49. 1,4-Diazobicyclo[2.2.2]octane-Catalyzed Coupling of Aldehydes and Activated Double Bonds[1])

Part 3

A Short and Practical Synthesis of Mikanecic Acid (4-Vinyl-1-cyclohexene-1,4-dicarboxylic Acid)

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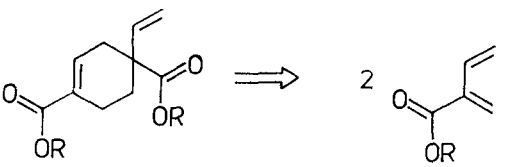
(19.XII.83)

Summary

The title dicarboxylic acid **1d** has been prepared in 24% overall yield *via* 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed coupling of ethanal and *tert*-butyl propenoate (**3**) to **4**, S_N2'-reaction to *tert*-butyl (*Z*)-2-bromomethyl-2-butenoate (**5a**), dehydrobromination to *tert*-butyl 2-methylidene-3-butenoate (**2c**), dimerization to di-*tert*-butyl 4-vinyl-1-cyclohexene-1,4-dicarboxylate (**1c**) and acidic ester cleavage. Acidic cleavage of easily obtainable **5a** affords (*Z*)-2-bromomethyl-2-butenoic acid (**5b**) in 68% yield with respect to ethanal.

4-Vinyl-1-cyclohexene-1,4-dicarboxylic acid (**1d**, Mikanecic acid) is a terpenoid dicarboxylic acid, the history and synthesis of which have been described by *Dreiding et al.* [2]. Using several precursors these authors generated the sensitive 2-methylidene-3-butenoates **2a** and **2b**, which on *Diels-Alder* dimerization gave the corresponding diesters **1a** and **1b**. A problem in the conversion of **1b** into **1d** was partial saponifica-

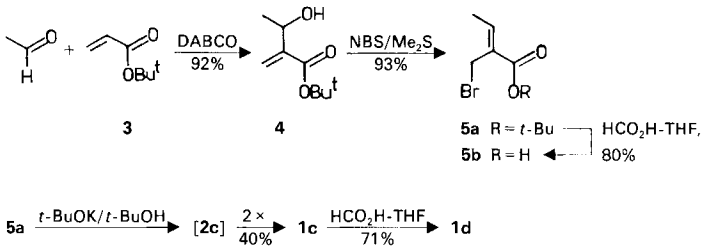


1a R = Me
1b R = Et
1c R = *t*-Bu
1d R = H

2a
2b
2c

[1]) Part 2: see [1].

Scheme



tion: a mixture of diethyl ester **1b**, monoethyl ester and mikanecic acid (**1d**) was obtained [2b]. Furthermore, a simple and efficient route to 2-methylidene-3-butenoates [2] [3] such as **2** is required.

We now describe a short route to **1d**, in which the di-*tert*-butyl ester **1c** is prepared and hydrolysed in the final step. The key *tert*-butyl 2-methylidene-3-butenoate (**2c**) is obtained in three stages as shown in the *Scheme*.

Coupling of ethanal and **3** in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) [1] [4] [5] afforded **4** in 92% yield. Treatment of **4** with *N*-bromosuccinimide/dimethyl sulfide gave the trisubstituted olefin **5** regioselectively (*i.e.* 100% S_N2'-reaction) and stereoselectively (only the (*Z*)-isomer was discernible by ^{1}H-NMR). Base-induced dehydrobromination of **5a** to **2c**, which has not been optimized, and *in situ Diels-Alder* dimerization to **1c**, were now the yield-limiting operations (40% overall). As a model reaction for the final step the base-sensitive *tert*-butyl ester **5a** was hydrolysed to (*Z*)-2-bromomethyl-2-butenoic acid (**5b**) [2b][2]) in 80% yield. Acidic hydrolysis of **1c** was similarly straightforward, affording free mikanecic acid (**1d**), which was easily isolated. The overall yield of **1d** was 24% and the reagents and starting materials are readily available.

We thank the *Fonds der Chemischen Industrie* for support of this work.

Experimental Part

tert-Butyl 3-Hydroxy-2-methylidene-butanoate (**4**). Freshly distilled ethanal (8.8 g, 0.2 mol, 11.3 ml), *tert*-butyl propenoate (**3**) (38.4 g, 0.3 mol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (2.5 g, 0.022 mol) were allowed to react at r.t. until the aldehyde had disappeared (GC control, *ca.* 7 days). The mixture was taken up in Et_2O (100 ml) and washed with H_2O. The combined aq. phase was washed with Et_2O (30 ml), the collected org. phase was dried ($MgSO_4$) and the Et_2O was distilled off. Residual solvent and **3** were removed with an oil pump to leave **4** (32 g, 92%), which was pure by spectroscopic and chemical criteria. IR ($CHCl_3$): 3600*w*, 3500 br. (OH), 2960*s*, 2920*w*, 1690*vs* (C=O), 1620*w* (C=C), 1445*w*, 1385*m*, 1360*s*, 1335*m*, 1140*vs* (C–O), 1080*s*, 950*m*, 890*w*, 840*m*. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.38 (*d*, *J* = 7, 3H, CH_3); 1.53 (*s*, 9H, CMe_3); 2.95 (br. *s*, 1H, OH); 4.59 (*q*, *J* = 7, HC=C); 6.11 (*s*, 1H, HC=C). ^{13}C-NMR ($CDCl_3$): 165.9 (*s*, C(1)); 146.0 (*s*, C(2)); 122.5 (*t*, CH_2); 81.0 (*s*, CMe_3); 66.5 (*d*, C(3)), 28.1 (*q*, $3CH_3$); 22.7 (*q*, C(4)). MS: 174 (0, M^+), 157 (5), 139 (4), 116 (7), 101 (21), 99 (33), 81 (25), 57 (100), 41 (42).

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[2]) The acid **5b** and its derivatives are of interest as fungicides and insecticides; see [6].

tert-*Butyl* (Z)-*2-Bromomethyl-2-butenoate* (**5a**). *N*-Bromosuccinimide (8 g, 46 mmol) in dry CH_2Cl_2 (60 ml) was cooled to 0° and $(CH_3)_2S$ (4 ml, 50 mmol) in CH_2Cl_2 (40 ml) was added dropwise, giving a white precipitate. After stirring for 10 min at 0° a solution of **4** (7.2 g, 42 mmol) in CH_2Cl_2 (40 ml) was added dropwise and the resulting suspension was stirred for 24 h at r.t., giving a clear solution. The mixture was diluted with light petroleum (100 ml) and poured into 200 ml of an ice/H_2O/NaCl mixture. The org. phase was separated and washed with 100 ml of a sat. solution of NaCl. The combined aq. phase was washed with Et_2O (2 × 100 ml) and the collected org. phase was dried ($MgSO_4$). After removal of the solvent, the sulfur compounds were removed on an oil pump. The residue was chromatographed on silica gel (Et_2O/CH_2Cl_2 1:1) giving **5a** (9.2 g, 93%). IR ($CHCl_3$): 2960*m*, 2920*w*, 1700*s* (C=O), 1635*w* (C=C), 1460*m*, 1450*w*, 1360*m*. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.52 (*s*, 9H, CMe_3); 1.89 (*d*, *J* = 7, 3H, CH_3); 4.21 (*s*, 2H, CH_2Br); 6.95 (*q*, *J* = 7, 1H, HC=C). ^{13}C-NMR ($CDCl_3$): 164.4 (*s*, C(1)); 131.9 (*s*, C(2)); 141.5 (*d*, C(3)); 80.8 (*s*, CMe_3); 28.1 (*q*, $3CH_3$); 24.3 (*t*, CH_2Br); 14.4 (*q*, CH_3). MS: 236/234 (0, M^+), 221 (0.6), 219 (0.6), 181 (15), 179 (15), 163 (22), 161 (22), 155 (8), 99 (18), 57 (100), 41 (36).

(Z)-*2-Bromomethyl-2-butenoic Acid* (**5b**) [2b]. A solution of **5a** (4.7 g, 20 mmol) in THF (20 ml) and formic acid (30 ml) was stirred for 16 h at r.t. After neutralization with aq. $NaHCO_3$ the acid **5b** was extracted with Et_2O and recrystallized from Et_2O/light petroleum giving **5b** (2.8 g, 80%). IR ($CHCl_3$): 3000 br. (OH), 1690*vs* (C=O), 1640 (C=C); 1420*m*, 1285*s*, 1180*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.94 (*d*, *J* = 7, 3H, CH_3); 4.25 (*s*, 2H, CH_2Br); 7.27 (*q*, *J* = 7, 1H, HC=C); 12.26 (*s*, 1H, CO_2H). MS: 180/178 (5, M^+), 99 (100, M-Br), 81 (27), 53 (60).

Di-tert-*Butyl 4-Vinyl-1-cyclohexene-1,4-dicarboxylate* (**1c**). To a solution of *t*-BuOK (1.8 g, 16 mmol) in *t*-BuOH (30 ml) was added **5** (3 g, 12 mmol). After stirring for 12 h at r.t. the solution was poured into Et_2O (100 ml) and washed with a sat. aq. solution (2 × 50 ml) of NaCl. The combined aq. layer was re-extracted with Et_2O (3 × 20 ml) and the united Et_2O phase was dried ($MgSO_4$). After removal of Et_2O the oily residue was freed from remaining solvent with an oil pump to give **1c** (1.6 g, 40%). IR ($CHCl_3$): 2980*m*, 2920*w*, 1700*s* (C=O), 1650*w* (C=C), 1475*w*, 1450*w*, 1390*m*, 1370*s*, 1280*s*, 1250*m*, 1160*s*, 1090*m*, 845*m*. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.48 (*s*, 9H, CMe_3); 1.49 (*s*, 9H, CMe_3); 1.60–2.41 (*m*, 6H, CH_2CH_2, CH_2); 5.08 (*dd*, *J* = 1, 18, 1H); 5.12 (*dd*, *J* = 1, 6, 1H) (HC=CH_2); 5.88 (*dd*, *J* = 6, 18, 1H, *H*C=CH_2); 6.85 (*m*, 1H, *H*C=CCO_2tBu). MS: 306 (0, M^+), 251 (2), 207 (5), 196 (23), 179 (11), 178 (22), 151 (24), 133 (14), 115 (11), 105 (16), 99 (11), 91 (14), 79 (14), 57 (100).

4-Vinyl-1-cyclohexene-1,4-dicarboxylic Acid (**1d**) [2]. A solution of **1c** (1 g, 3.2 mmol) in THF (10 ml) and formic acid (10 ml) was stirred overnight at r.t. After neutralization with aq. $NaHCO_3$, the acid **1d** was extracted with Et_2O. After evaporation of the Et_2O the crude acid was re-crystallized from Et_2O/light petroleum 1:1 giving **1d** (0.45 g, 71%). IR (KBr): 3000*w* (OH), 1690*vs* (C=O), 1645*m* (C=C), 1420*m*, 1285*s*, 1200*w*, 1100*w*, 920*m*, 760*w*, 730*w*, 710*w*. ^{1}H-NMR (90 MHz, (D_6)DMSO): 1.50–2.65 (*m*, 6H, CH_2CH_2, CH_2); 5.08 (*m*, *AB*-part of an *ABX*-system, 2H, HC=CH_2); 5.88 (*m*, *X*-part, 1H, *H*C=CH_2); 6.85 (br.*s*, 1H, *H*C=C–CO_2H); 12.45 (br. *s*, 2H, 2 OH). MS: 196 (11, M^+), 178 (65), 151 (86), 133 (68), 105 (100), 91 (55), 79 (83), 77 (87).

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