A New Hydrindanone Synthesis

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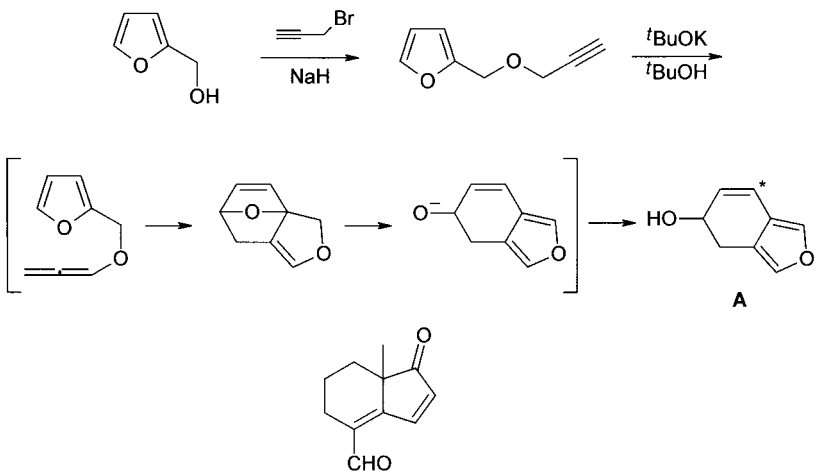
The *Kanematsu* transformation was employed for the preparation of tetrahydroisobenzofuran-4-carboxylic acid (**12**), α-methylation, subsequent conversion into the diazoethanone **14**, and, finally, treatment with dirhodium tetraacetate of which furnished the hydrindanone **1** of the steroid C-D ring structure.

1. Introduction. – As a part of a study of synthesis of hydrindanone of the steroid C-D ring type (*e.g.* **1**) by way of intramolecular α-diazo ketone/furan interactions [1–3], compounds of the hydroisobenzofuran structure were needed as starting materials. Luckily, *Kanematsu* and co-workers, by their transformation process [4], had made these substances readily available (*Scheme 1*).

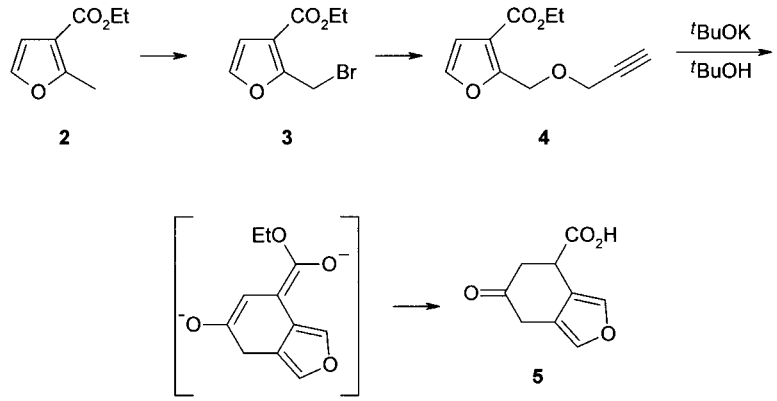
Whereas furan **A** appeared to be a propitious starting compound, it required a carboxy-group equivalent at the starred position for the projected reaction sequence to succeed. Hence, the *Kanematsu* procedure was modified to accommodate the presence of an alkoxycarbonyl group in the initial furan.

Scheme 1



2. Results and Discussion. – Commercially available ester **2** was brominated (*N*-bromosuccinimide (NBS), $(PhCO_2)_2$ in CCl_4; 73% yield), and the resulting bromo compound **3** was converted into ether derivative **4** ($HC{\equiv}CCH_2OH$, NaH in THF; 78% yield). Exposure of the latter to the *Kanematsu* reaction led to keto acid **5**, albeit in only 10% yield (*Scheme 2*)[1]). Presumably, ester interchanges and double-bond migration may account for this unsatisfying result.

Scheme 2



Therefore, a sturdy carboxylic-acid derivative strong enough to survive the *Kanematsu* transformation had to be chosen, and the *N*,*N*-dimethylamide became the leading candidate. Hydrolysis of ester **4** (5% aq. NaOH soln.; 94% yield) and treatment of the resultant acid **6** with oxalyl chloride and then with Me_2NH furnished amide **7** in 83% yield. *Kanematsu* transformation of the latter produced keto amide **8** (80% yield; *Scheme 3*).

Conversion of keto amide **8** to its thioacetal derivative **9** ($HSCH_2CH_2SH$, BF_3; 53% yield) [5], reduction of the latter (*Raney*-Ni, EtOH; 79% yield) [6], and hydrogenation of the resultant olefin derivative **10** (H_2, 5% $Pd/BaSO_4$, MeOH; 92% yield) gave amide **11**, whose hydrolysis (20% KOH, EtOH; 89% yield) liberated acid **12**. α-Methylation of the latter (MeI, lithium diisopropylamide (LDA), THF, 72% yield) afforded acid **13** (*Scheme 3*)[2]).

Reaction of acid **13** with a CH_2Cl_2 solution of oxalyl chloride and thereafter an ethereal solution of diazomethane led to diazo ketone **14** (61% yield), whose decomposition in the presence of $[Rh_2(OAc)_4]$ in CH_2Cl_2 solution afforded keto aldehyde **1** in 66% yield[3]) (for a detailed discussion on α-diazo ketone/furan interactions, see [1–3] [7]).

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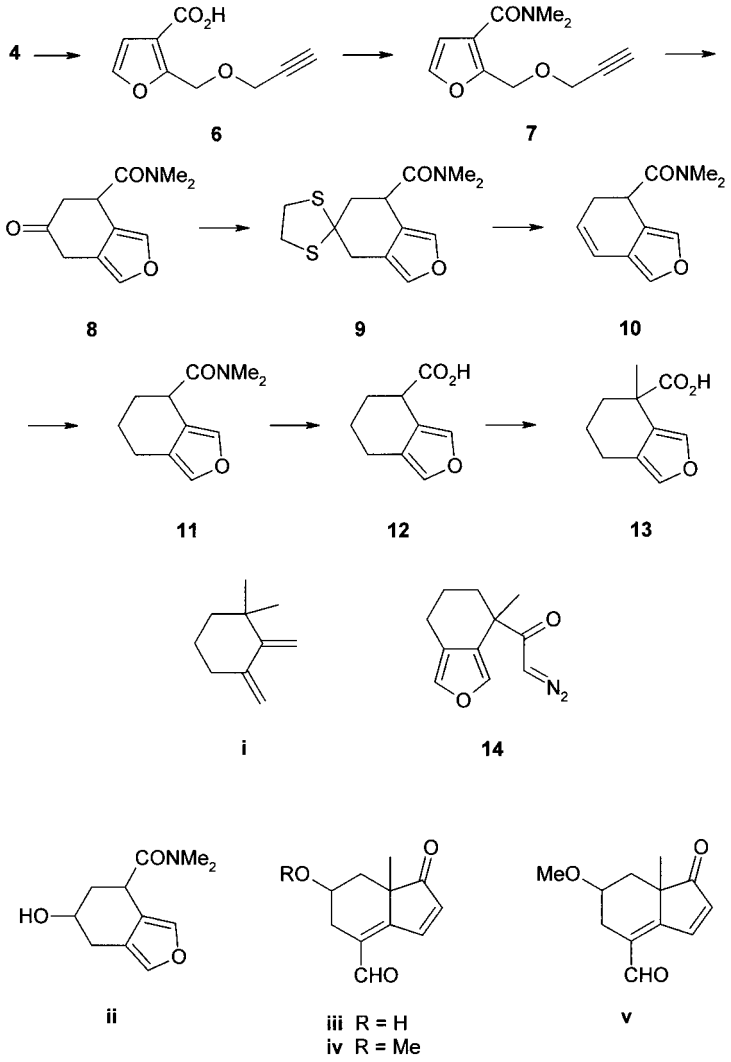
[1]) The reactions depicted in *Scheme 2* were performed by *Haripada Khatuya* in La Jolla.

[2]) It is noteworthy that acid **13** possesses the C-skeleton of certain monoterpenes, *e.g.* δ-pyronene (**i**) [8].

[3]) It is worth mentioning that exposure of hydroxyamide **ii**, the product of borohydride reduction of keto amide **8**, to the **11** → **1** reaction sequence yielded keto aldehydes **iii**, **iv**, and **v**.

Scheme 3



Experimental Part

General. All extracts were dried over Na_2SO_4. Column chromatography: 70-230-mesh *Merck* silica gel. Melting points: micro hot stage; uncorrected. IR Spectra: $CHCl_3$ solns; *Jasco-FT-IR-410* apparatus; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: at 200.1 and 50.3 MHz, resp. $CDCl_3$ solns.; GC/MS: *Hewlett-Packard* apparatus, model *5890*. Elemental analyses: *Carlo Erba* model *1106* elemental analyzer.

Ethyl 2-(Bromomethyl)-3-furoate (**3**). A soln. of NBS (4.2 g, 24 mmol) in CCl_4 (42 ml) was added dropwise to a soln. of **2** (3.5 g, 23 mmol) and dibenzoyl peroxide (40 mg) in CCl_4 (11 ml), and the mixture was refluxed for 5 h. The soln. was washed once with H_2O (30 ml), dried, and evaporated. Chromatography (CH_2Cl_2) of the residue yielded 3.9 g (73%) of **3**. Yellow oil. IR: 1720. ^1H-NMR: 1.29–1.40 (*t*, *J* = 7.1, 3 H); 4.20–4.40 (*q*, *J* = 7.1, 2 H); 4.75 (*s*, 2 H); 6.62–6.65, 7.22–7.25 (2*d*, *J* = 2.0, 2 H). ^{13}C-NMR: 14.48; 21.15; 60.52; 111.34; 111.98; 114.02; 140.68; 163.22. GC/MS: 232 ($M^{+\cdot}$). Anal. calc. for $C_8H_9BrO_3$: C 41.23; H 3.89; found: C 41.19, H 3.92.

Ethyl 2-[(Prop-2-ynyloxy)methyl]-3-furoate (**4**). A soln. of prop-2-yn-1-ol (1.0 g, 18 mmol) in dry THF (0.8 ml) was added dropwise at 0° to a suspension of 60% NaH (0.8 g, 20 mmol) in THF (4.3 ml). The mixture was stirred at r.t. under N_2 for 30 min. Then a soln. of **3** (3.9 g, 17 mmol) in THF (4.3 ml) was added dropwise and the mixture was stirred for 4 h. The suspension was poured into H_2O (30 ml), neutralized with 2% citric acid/H_2O, and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phase was washed with brine, dried, and evaporated and the residue chromatographed (CH_2Cl_2): 2.3 g (78%) of **4**. Yellow oil. IR: 1714. ^{1}H-NMR: 1.30–1.41 (*t*, *J* = 7.5, 3 H); 2.45–2.48 (*t*, *J* = 2.2, 1 H); 4.18–4.21 (*d*, *J* = 2.2, 2 H); 4.22–4.37 (*q*, *J* = 7.5, 2 H); 4.88 (*s*, 2 H); 6.68–6.72, 7.38–7.42 (2*d*, *J* = 2.0, 2 H). ^{13}C-NMR: 14.57; 57.75; 60.57; 62.11; 74.82; 78.39; 110.84; 117.08; 142.55; 155.96; 163.16. GC/MS: 208 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{12}O_4$: C 63.45, H 5.81; found: C 63.43, H 5.84.

2-[(Prop-2-ynyloxy)methyl]-3-furoic Acid (**6**). A soln. of **4** (2.05 g, 10 mmol) in EtOH (21.5 ml) and 5% NaOH/H_2O (21.5 ml) was stirred at 40° for 1 h. The mixture was acidified to pH 2 with 10% HCl soln. and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phase was washed with brine, dried, and evaporated: 1.7 g (94%) of **6**. Yellow solid. M.p. 75–77°. IR: 3500, 1720. ^{1}H-NMR: 2.48–2.51 (*t*, *J* = 2.6, 1 H); 4.22–4.28 (*d*, *J* = 2.6, 2 H); 4.92 (*s*, 2 H); 6.65–6.68, 7.41–7.44 (2*d*, *J* = 2.0, 2 H); 12.00 (br. *s*, 1 H). ^{13}C-NMR: 57.87; 62.01; 75.06; 78.95; 111.05; 116.15; 142.71; 157.51; 168.93. GC/MS: 180 ($M^{+\cdot}$). Anal. calc. for $C_9H_8O_4$: C 60.00, H 4.48; found: C 60.02, H 4.47.

N,N-*Dimethyl-2-[(prop-2-ynyloxy)methyl]-3-furoamide* (**7**). A 2M soln. of oxalyl chloride in CH_2Cl_2 (9.8 mmol, 6.5 ml) was added to **6** (1.6 g, 8.9 mmol) in dry CH_2Cl_2 (10.5 ml). The resulting mixture was stirred under N_2 at 30° for 4 h. After evaporation, the residual acid chloride was dissolved in dry THF (50 ml), and this soln. was added dropwise to 89 ml of a 40% soln. of $(Me)_2NH$ in THF (89 ml). The mixture was stirred at r.t. for 2 h, poured into H_2O (300 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phase was washed with brine, dried, and evaporated: 1.54 g (83%) of **7**. Yellow oil. IR: 1645. ^{1}H-NMR: 2.42–2.45 (*t*, *J* = 2.5, 1 H); 3.00 (*s*, 6 H); 4.15–4.19 (*d*, *J* = 2.5, 2 H); 4.60 (*s*, 2 H); 6.38–6.42, 7.36–7.39 (2*d*, *J* = 2.0, 2 H). ^{13}C-NMR: 34.46; 38.30; 56.75; 61.12; 74.57; 78.58; 109.48; 119.58; 141.61; 150.22; 164.54. GC/MS: 207 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{13}NO_3$: C 63.76, H 6.32, N 6.76; found: C 63.74, H 6.35, N 6.75.

4,5,6,7-Tetrahydro-N,N,-*dimethyl-6-oxoisobenzofuran-4-carboxamide* (**8**). ^{t}BuOK (1.78 g; 15.6 mmol) was added to a soln. of **7** (1.54 g, 7.44 mmol) in ^{t}BuOH (9.6 ml). The mixture was refluxed under N_2 for 1 h, cooled, poured into H_2O (50 ml), neutralized with 2% citric acid/H_2O and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. phase was washed with brine, dried, and evaporated. Chromatography (CH_2Cl_2/MeOH 98:2) of the residue yielded 1.23 g (80%) of **8**. White solid. M.p. 58–60°. IR: 1710, 1640. ^{1}H-NMR: 2.30–2.90 (*m*, 2 H); 2.91, 3.18 (2*s*, 6 H); 3.29–3.68 (*m*, 2 H); 4.22–4.37 (*dd*, *J*(1,2) = *J*(1,3) = 4.8, 1 H); 7.18–7.32 (*m*, 2 H). ^{13}C-NMR: 34.56; 34.59; 35.83; 37.47; 42.40; 119.40; 119.76; 137.29; 138.57; 171.47; 207.20. GC/MS: 207 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{13}NO_3$: C 63.76, H 6.32, N 6.76; found: C 63.74, H 6.34, N 6.77.

4,5,6,7-Tetrahydro-N,N-*dimethyl-6-oxoisobenzofuran-4-carboxamide Ethylene Dithioketal* (**9**). To a soln. of **8** (500 mg, 2.41 mmol) and ethane-1,2-dithiol (375 mg, 3.9 mmol) in dry CH_2Cl_2 (15 ml), stirred at 0° under N_2, $BF_3 \cdot Et_2O$ (0.085 ml) was added, and after 20 min, stirring was continued at r.t. for 18 h. The mixture was washed twice with 5% NaOH/H_2O (10 ml) and brine, dried, and evaporated. Chromatography (CH_2Cl_2/MeOH 98:2) of the residue yielded 360 mg (53%) of **9**. Yellow solid. M.p. 67–68°. IR: 1644. ^{1}H-NMR: 2.15–2.60 (*m*, 2 H); 2.95, 3.10 (2*s*, 6 H); 2.80–3.10 (*m*, 2 H); 3.25–3.40 (*m*, 4 H); 4.02–4.10 (*m*, 1 H); 7.05–7.20 (*m*, 2 H). ^{13}C-NMR: 35.86; 36.22; 37.21; 37.65; 38.89; 39.39; 42.17; 65.94; 118.67; 120.77; 137.87; 137.91; 172.38. GC/MS: 283 ($M^{+\cdot}$). Anal. calc. for $C_{13}H_{17}NO_2S_2$: C 55.10, H 6.05, N 4.94; found: C 55.08, H 6.08, N 4.93.

4,5-Dihydro-N,N-*dimethylisobenzofuran-4-carboxamide* (**10**). To a suspension of *Raney*-Ni (previously deactivated by refluxing for 1 h in acetone; 2.9 g) in abs. EtOH (9 ml), a soln. of **9** (340 mg, 1.2 mmol) in abs. EtOH (8 ml) was added, and the mixture was refluxed for 5 h, cooled, and filtered over *Celite*. The filtrate was evaporated and the residue purified by CC (CH_2Cl_2/MeOH 98:2): 180 mg (79%) of **10**. Yellow oil. IR: 1646. ^{1}H-NMR: 2.26–2.43, 2.62–2.83 (2*m*, 2 H); 3.05, 3.15 (2*s*, 6 H); 3.82–3.95 (*m*, 1 H); 5.83–5.97, 6.42–6.51 (2*m*, 2 H); 7.05–7.30 (*m*, 2 H). ^{13}C-NMR: 27.03; 34.27; 35.75; 37.37; 118.01; 119.01; 121.35; 126.68; 136.81; 137.09; 172.56. GC/MS: 191 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{13}NO_2$: C 69.09, H 6.85, N 7.32; found: C 69.06, H 6.87, N 7.33.

4,5,6,7-Tetrahydro-N,N-*dimethylisobenzofuran-4-carboxamide* (**11**). To a soln. of **10** (150 mg, 0.79 mmol) in MeOH (5 ml), 5% Pd/$BaSO_4$ (15 mg) was added, and the resulting suspension was kept under H_2 (55 psi) in a *Parr* hydrogenation apparatus for 24 h. The mixture was filtered over *Celite* and the filtrate evaporated: 140 mg (92%) of **11**. Yellow oil. IR: 1646. ^{1}H-NMR: 1.47–2.12 (*m*, 6 H); 2.98, 3.08 (2*s*, 6 H); 3.65–3.78 (*m*, 1 H); 7.11–7.34 (*m*, 2 H). ^{13}C-NMR: 19.38; 21.94; 26.60; 34.14; 35.58; 35.93; 120.66; 120.97; 137.38; 137.42; 173.72. GC/MS: 193 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{15}NO_3$: C 68.37, H 7.82, N 7.25; found: C 68.34, H 7.84, N 7.21.

4,5,6,7-Tetrahydroisobenzofuran-4-carboxylic Acid (**12**). A soln. of **11** (1 g, 5.2 mmol) in EtOH (30 ml) and 20% KOH/H_2O (30 ml) was stirred at 70° for 18 h. The mixture was acidified to pH 2 with 10% HCl soln. and extracted wtih AcOEt (4 × 50 ml). The combined org. phase was washed with brine, dried, and evaporated: 760 mg (89%) of **12**. White solid. M.p. 147–150°. IR: 3600, 1699. ^{1}H-NMR: 1.79–2.68 (*m*, 6 H); 3.73–3.86 (*m*, 1 H); 7.09–7.35 (*m*, 2 H); 11.50 (br. *s*, 1 H). ^{13}C-NMR: 19.96; 22.08; 26.42; 38.21; 116.89; 118.34; 136.61; 137.79; 179.29. GC/MS: 166 ($M^{+\cdot}$). Anal. calc. for $C_9H_{10}O_3$: C 65.05, H 6.07; found: C 65.07, H 6.04.

4,5,6,7-Tetrahydro-4-methylisobenzofuran-4-carboxylic Acid (**13**). To a soln. of lithium diisopropylamide (LDA; 6.62 mmol) in anh. THF (6 ml), kept at 0° under N_2, a soln. of **12** (500 mg, 3.01 mmol) in anh. THF (4 ml) was added dropwise within 1 h. The mixture was heated at 50° for 2 h. Then a soln. of freshly distilled MeI (1.28 g, 9.03 mmol) in anh. THF (1 ml) was added dropwise at 0°, and stirring was continued for 3 h at r.t. The soln. was poured into H_2O (50 ml), acidified to pH 2 with 10% HCl soln., and extracted with AcOEt (4 × 50 ml). The combined org. phase was washed with brine, dried, and evaporated. Chromatography (CH_2Cl_2/MeOH 9:1) of the residue yielded 390 mg (72%) of **13**. White solid. M.p. 159–162°. IR: 3600, 1694. ^{1}H-NMR: 1.47 (*s*, 3 H); 1.82–2.69 (*m*, 6 H); 7.08 (*s*, 1 H); 7.32–7.36 (*m*, 1 H); 11.30 (br. *s*, 1 H). ^{13}C-NMR: 25.77; 29.70, 34.24; 34.51; 48.95; 117.34; 119.64; 138.46; 139.75; 182.69. GC/MS: 180 ($M^{+\cdot}$). Anal. calc. for $C_{10}H_{12}O_3$: C 66.65, H 6.71; found: C 66.63, H 6.74.

2-Diazo-1-(4,5,6,7-tetrahydro-4-methylisobenzofuran-4-yl)ethan-1-one (**14**). Freshly distilled oxalyl chloride (140 mg, 1.12 mmol) was added dropwise to a stirred soln. of **13** (100 mg, 0.56 mmol) in dry CH_2Cl_2 (2.5 ml) at 35° under N_2, and stirring was continued for 2 h. The soln. was evaporated and the residual acid chloride dissolved in dry Et_2O (2.5 ml). This soln. was added dropwise within 0.5 h to a stirred soln. of diazomethane (0.75 mmol) and freshly distilled Et_3N (0.56 mmol) in dry Et_2O (5 ml) at 0°. Stirring was continued for 2 h. The mixture was filtered, and the filtrate evaporated. Chromatography (short column of neutral alumina (activity III), CH_2Cl_2) of the residue yielded 70 mg (61%) of **14**. Yellow oil. IR: 2106, 1626. ^{1}H-NMR: 1.39 (*s*, 3 H); 1.75–2.63 (*m*, 6 H); 5.93 (*s*, 1 H); 7.22 (*s*, 1 H); 7.54–7.58 (*m*, 1 H). ^{13}C-NMR: 19.38; 22.66; 26.51; 34.52; 45.57; 54.07; 117.66; 118.34; 131.11; 135.30; 195.55.

*5,6,7,7a-Tetrahydro-7a-methyl-1-oxo-1*H*-indene-4-carbaldehyde* (**1**). A soln. of **14** (70 mg, 0.34 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise within 1 h to a suspension of [$Rh_2(OAc)_4$] (4 mg, 0.009 mmol) in dry CH_2Cl_2 (5 ml), kept at r.t. under N_2. The mixture was stirred for 20 min and evaporated. Chromatography (CH_2Cl_2/MeOH 98:2) of the residue yielded 40 mg (66%) of **13**. Yellow oil. IR: 1673, 1631. ^{1}H-NMR: 1.36 (*s*, 3 H); 1.32–2.39 (*m*, 6 H); 6.29–6.32 (*d*, J = 5.5, 1 H); 7.89–7.92 (*d*, J = 5.5, 1 H); 10.20 (*s*, 1 H). ^{13}C-NMR: 22.62; 25.56; 30.84; 37.98; 45.11; 129.84; 140.57; 149.89; 160.31; 186.77; 199.93. GC/MS: 176 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{12}O_2$: C 74.98, H 6.86; found: C 74.96, H 6.87.

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