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Resin-Bound Anionically Induced Domino Reactions; Synthesis of Functionalized Carbocyclic Compounds

Hans-Jürgen Gutke and Dietrich Spitzner*[1]
**Institut für Chemie, Abt. Organische Chemie, Universität Hohenheim, Garbenstraße 30,
D-70599 Stuttgart, Germany**

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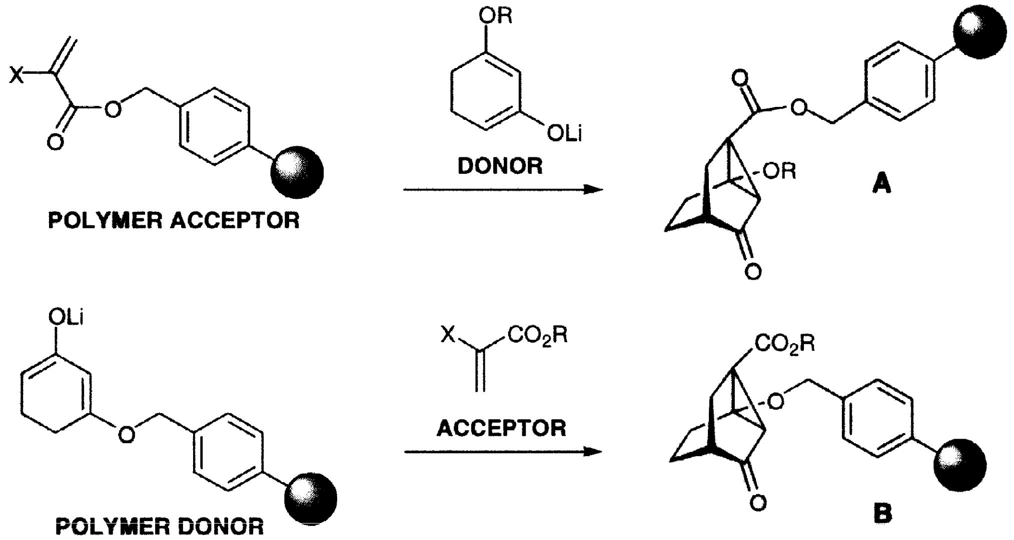
Abstract: The anionically induced Domino reaction of resin-bound Li-dienolate with an α-halo-α,β-unsaturated ester gave the corresponding immobilized tricyclo[3.2.1.0^{2,7}]octane, which can be olefinated or oxidized. The cycles are cleaved from the resin by acid. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Michael addition; resin-bound Domino reactions; small-molecular weight compound libraries.

Domino reactions[1] are ideally suited for the generation of small-molecular weight compound libraries.[2] We report about the synthesis of highly functionalized bicyclo[3.2.1]octanes from tricyclo[3.2.1.0^{2,7}]octane **5** generated by an anionically induced Domino reaction on a resin. Both, tricyclo[3.2.1.0^{2,7}]octanes and bicyclo[3.2.1]octanes are used as starting compounds in the total synthesis of terpenoid natural products.[3]



This Domino reaction between a donor (Li dienolate) and an acceptor (usually an α-halo-α,β-unsaturated ester) is performed in an aprotic medium (THF, toluene) in one pot without intermediate work-up.

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[1] e-mail: spitzner@uni-hohenheim.de

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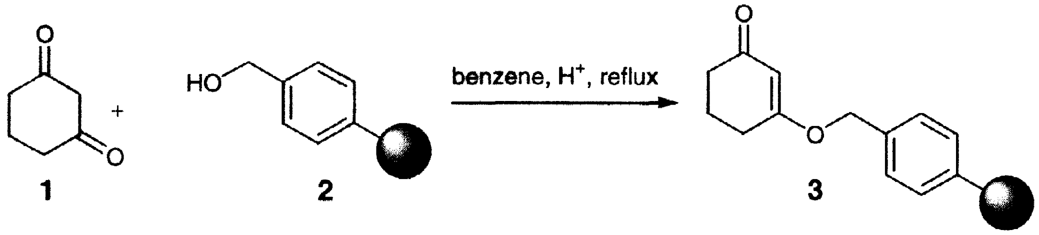
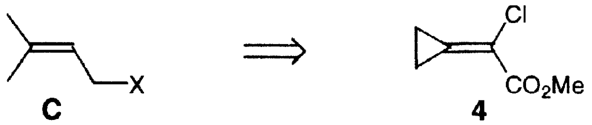
Enantiomerically pure tricyclo[3.2.1.0^{2,7}]octanes may also be obtained by a diastereoselective Domino reaction (d.e. >95%) from chiral α,β-unsaturated esters.[4] Two Michael additions and an intramolecular γ-elimination form directly tricyclo[3.2.1.0^{2,7}]octanes of type **5**, which may be modified with ylid **8** (Wittig olefination) to the corresponding tricyclo[3.2.1.0^{2,7}]octanes of type **7**.

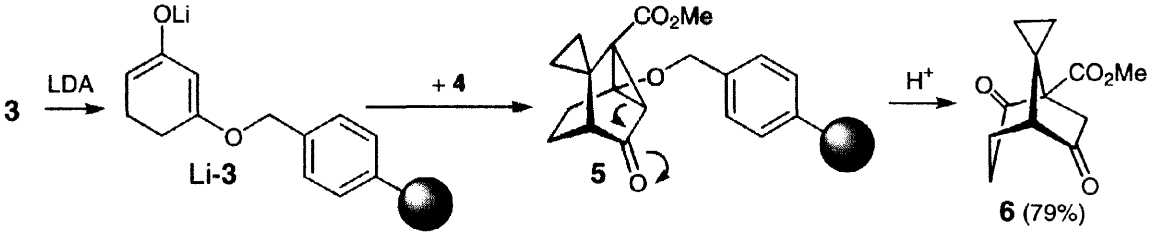
Moreover, the regioselective insertion of an additional oxygen atom into type **5** compounds is possible with MCPBA (Baeyer-Villiger oxidation) which extends the number of skeletons.[5] We envisaged their use in non-peptide libraries. In general, the anionically induced Domino reaction on a polymer can be performed either with immobilized acceptors[6] or with a polymer bound lithium dienolate, generated under kinetic control, as a donor. Tricyclo[3.2.1.0^{2,7}]octanes are obtained in both cases although differently bound to the polymer backbone (ester bond in **A** *vs.* ether bond in **B** between carbocycle and the polymer backbone). In the first case the liberation of the Domino product from the resin should be performed under reductive conditions (DIBAL) or by base hydrolysis. We started from polymer bound 1,3-cyclohexanedione **3**[7], which is available from the hydroxymethyl phenyl resin **2**[8] and 1,3-cyclohexanedione (**1**). Polymer **3** was treated with an excess of LDA



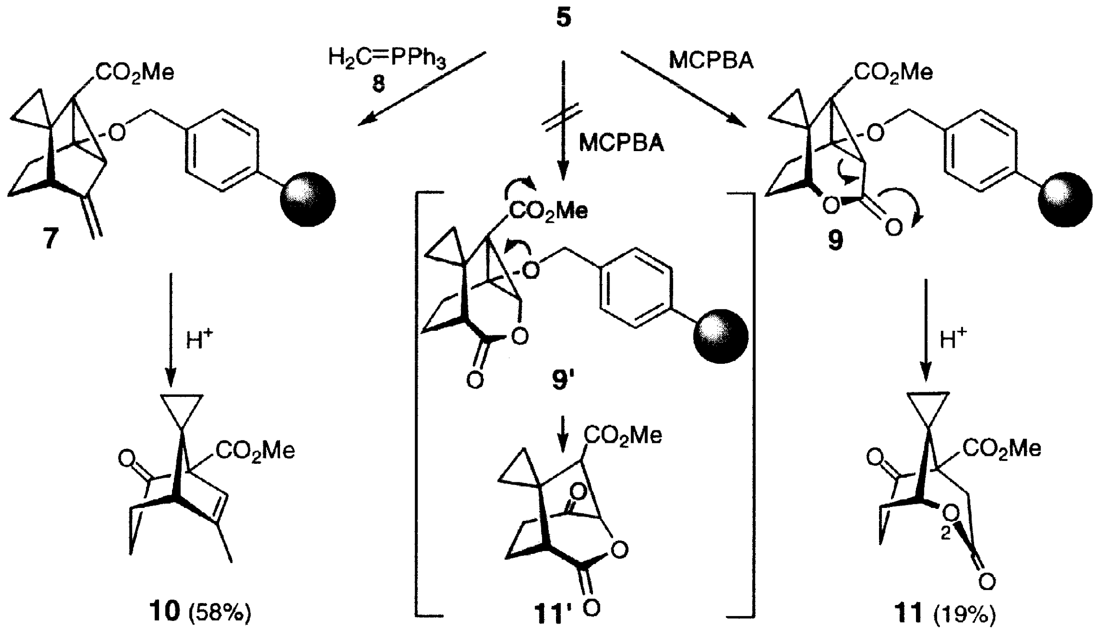
to give the corresponding kinetic enolate Li-**3**. The bulk amount of base and other monomers were removed by careful washing of the resin. The anionically induced Domino reaction was performed with ester **4**[9] as an acceptor. This ester possesses excellent Michael acceptor properties and has been used in similar Domino



reactions. It represents an equivalent of activated isoprene **C** but other α-halo-α,β-unsaturated esters[10] except β-disubstituted esters (e.g. α-halo-senecioic esters) may be used as well. Acidic hydrolysis (20% HCl in



dichloromethane, 20°C, 12 h and sonication 2 h) gave (selective opening of the "push-pull" substituted cyclopropane ring[11]) directly the pure dione **6** (79%). The amount of polymer-bound tricyclo[3.2.1.0^{2,7}]octane **5** was split; one part was treated with excess phosphorane **8** to give the intermediate olefin **7** and the other part was oxidized with *m*-chloroperbenzoic acid (MCPBA) in buffered ($NaHCO_3$) dichloromethane to give **9**. Acidic hydrolysis with conc. HCl in dichloromethane of both, **7** and **9** gave the spirobicyclic olefin **10**[12] (overall yield 58%) and the lactone **11** (overall yield 19%) as single compounds, respectively. The alternative polymer lactone **9'** was not formed. The cleavage compound **11** shows only one doublet (δ 82.04 for *C*HO) in the ^{13}C NMR instead of three for the alternative lactone **11'**. The cleavage from the polymer backbone occurs in all cases very readily due to the fragility of the "push-pull" substituted cyclopropane moiety. This opening may be considered as a retrograde aldol reaction. It is noteworthy to mention that the carbocycles formed on the resin are much cleaner than from the usual Domino reaction. The polymer bound cycles bear functions suitable for many more chemical reactions on the resin which may lead to new compounds.



EXPERIMENTAL

General: THF and toluene were freshly distilled from sodium/benzophenone. All other solvents were distilled prior to use. Diisopropylamine was distilled from calcium hydride. *n*-Butyllithium was obtained as solution in hexane from Chemetall, Frankfurt, Germany, and titrated prior to use. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were measured on a Unity-Inova Varian 300 spectrometer at 300.13 and 75.48 MHz, resp. Mass spectra were recorded on a Finnigan MAT 8200. The analytical TLC was performed with silica gel 60 F_{254}, Merck, Darmstadt, Germany. Preparative column chromatography was performed on silica gel 60, Macherey & Nagel, Düren, Germany. Reactions involving air and/or moisture sensitive reagents were conducted under an atmosphere of argon, and the glassware was oven dried (140°C) and purged with argon. All melting points were determined with a Büchi melting-point apparatus and are uncorrected. Elemental analyses were obtained from Mikroanalytisches Laboratorium, Universität Stuttgart, Germany.

Resin 3: A mixture of 4.74 g hydroxymethyl phenyl resin **2** (1.02 mmol OH/g, 4.83 mmol), 5.00 g 1,3-cyclohexanedione (**1**) and 30 mg of *p*-toluenesulfonic acid was refluxed in 60 ml benzene for 2 d. The water formed was adsorbed on molecular sieve (3 Å), placed in a Dean Stark trap. The mixture was filtered and the modified polymer resin washed with benzene (2 x 70 ml) and dichloromethane 3 x 100 ml) and dried in vacuum to yield 4.85 g of the yellowish polymer **3**. – FT-IR (KBr): $\nu_{(C=O)}$ 1652 cm^{-1} for the enone **3**. (lit. cit.[7]: 1652 cm^{-1}).

Domino Reaction with Resin 3: 1.00 g of polymer **3** was allowed to swell in toluene for 1 h . This suspension was cooled to –60°C and a precooled solution of freshly prepared LDA [5 mmol in 15 ml THF, from 3.1 ml *n*-butyllithium (1.6 M in hexane) and 0.78 ml of diisopropylamine] was added dropwise . Mixing was effected by passing a stream of argon through the reaction mixture. The whole was allowed to warm to –20°C and kept at this temperature for 1 h. The reaction mixture was cooled again to –60°C and most of the solution, containing the excess base and other soluble material was removed with a syringe. A solution of 0.733 g (5 mmol) of the ester **4** in 20 ml THF was added and the mixture allowed to warm to –20°C slowly. After 1 h at this temperature the reaction vessel was sonicated at 0°C for 20 min and the modified polymer filtered off, washed with dichloromethane (3 x 30 ml) and dried *in vacuo.* Yield: 1.14 g of polymer **5**. – FT-IR (KBr): ν = 1734 cm^{-1} (C=O), 1492, 14.52, 1234. – ^{13}C-NMR (75.4 MHz, C_6D_6): δ = 5.50 (cyclopropyl), 9.50 (cyclopropyl), 166.03 (ester C=O), 205.53 (ketone C=O).

Hydrolysis of Resin 5; Bicyclo[3.2.1]octane 6: To a suspension of 0.812 g of polymer **5** in 20 ml of dichloromethane were added 5 drops of HCl (20%) and the whole agitated for 12 h. Additionally the suspension was sonicated for 2 h. The reaction mixture was filtered and the polymer washed with dichloromethane (3 x 30 ml). The solvent was evaporated and the residue filtered through a column of silica gel (elution with petrolether/ether 1:1). The filtrate was concentrated to yield 0.108 g (79%) of crystalline ester **6**, mp 82-86°C (lit.[13] 85°C), which was identical with an authentic sample. – EI-MS (70 eV) m/z (%): 222 (M$^+$,41), 194 (13), 190 (21), 162 (22), 55 (100).

Olefination of Resin 5: A suspension of 0.584 g of polymer **5** in 30 ml of THF was treated with a solution of 5 mmol of phosphorane **8** in 30 ml of THF (prepared from 1.82 g methyl triphenyl phosphonium bromide and 0.560 g of potassium *t*-butoxide) at room temperature for 24 h. The reaction mixture was filtered and the polymer washed with dichloromethane (2 x 15 ml), methanol (1 x 15 ml), water (2 x 30 ml) and ethanol (2 x 10 ml) and the residue dried *in vacuo*. Yield: 570 mg of the polymer **5**. For the acidic cleavage a suspension of 354 mg of **5** in 10 ml of dichloromethane together with 2 drops of conc. HCl were sonicated for 5 h. The mixture was filtered, the polymer washed with dichloromethane (3 x 30 ml) and the solvent evaporated. Filtration through a column of silica gel (elution with petrolether/ether 1:1, $R_f = 0.46$) gave 51 mg (58%) of the ketone **10**, oil, identical with an authentic sample.[11]– EI-MS (70 eV) m/z (%): 220 (M^+, 22), 202 (16), 164 (100), 133 (59), 105 (95).

Baeyer-Villiger Oxidation of Resin 5; Lactone 9: To a suspension of 0.516 g of polymer **5** in 30 ml of dichloromethane was added a mixture of 0.7 g of solid $NaHCO_3$ and 0.9 g of MCPBA (50-60%, Merck, Darmstadt, Germany). The reaction mixture was refluxed for 2 h and then filtered. The polymer **9** was washed successively with dichloromethane (2 x 10 ml), methanol (2 x 10 ml), water (3 x 30 ml) and finally with methanol (2 x 20 ml) and dried *in vacuo* to yield 0.520 g of the oxidized polymer.

Acidic Cleavage; Lactone 11: 0.520 g of polymer **9** were suspended in 10 ml of dichloromethane acidified with 2 drops of conc. HCl and sonicated for 4 h. The mixture was filtered and the polymer washed with dichloromethane (3 x 30 ml). The solvent was evaporated and the residue filtered through a column of silica gel (elution with ether, monitored by TLC, $R_f = 0.57$) to give 20 mg (19%) of lactone **11**, white crystals, mp. 106°C. – IR (KBr): $\nu = 2956\ cm^{-1}$, 1722, 1435, 1404, 1200, 1046. – ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.64 - 0.52$ (m, 2 H, cyclopropyl), 0.91 - 0.83 (m, 1 H, cyclopropyl), 1.75 - 1.66 (m, 1 H, cyclopropyl), 2.46 - 2.18 (m, 2 H), 2.74 - 2.53 (m, 2 H), 3.03 (AB, d, $J_{AB} = 19.1$ Hz, 2 H, 4´-H), 3.44 (AB, $J_{AB} = 19.1$ Hz, 2 H, 4´-H), 3.72 (s, 3 H, OCH_3), 3.85 (t, $J = 3.0$ Hz, 1 H, 1´-H). – ^{13}C-NMR (75.4 MHz, $CDCl_3$): $\delta = 204.32$ (s, ketone), 168.42 (s, carboxyl), 167.64 (s, carboxyl), 82.04 (d, C-1´), 58.50 (s), 52.61 (q), 37.19 (t), 32.86 (t), 29.82 (t), 23.88 (s, C-1), 9.53 (t, cyclopropyl), 8.93 (t, cyclopropyl). – EI-MS (70 eV) m/z (%): 338 (M^+, 2), 206 (14), 178 (100), 150 (47). – Calcd. for $C_{12}H_{14}O_5$ (238.2): C 60.50%; H 5.92%. Found: C 59.99%; H 5.91%.

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