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A Facile Access to Substituted Indeno[1,7-bc]furans

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Abstract: *The reaction of 4-oxo-β-ionone* ***1*** *with 2 eq. HCN from NaCN in MeOH leads in excellent yield stereospecifically to a cis-fused tricyclic ring system of the indeno[1,7-bc]furan type* ***5****. Acid catalyzed hydrolysis of the imino group in* ***5*** *gives lactone* ***6a*** *which was used to determine the basic structure of the new indeno[1,7-bc]furans by X-ray analysis. The new compounds were fully characterized by* ^{1}H *and* ^{13}C *NMR and the assignments supported by NOE (****6a****) and* ^{1}H*-detected one-bond and multiple-bond* ^{1}H, ^{13}C*-COSY (****6a-c****).*

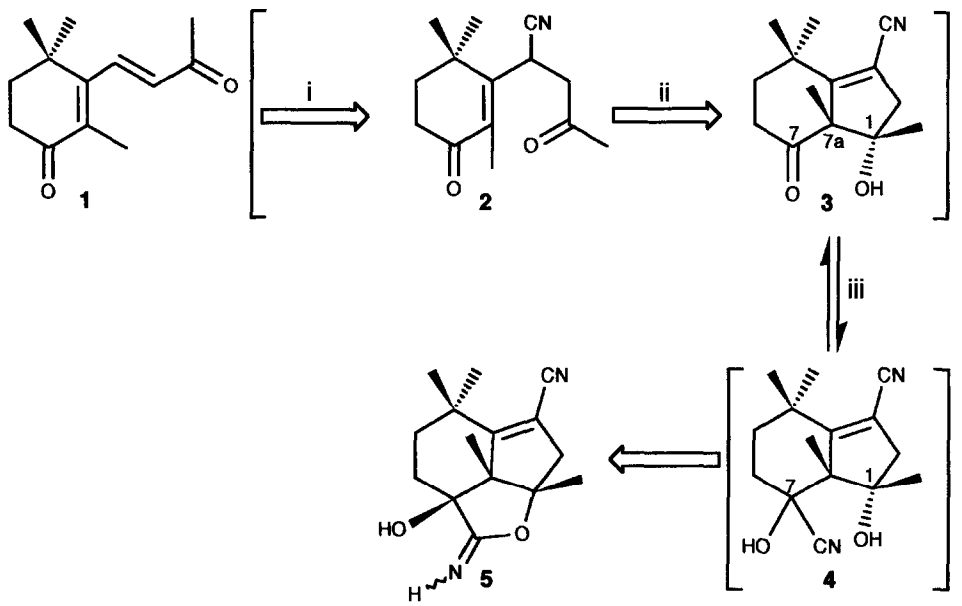
INTRODUCTION

Tricyclic lactones of the indeno[1,7-bc]furan-2-one type are useful building blocks for the preparation of 11-deoxyprostanoids and 11-oxosteroids. Intramolecular Diels-Alder reactions between oxygenated dienes and attached butenolides make them available[1] Intermolecular cycloaddition of 5-substituted 2-ethenylcyclopentenes with N-phenylmaleimide and rearrangement of the resulting products on silica gel is another entry into this class of compounds[2] We now report on a much more effortless approach to that cis-fused tricyclic ring system

RESULTS AND DISCUSSION

The novel route to angularly methylated indeno[1,7-bc]furan-2-ones starts with a one-pot reaction proceeding from (E)-4-oxo-β-ionone **1** which can be obtained by oxidation of industrially accessible (E)-β-ionone[3], or by a dirhodium tetraacetate catalyzed intramolecular reaction of an appropriate 2-(diazoacyl)furan[4]. Together with 2 eq. NaCN a methanolic solution of **1** is simply stirred at room temperature to give the cyclic iminoester **5** in yields up to about 90%.

Although we did not succeed in trapping and identifying of any intermediate, we suggest the reaction to proceed *via* the sequence presented in Scheme 1 Accordingly, Michael addition of HCN to **1** leads to **2** Then the formation of **3** is initiated by deprotonation of **2** at the C-atom which bears the cyano group. Addition of a further HCN molecule to the keto group of **3**, which as a consequence of the ring closure is now an isolated one, gives cyanohydrin **4** Finally, in **4** the cyano group at C(7) is attacked by the hydroxyl at carbon atom 1 to form **5** The structures of compounds **5** and **6b-c** were elucidated by means of spectroscopic methods (^1H, ^{13}C NMR, MS, IR, see experimental part) basing on a single-crystal X-ray diffraction and complete spectroscopic analysis of the tricyclic lactone **6a** (Fig. 2) that was derived from **5** by acid catalyzed hydrolysis.



Scheme 1

Preparation of the racemic (E/Z)-imine **5** *via* the proposed intermediates **2, 3** and **4.** Reagents and conditions i, NaCN, ii, MeO^- and /or CN^-, iii, NaCN, room temperature Solvent. MeOH

A more detailed discussion of the stereospecific formation of **5** has to consider that the intermediate appearance of **3** with methyl groups at C-atoms 1 and 7a in cis position seems to be a consequence of the thermodynamically preferred chair form of the six-membered ring including the possibility to form a hydrogen-bridge between the 1α-hydroxy and the 7-oxo group (Fig 1)

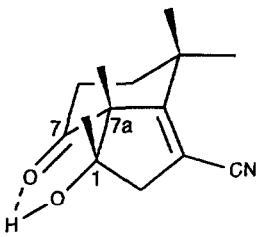
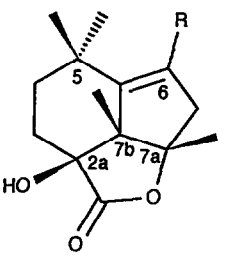


Figure 1. Sterical arrangement of **3**

After formation of the cyanohydrin **4** only the 7-cyano group in α-position can be attacked by the 1α-hydroxyl to give **5.** Because the addition of HCN to carbonyl groups is a reversible reaction, ring closure of (7α-cyano)-**4** to **5** removes this stereoisomer of **4** continuously from the equilibrium with its counterpart bearing a 7β-cyano group. Acid catalyzed hydrolysis of the imino group in **5** gave **6a**, whereas stepwise hydrolysis of the 6-carbonitrile of **6a** led to the carboxamide **6b** and to the carboxylic acid **6c** (experimental part). Noteworthy is the stability of the lactone ring which even under strong acidic or basic conditions could not be opened hydrolytically.



6

Figure 2. Structure of the racemic lactone **6**
6a, R = CN; **6b**, R = $CONH_2$; **6c**, R = COOH

EXPERIMENTAL PART

General

M.p.'s were measured on a Büchi SMP-20 in open capillaries and are uncorrected. IR spectra were obtained in KBr with a Nicolet FT/IR 719. ^{1}H-NMR spectra at 400 MHz and ^{13}C-NMR spectra at 100.6 MHz were recorded on a AM-400 Bruker-Spectrospin FT-NMR spectrometer with Aspect 3000 computer, pulse programmer and 160 Mbyte disk. Solutions in [$^2H_6$]DMSO with Me_4Si as

internal standard were studied All coupling constant values J are given in Hz Mass spectra were determined on a AEI MS-9 updated with a ZAB console and data system 3000 (70 eV, Electron impact) All new compounds are racemates

Materials

A sample of 4-oxo-β-ionone **1** was kindly provided by our vitamin research department It was recrystallized twice from hexane at -10° C, m.p 52 - 53 5°C NaCN p a and MeOH p a were obtained from Merck.

Syntheses

2,2a,3,4,5,7,7a,7b-Octahydro-2aβ-hydroxy-2-imino-5,5,7aβ,7bβ-tetramethylindeno÷[1,7-bc]furan-6-carbonitrile (5)[5]

NaCN (38.2 g, 0 78 mol) was added to a solution of **1** (80 0 g, 0.388 mol) in MeOH (800 ml) and stirred under N_2 for 24 h at room temperature The brown solution was chilled to 10°C and filtered The precipitate was washed with 150 ml MeOH and twice with 150 ml H_2O to yield **5** (87 3 g, 86.5%, m.p. 230°C). Recrystallization from MeOH raised the m p. to 236°C. (Found C,69 47, H,7.83, N,11.1 $C_{15}H_{20}N_2O_2$ requires C,69.2, H,7.74, N,10.76%) IR ν_{max}/cm^{-1} 3258 (NH), 3103 (OH), 2218 (conj CN), 1678 (C=N)

The imine **5** existed as a 2 1 mixture of (E/Z) isomers with unknown assignment Only DEPT-135 and no 2D experiments were performed and thus the assignments of ^1H and ^{13}C are given in analogy to **6a-c.** The following assignments consider both isomers and are given in the order of main and minor isomer. ^1H-NMR δ 1 122 , 1 108 (3 H, 2s, 7bβ-Me), 1 177, 1.163 (3 H, 2s, 5-Me), 1.232, 1.052 (1H, t x d, J ~ 13.5, 4, 4α-H), 1.341 (3 H, s, 5-Me), 1.381 (3 H, s, 7aβ-Me) 1 469 (1 H, d x t, J 14, 3 7, 4β-H), 1,801, 1 837 (1 H, t x d, J ~ 13 7, 4,3α-H), 2 000 (1 H, d x t, J ~13 7, 3 5, 3β-H), 2 569, 2 612 (1 H, 2d, J 17, 7-H), 2 861 (1 H, d, J 17, 7-H), 5 761, 5 735 (1 H, 2s, OH, exchanges with D_2O), 7 594 (1 H, s, NH, exchanges with D_2O) ^{13}C-NMR δ 14 50, 14 61 (7bβ-Me), 20 79 (7aβ-Me), 25.98, 25 92 (5-Me), 27 65, 27 50 (3-C), 29 90, 29.79 (5-Me), 36.03 (5-C), 37 28, 37 13 (4-C), 44.70, 44 67 (7-C), 60.54, 60 30 (7a-C), 77.21, 77 60 (2a-C), 92 10, 91 60 (7b-C), 102 63, 102 89 (6-C), 117 21 (CN), 169 37, 169 67, 170 03, 174 93 (2-C and 5a-C) MS m/z 260 (M^+, 2.8%), 217 (13,), 216 (9), 203(15), 202 (100), 199 (15), 161 (14), 160 (24), 158 (18), 146 (23), 142 (39), 132 (14), 97 (28), 91 (12), 85 (17), 83 (26), 81 (13), 71 (28), 69 (40), 67 (10), 55 (55), 45 (11), 43 (74), 41 (45), 39 (29), 29 (24)

2,2a,3,4,5,7a,7b-Octahydro-2aβ-hydroxy-5,5,7aβ,7bβ-tetramethyl-2-oxoindeno÷[1,7-bc]furan-6-carbonitrile (6a)

A solution of **5** (63 5 g, 0 24 mol) in HCl (25%, 2 5 l) was stirred for 24 h at 60° C After having reduced the solution to 800 ml it was chilled to 0° - 3°C and filtered The solid was washed several times with water to give crude **6a** (59.5 g, 93%). Recrystallization from 2-propanone raised the m p to 218° - 219°C (Found C,68.82, H,7 59, N,5.51. C_{15} $H_{19}NO_3$ requires C,68 94, H,7 33, N,5 36%) ν_{max}/cm^{-1} 3461 (OH), 2221 (conj CN), 1767 (5-ring lactone C=O)

^1H and ^{13}C assignments of **6a** (4 mg) were based on 400 MHz 1D NOE difference experiments, DEPT-135, ^1H-detected one-bond hetero COSY with ^{13}C GARP decoupling during acquisition ($^1J_{CH}$ = 140 Hz, 300 experiments, 2.5 h total accumulation time) and ^1H-detected long-range hetero COSY (J_{CH} = 7 Hz, 300 experiments, 10 h) The one-bond hetero COSY (pulse sequence E of Lit [6]) links carbons and their directly attached protons, whereas the long-range version[7] reveals connectivities *via* two- and three-bond couplings between protons and neighbouring carbons These experiments allow an unambiguous assignment of the proton and carbon signals and provide important structural information Some relevant results are given as follows

The two geminal methyl groups at 5-C were identified by corresponding three-bond cross peaks between the protons of each group and the carbon of the other one. Moreover, cross peaks between the same protons and those of a further methyl group (at 7b-C) and carbon 5a-C helped to identify the latter methyl group. The protons of the remaining methyl group at 7a-C showed cross peaks with 7a-C, 7b-C and 7-C as expected The carbon atoms 4-C and 3-C were distinguished by cross peaks of the former to the protons of both 5-C methyl groups. Stereospecific assignment of these two geminal methyl groups was posssible by 1D NOE difference experiments and subsequent linking of the ^1H signals to the corresponding ^{13}C shifts *via* one-bond correlation ^1H-NMR δ 1 058 (1 H, t x d, J ~13.5, 4 3, 4α-H), 1 156 (3 H, s, 7bβ-Me), 1 182 (3 H, s, 5α-Me),1 360 (3 H, s, 5β-Me), 1 448 (3 H, s, 7aβ-Me), 1 554 (1 H, d x t, J 14, 4, 4β-H), 1 835 (1 H, t x d, J 14, 4 5, 3α-H), 1 931 (1 H, d x t, J 14 4, 4, 3β-H), 2 684 (1 H, d, J 17.3 gem 7β-H), 2 970 (1 H, d, J 17.3 gem 7α-H), 6 324 (1 H, s, OH)

Relevant 1D NOE difference results

Irradiation at		Enhancement (in %)					
7a-Me	(1 448 ppm)	7b-Me	2 2,	7β-H	5 8,	OH	2 5
7b-Me	(1 156 ppm)	7a-Me	>0,	7β-H	2 5,	OH	3 8
5β-Me	(1 360 ppm)	5α-Me	2 5,	4α-H	>0		
5α-Me	(1,182 ppm)	5β-Me	>0,	3α-H	5,	4β-H	2.9

^{13}C-NMR: δ 13.97 (7b-Me), 20 56 (7aβ-Me), 25 64 (5α-Me), 26 57 (3-C), 29 58 (5β-Me), 35.98 (5-C), 36 78 (4-C), 44 03 (7-C), 59 37 (7b-C), 76 40 (2a-C), 92 46 (7a-C),103.26 (6-C), 116.87 (CN), 168 87 (5a-C), 175 39 (2-C) MS m/z 217 (19, M- CO_2), 202 (100), 199 (20), 184 (11), 161(11), 160 (10), 158 (15),146 (22),144 (17),133 (12), 131 (16), 91(10), 77(11), 69 (15), 57(15), 55 (33), 43 (50), 41(25), 39 (13), 29 (13)

X-Ray Crystallographic Structure Determination of **6a.**

Crystal size 0.25 x 0.35 x 0 35 mm^3 Data were collected on a Nicolet R3m four circle diffractometer fitted with a graphite monochromator and the LT1 cooling apparatus Scan mode omega, scan speed 0.8° min^{-1}, minimum speed Strong reflections were measured up to 10.2° min^{-1}, scan width 0.9° 2Θ range 0 - 50°. Peak-background ratio 5 1. Total reflections observed 1877, rejection criterion $I > 2{,}5\sigma(I)$. Structure determination and refinement The structure was determined by direct methods using SHELXTL-86 system. Refinement proceeded smoothly to convergence at R = 0.040 with anisotropic refinement of all non-H-atoms. Weights $w = 1/\sigma^2(F) + 0\,001\,|F|^2$ 8

Crystal data $C_{15}H_{19}NO_3$, *M* = 261 32, Monoclinic, space group $P2_1/n$, a = 8 080(4), b = 10.655(4), c = 15 492(6) Å, β = 98.13(3), Z = 4, D = 1 288 g cm^{-3}, $\mu(Mo\text{-}K_\alpha)$ = 0.9 mm^{-1}, F(000) 560, λ = 0 071069 Å, T = 190 K

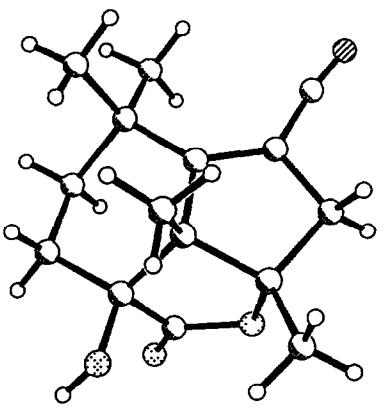


Figure 3 Projection of **6a.**

2,2a,3,4,5,7,7a,7b-Octahydro-2aβ-hydroxy-5,5,7aβ,7bβ-tetramethyl-2-oxoindeno÷[1,7-bc]furan-6-carboxamide (6b)

To a solution of **6a** (25 g, 96 mmol) in MeOH (275 ml) and aq. NaOH(140 ml, 6 mol dm^{-3}) H_2O_2 (77.5 ml, 0.88 mol dm^{-3}) was added dropwise during 3 h at ca 40°C After further 2 h stirring the solution was chilled to ca. 3°C and filtered The solid was washed several times with water to yield crude **6b** (23.46 g, 88%, m.p. 259°C from dichloromethane) Recrystallization from water gave **6b** x H_2O, m.p 263° - 264°C (Found C,64.0, H,8 14, N ,5 0 $C_{15}H_{21}NO_4$ x H_2O requires C,64.03; H,8.24; N,4.98%) Spectroscopic data are given for anhydrous **6b** IR ν_{max}/cm^{-1} 3386 (NH_2), 1749 (5-ring lactone C=O), 1645 (amide C=O)

The assignments of the ^{1}H and ^{13}C spectra of **6b** (4 mg) were based on DEPT-135, ^{1}H-detected one-bond (300 experiments, 2.5 h) and long-range ^{1}H, ^{13}C COSY (300 experiments, 10 h) Since no NOE experiments were performed, an unambiguous stereospecific assignment of the geminal methyl groups at 5-C was not possible ^{1}H-NMR δ 1 011 (1 H, t x d, J 14, 4, 4α-H), 1 113 (3 H, s, 7bβ-Me), 1 130 and 1 150 (2 x 3H, 2s, 2 x 5-Me), 1 387 (1 H, d x t, J 14, 4, 4β-H), 1 416 (3 H, s, 7aβ-Me), 1 750 (1 H, t x d, J 14, 4, 3α-H), 1 875 (1 H, d x t, J 14, 4, 3β-H), 2 61 and 2 65 (2 H, AB-Spectrum, J 17 5, 7-H), 6 003 (1 H, s, OH), 7 149 and 7 492 (2 H, 2s, NH_2) ^{13}C-NMR δ 14 66 (7aβ-Me), 21 05 (7bβ-Me), 25 81 (5-Me), 26 95 (3-C), 28 77 (5-Me), 34 46 (5-C), 37 70 (4-C), 45 17 (7-C), 58.66 (7b-C), 76.45 (2a-C), 92 57 (7a-C), 129 96 (6-C), 146 16 (5a-C), 170 61 (amide-C), 176 27 (2-C) MS m/z 279 (23, M - H_2O), 235 (27), 220 (47), 218 (38), 207 (14), 203 (25), 177 (45), 175 (25), 162(43), 147(36), 135 (34), 133 (60), 121 (27), 119 (59), 105 (23), 91 (40), 83 (12), 79 (23), 77 (30), 69 (29), 57 (19), 55 (52), 53 (19), 44 (29), 43 (100), 41 (56), 39 (23)

2,2a,3,4,5,7a,7b-Octahydro-2aβ-hydroxy-5,5,7aβ,7bβ-tetramethyl-2-oxoindeno+[1,7-bc]furan-6-carboxylic acid (6c)

To a solution of **6b** (1 0 g, 3 36 mmol) in HCl (conc , 25 ml) an aq solution of $NaNO_2$ (2 46g, 35 7 mmol) was added dropwise during 1 h at 20°C The reaction mixture was then stirred for 4 5 h at 70°C Chilling, filtration and washing with water yielded **6c** (0 79 g, 79%), m p 217°- 218°C (Found C,64 17, H, 7 23, $C_{15}H_{20}O_5$ requires C,64 27, H,7 19%) IR ν_{max}/cm^{-1} 1733 (5-ring lactone C=O), 1701 (carboxylic acid C=O)

Analogously to **6b** the assignments of **6c** were based on DEPT-135, one-bond and long-range hetero COSY applying the same experimental conditions as with **6b.** ^{1}H-NMR: δ 1 047 (1 H, t x d, J 14, 4, 4α–H), 1 123 (2 x 3H, s, 2 x 5-Me), 1 153 (3 H, s, 7bβ-Me), 1 420 (3 H, s, 7aβ-Me), 1 505 (1 H, d x t, J 14, 4, 4β-H), 1 775 (1 H, t x d, J ~ 13 5, 4, 3α-H), 1.890 (1 H, d x t, 14, 4 6, 3β-H), 2 640 (1 H, d, 17 3, 7-H), 2 780 (1 H, d, 17 3, 7-H), 6 083 (1 H, s, 2a-OH), 12 800(1 H, s, HOOC) ^{13}C-NMR δ 14 48 (7bβ-Me), 20 75 (7aβ-Me), 25.98 (5-Me), 27 16 (3-C), 28 31 (5-Me), 34 32 (5-C), 37 04 (4-C), 44 51 (7-C), 59 08 (7b-C), 75 99 (2a-C), 92 36 (7a-C), 126 75 (6-C), 150 83 (5a-C), 169 37 (COOH), 176 13 (2-C) MS m/z 279 (M^+, 2%), 236 (M - CO_2, 34), 222 (12), 221 (89), 218 (23), 203 (34), 175 (23), 162 (29), 147 (32), 135 (23), 133 (47), 119 (20), 107 (14), 97 (23), 91 (26), 83 (23), 77 (18), 71 (24), 69 (48), 67 (13), 57 (44), 55 (55), 43 (100), 41 (54), 39 (17), 29 (25)

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5 Optimized procedure Substitution of NaCN by KCN or addition of water lowers the yield of **5**, which also depends on the starting concentration of **1** given in brackets 67.4% (0.97 mol dm^{-3}), 76.7% (0.65 mol dm^{-3}), 86 5% (0.48 mol dm^{-3}), 79 4% (0.32 mol dm^{-3})

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