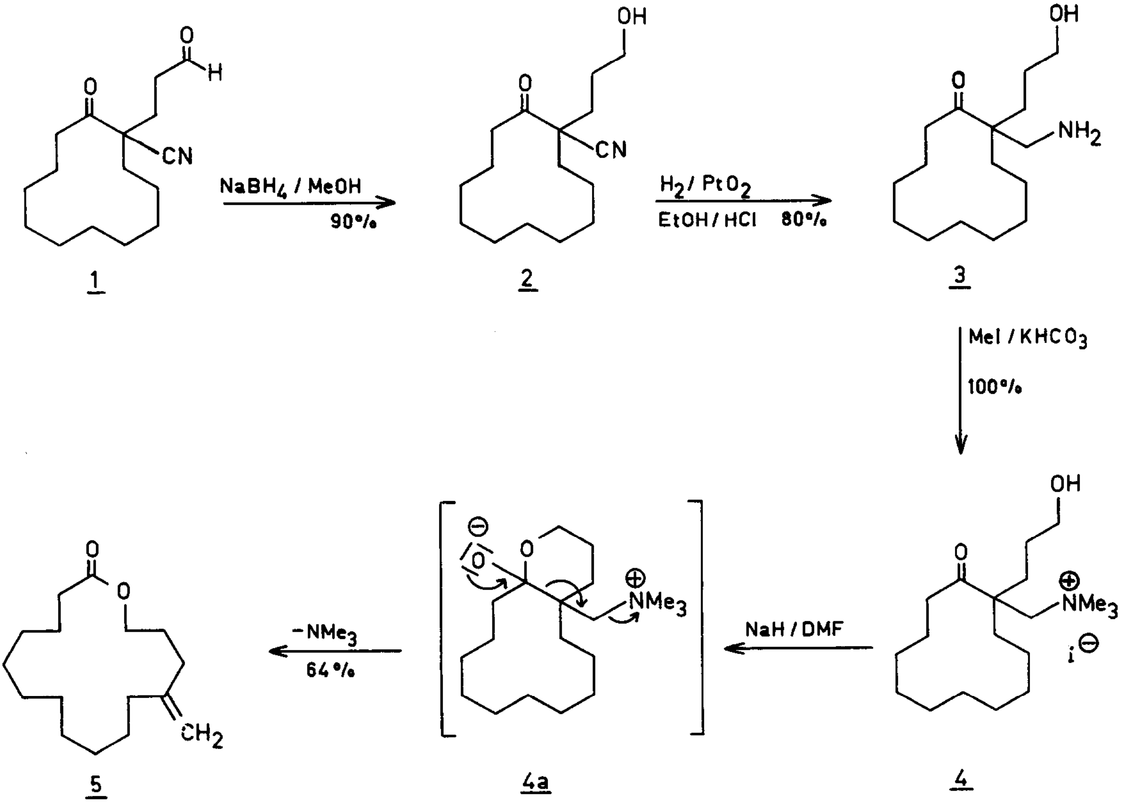
$$^{\ominus}|\bar{\underline{O}} - CR^1R^2 - CR^3R^4 - X \longrightarrow O = CR^1R^2 + {}^{\ominus}CR^3R^4 - X$$

In case of replacement of -X by $-CH_2-Y$ (Y stands for a leaving group) the ring enlargement will proceed via fragmentation reaction. The following report describes the realization of this reaction type.

The aldehyde group in 1-(2-formylethyl)-2-oxocyclododecane-1-carbonitrile (1) prepared by Michael reaction of 2-oxocyclododecane-1-carbonitrile and acrylaldehyde[5] was reduced with $NaBH_4$/MeOH selectively[6] to 1-(3-hydroxypropyl)-2-oxocyclododecane-1-carbonitrile (2)[7]. The reduction of the nitrile group in 2 was achieved by catalytic hydrogenation [3 at H_2/PtO_2 in EtOH/conc.$HCl-H_2O$

(v/v 50:1)] to give 2-aminomethyl-2-(3-hydroxypropyl)cyclododecanone (3, 80% yield). The latter was transformed by MeI in $KHCO_3$/MeOH to [2-(3-hydroxypropyl)-1-oxocyclododecyl]-methylene-trimethylammonium-chloride (4). Addition of 2 equ. of NaH to a solution of 4 in DMF produced 12-methylene-15-pentadecanolide (5) in 64% yield[8]. The reaction was carried out in the presence of a 4 Å molecular sieves in order to trap the crystal water of 4. The reaction was performed under Ar atmosphere at 25°C for 1.5 h. Prolongation of the reaction time lowered the yield of 5, but 4 was still detectable.

Though reactions mentioned at the beginning of this paper seem to require cis configuration of $-\underline{O}|^{\ominus}$ and NO_2[1] and $-\underline{O}|^{\ominus}$ and $-SO_2\phi$[9] in the intermediates we believe that during the transformation of 4 → 5 the known stereochemical mode of a fragmentation reaction takes place. We can not exclude that one part of the intermediate 4a exists in the stereoelectronic not favored configuration (cis arrangement of $-\underline{O}|^{\ominus}$ and $-CH_2-N(Me)_3^{\oplus\,+}$). An electrostatic interaction of the both



groups could prevent the equilibrium between these configurations. This could be responsible for reisolation of 4 after the reaction.

Another synthetic route to macrolides by fragmentation reactions was described earlier[10].

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References and Notes

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[7] The compounds 2 - 5 were completely characterized [IR, ^{1}H-NMR, ^{13}C-NMR, EI-MS, CI-MS, and combustion analysis (without 4)]. The important data are:

Compound 2: Mp = 71.2 - 71.8°C. IR($CHCl_3$): 3520 + 3460 (OH), 2235 (CN), 1720 (CO) cm^{-1}; ^{1}H-NMR($CDCl_3$, 200 MHz): 3.68 (t, J = 6 Hz, $-CH_2OH$), 2.86 - 2.72 (m, $-CH_2CO$) ppm; ^{13}C-NMR($CDCl_3$, 50 MHz): 204.0 (CO), 120.2 (CN), 61.9 (CH_2OH), 55.4 (quart. C), 35.2 - 20.9 ppm (12 CH_2). EI-MS (rel.%): m/z 265 (4, $M^{+\cdot}$), 236 (4), 192 (9), 166 (9), 150 (11), 136 (14), 122 (15), 112 (89), 98 (40), 84 (24), 67 (44), 55 (82), 41 (100).

Compound 3: Mp = 104 - 105°C; IR(KBr): 3350, 1695 cm^{-1}; ^{1}H-NMR: 3.65 (t, J = 6 Hz), 3.07 + 2.74 (2 d, J = 13.2, $-CH_2NH_2$), 2.84 - 2.61 (m) ppm; ^{13}C-NMR: 214.8, 62.8, 56.0, 42.6 (CH_2NH_2), 33.2 - 20.2 ppm (12 CH_2); EI-MS: m/z 269 (1, $M^{+\cdot}$), 252 (1), 240 (13), 123 (5), 116 (16), 98 (15), 84 (21), 70 (14), 55 (97), 41 (100).

Compound 4: Mp = 95°C (decomp.); IR(KBr): 3380, 1703 cm^{-1}; ^{13}C-NMR (25°C): 212.14 + 212.11 + 212.06, several signals are splitted; (50°C): 212.3, 67.4 (CH_2N^+), 60.9 (CH_2OH), 56.7 ppm (CH_3); CI-MS (isobutane): m/z 298 ($[M+1-CH_3I]^+$).

Compound 5: Oil, musk-like smell; IR(film): 1737 (lactone), 1643 + 888 (=CH_2) cm^{-1}; ^{1}H-NMR: 4.73 (d with fine structure, J = 9 Hz), 4.16 (t, J = 5.6, -CH_2-O), 2.34 (t, J = 6.6, CH_2COO); ^{13}C-NMR: 173.8 (COO), 149.0 (*C*=CH_2), 109.6 (=CH_2), 63.8 (CH_2-O), 36.2 - 24.9 ppm (12 CH_2). EI-MS: m/z 252 (12, $M^{+\cdot}$), 237 (1), 224 (3), 109 (11), 95 (45), 82 (85), 67 (66), 55 (26), 41 (100).

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