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Preparation of Diastereomerically Pure 9-Carboxybicyclo[6.1.0]nonane Derivatives

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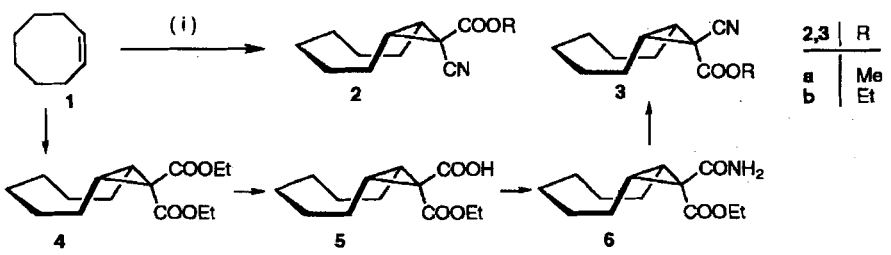
Abstract. Reactions of cyclooctene (**1**) with dibromocyanoacetic esters and copper(I) bromide give (8–10) : 1 mixtures of isomers (**2**, **3**), not stereochemically pure compounds as reported by others. The stereochemistry is elucidated by independent synthesis of one diastereomer (**3a**). Carbenoid addition of alkoxycarbonylmethylene to **1** and 1,5-cyclooctadiene leads also to *exo/endo* adduct mixtures. Methods are developed to generate diastereomerically pure compounds (***exo*-7a**, ***exo*-8**, ***endo*-9**, ***exo*-10**, ***endo*-10**) from these. *Endo* esters of this series undergo very facile base catalyzed epimerization.

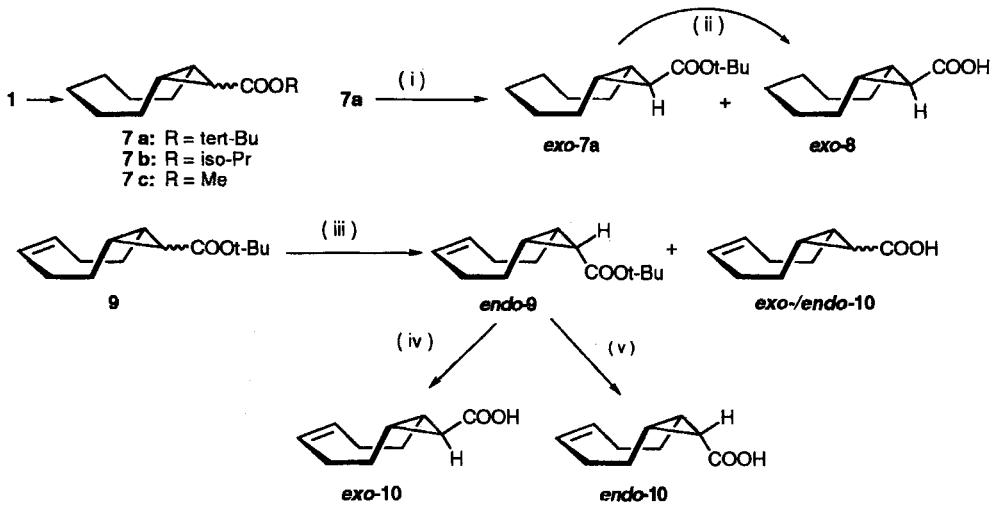
We take interest in the stereochemistry of 9-substituted bicyclo[6.1.0]nonanes and -nonenes formed by cyclopropannelation of eight-membered rings [1–3]. Debrominative addition of dibromocyanoacetic ester induced by Cu or Cu_2Br_2 to alkenes was reported first in 1958 [4] and later extended by Kawabata et al. [5]. These authors found that the reactions are not stereospecific normally and seem to occur *via* intermediate radicals. Nevertheless only one (liquid) isomer was observed with cyclooctene (**1**) and the respective ethyl ester by glc and NMR analysis. No stereochemistry was assigned.

Repeating the reaction with methyl and ethyl dibromocyanoacetates, compounds **2a,b** and/or **3a,b** were obtained which could be crystallized from methanol. The ethyl (**b**) ester had ^{1}H NMR data matching those of Kawabata et al. An independent synthetic route to **3b** was sought therefore to ascertain the stereochemistry. **1** was treated with ethyl diazomalonate in the presence of copper powder to give **4**. It is well known that the *exo* ester group in such structures is saponified preferentially [6], and thus **5** and subsequently **6** and **3b** can be prepared by conventional methods.

Melting points of **3b** and the compound made by the Kawabata route were different, so that the latter has to be **2b**. The characteristic ethyl signals in the ^{1}H NMR spectra of the two isomers exhibit only very small positional differences, so that the presence of a little **3b** in raw **2b** may be overlooked easily. The ^{13}C NMR data, however, are not so similar (see experimental part). Integration of the 300 MHz spectra of the raw products showed the **2b/3b** and **2a/3a** ratios to be about 8 : 1 and



Scheme 1 (i) $Br_2C(CN)COOR$, Cu_2Br_2, DMSO, 100 °C, 2h; yields: **2a** 8.3%, **2b** 12%



(I) 2 eq. *t*-BuOK + 1 eq. H_2O, ether, r. t., 4 h. (ii) *p*-TosOH, benzene reflux, 2.5 h.
(iii) 1.5 eq. KOH, *t*-BuOH, reflux 2 h. (iv) 2 eq. *t*-BuOK + 1 eq. H_2O, ether, r. t., 48 h.
(v) trace H_3PO_4 (99%), 100–120 °C, 3 h.

Scheme 2

10:1, respectively. The preponderance of compounds **2** is in line with a radical intermediate which will favor the more voluminous ester group on the outer side. No adduct was obtained when 1,5-cyclooctadiene was treated by the Kawabata method. This may be due to competing fast intra- and intermolecular radical reactions.

Dirhodium tetracetate was used for the carbenoid reaction of **1** with methyl, isopropyl, or *tert*-butyl diazoacetates to give **7a-c** as (1.2–1.3) : 1 *exo/endo* mixtures. This contrasts to the reported similar $Rh_2(OAc)_4$ catalyzed reaction of cyclohexene in which a much stronger *exo* preference occurred [7]. In our hands, 1,5-cyclooctadiene led even to a 1:1.1 ratio of ***exo***- and ***endo*-9**. For a selective saponification of **7a**, we tried a method introduced by Gassman for hindered esters [8]. This utilizes so-called „anhydrous KOH" at room temperature (2 equivalents of *tert*-BuOK and 1 equivalent of water in excess anhydrous ether). Surprisingly, only exo acid (***exo*-8**) and some unchanged ester (***exo*-7a**) were obtained. Thus, ester ***endo*-7a** must have been isomerized under these relatively mild conditions. Applying the less basic reagent KOH/*tert*-butanol to the *exo/endo* ester mixture **9** at 83 °C, we were able to avoid this epimerization almost completely: ***endo*-9** could be isolated along with a diastereomeric mixture of the acids **10**. When this ester ***endo*-9** was treated again, however, with the „anhydrous KOH" for a prolonged time, virtually quantitative transformation into acid ***exo*-10** was achieved. On the other hand, the acid ***endo*-10** could be made in pure form from the ester ***endo*-9** by acid hydrolysis with 98% phosphoric acid.

We have shown how pure diastereomers of this series can be made inspite of the facile epimerization of the endo esters. ***Endo*-10** is a valuable starting material for further intramolecular reactions.

Experimental

Ethyl 9-endo-*cyano-bicyclo[6.1.0]nonane-*9-exo-*carboxylate* (**2b**)

The compound was prepared as described [5a]. The yellowish oil obtained was crystallized from methanol in the cold; m.p. 66–67 °C; 12% yield. The yield seems to be strongly dependent on the quality of the commercial (Fluka) or freshly prepared Cu_2Br_2. – ^{1}H NMR (250 MHz): δ 4.23 (q, 2H), 2.13–1.44 (m, 14 H), 1.33 (t, 3H). – ^{13}C NMR (62.89 MHz): δ 168.3 (CO), 116.4 (CN), 62.6 (ester-CH_2), 34.7 (C-1, C-8), 28.0, 26.2, 24.0, 23.3, 14.1 (CH_3). – Analysis of the expanded 300 MHz ^{1}H NMR spectrum of the raw product showed that about 12% of **3b** had been present.

Methyl 9-endo-*cyano-bicyclo[6.1.0]nonane-*9-exo-*carboxylate* (**2a**)

Obtained analogously. M.p. 63–64 °C (from methanol), yield 8.3%. – ^{1}H NMR (250 MHz): δ 3.80 (s, 3 H), 2.13–1.45 (m, 14 H). – Anal. calcd. for $C_{12}H_{17}NO_2$ (207.3): C 69.54 H 8.27 N 6.76; found C 69.51 H 8.21 N 6.73. – Analysis of the expanded 300 MHz ^{1}H NMR spectrum of the raw product showed that about 10% of **3a** had been present (Integral of signals at δ 3.80 and 3.78).

*Ethyl 9-*exo*-carboxy-bicyclo[6.1.0]nonane-9-*endo*-carboxylate* (**5**)

A mixture of 90 g (0.82 mol) of **1** and 2 g of Cu powder were stirred at 130 °C, and 20 g (0.11 mol) of diethyl diazomalonate were dropped in within 2 h. The liquid was cooled, unreacted **1** was distilled off, and the residue was fractionated. At 130–132 °C/0.2 Torr 11.9 g (42%) of **4** were obtained which were used without further purification.

3 g (11.3 mmol) of **4** and 640 mg (11.4 mmol) of KOH were dissolved in 30 ml of methanol, and the solution was refluxed for 60 h. The solvent was evaporated, and the residue was dissolved in 20 ml of water, and acidified to pH 1 with conc. HCl at 5 °C. Water was decanted, the oily organic material was taken up in ether, and dried with Na_2SO_4. Ether was removed, and the residue was crystallized twice from petroleum ether. M.p. 94–95 °C; yield 1.83 g (67%). – ^{1}H NMR (250 MHz): δ 4.24 (q, 2 H), 2.05–1.20 (m, 14 H), 1.30 (t, 3H). – Anal. calcd. for $C_{13}H_{20}O_4$ (240.3): C 64.98 H 8.39; found C 64.71 H 8.63.

9-endo-*Ethoxycarbonylbicyclo[6.1.0]nonane-9-*exo*-carboxamide* (**6**)

1 g (4.2 mmol) of **5** were heated with 10 ml of thionyl chloride for 20 min. Excess $SOCl_2$ was removed, and the residue was taken up in 5 ml of dioxane and treated with 30 ml of conc. ice-cold ammonia. The precipitate was filtered off after 30 min. and recrystallized from methanol. M.p. 151–152 °C, 720 mg (72%) yield. – Anal. calcd. for $C_{13}H_{21}NO_3$ (239.3): C 65.25 H 8.84 N 5.85; found C 65.10 H 8.91 N 5.75.

*Ethyl 9-*exo*-cyano-bicyclo[6.1.0]nonane-9-*endo*-carboxylate* (**2a**)

0.5 g (2.09 mmol) of **6** were dissolved in 20 ml of dry $CHCl_3$ and stirred with 1.8 g (12.6 mmol) of P_2O_5 for 2 h at room temperature. Thereafter the mixture was poured onto ice. The organic phase was separated, dried (Na_2SO_4), and concentrated. The solid formed was recrystallized from methanol. M.p. 52–54 °C, 170 mg (36%) yield. – ^{1}H NMR (250 MHz): δ 4.22 (q, 2H), 1.99–1.26 (m, 14 H), 1.32 (t, 3H). – ^{13}C NMR (62.89 MHz): δ 165.4 (CO), 120.6 (CN), 62.0 (ester-CH_2), 36.2 (C-1, C-8), 28.3, 26.1, 20.4, 20.1, 14.2 (CH_3).

General method for the reactions with diazoacetic esters

136 g (1.23 mol) of **1** (or cycloocta-1,5-diene) and 70 mg (0.15 mmol) of $Rh_2(OAc)_4$ were stirred at room temperature, and 171 mmol of the appropiate diazoacetic ester were dropped in within 4 h at r.t. (preparation of **7**) or at 65–70 °C (preparation of **9**). Evolution of nitrogen occurred. (In case of the *tert*-butyl ester, the mixture was warmed to 35 °C and stirred for 14 h). The mixture was filtered, the unreacted **1** was distilled off, and the residue was fractionated.

tert-*Butyl bicyclo[6.1.0]nonane-*exo*-/endo-9-carboxylate* (**7a**)

b.p. 83–85°C/0.8 Torr, 24.1 g (63%) yield. *exo/endo* = 1.2. – ^{1}H NMR (250 MHz): δ 2.09–2.02 (m, 2 H), 1.84–0.92 (m, 13 H), 1.442 (s, *t*-Bu), 1.437 (s, *t*-Bu). – Anal. calcd. for $C_{14}H_{24}O_2$ (208.3) C 74.95 H 10.78; found C 74.69 H 11.00. – Pure ***exo*-7a** was obtained by adding 1.34 g (6 mmol) of the **7a** mixture to a suspension of 2.66 g (26 mmol) of *t*-BuOK in 50 ml of absol. ether which was treated with 0.12 ml of water at 0 °C and by stirring for 4 h at room temperature. The solution was poured onto ice, separated, dried (Na_2SO_4), and evaporated. Yield 620 mg (95% in respect to amount originally present). – ^{1}H NMR (250 MHz): δ 2.08–2.02 (m, 2 H), 1.84–1.03 (m, 12 H), 1.437 (s, 9 H), 1.00 (t, J = 4.3 Hz; 1 H).

Isopropyl bicyclo[6.1.0]nonane-exo-/endo-9-carboxylate (**7b**),

b.p. 110–112 °C/1.2 Torr, 20.5g (58%) yield.– *exo/endo* = 1.3. – ^{1}H NMR (250 MHz): δ 4.98 (septet), 4.97 (septet; together 1 H), 2.16–2.03 (m, 1 H), 1.92–0.94 (m, 14 H), 1.22 (d, 6 H). – Anal. calcd. for $C_{13}H_{22}O_2$ (210.3) C 74.24 H 10.54; found C 74.04 H 10.61.

Methyl bicyclo[6.1.0]nonane-exo-/endo-9-carboxylate (**7c**)

b.p. 124–127 °C/12 Torr, 9.66 g (31%) yield. – *exo/endo* = 1.2. – ^{1}H NMR (250 MHz): δ 3.64 (s), 3.63 (s; together 3 H), 2.08–1.0 (m, 15 H) (*cf.* lit. [9]).

tert-Butyl bicyclo[6.1.0]non-4-ene-exo-/endo-9-carboxylate (**9**),

b.p. 86–93 °C/0.55 Torr, 34.5g (91%) yield. *exo/endo* = 0.9. – ^{1}H NMR (250 MHz): δ 5.67–5.54 (m, 2 H), 2.55–1.26 (m, 10 H), 1.61 (t, J = 8.85 Hz, C-9-*exo*-H), 1.46 (s, *endo-t*-Bu), 1.43 (s, *exo-t*-Bu) , 1.09 (t, J= 4.1, C-9-*endo*-H). – Anal. calcd. for $C_{14}H_{22}O_2$ (206.3) C 75.63 H 9.97; found C 75.74 H 10.04.

*Bicyclo[6.1.0]nonane-*exo*-9-carboxylic acid* (***exo*-8**)

(a) By heating 600 mg (2.7 mmol) of ***exo*-7a** in 25 ml of benzene with 100 mg of *p*-toluenesulfonic acid for 2.5 h. The solution was extracted twice with 10 ml of 0.5 M NaOH. The alkaline extract was acidified (conc. HCl), and the precipitate was recrystallized from methanol/water 1:1. M.p. 120–121°C (lit. : 121°C [10]), yield 110 mg (24%). – ^{1}H NMR (250 MHz): δ 2.09–2.04 (m, 2H), 1.68–0.98 (m, 12 H), 1.10 (t, J = 4.3, 1 H). – ^{13}C NMR (62.89 MHz): δ 180.8, 29.1, 28.4, 26.5, 25.9, 25.8. – (b) By workup of the aqueous alkaline phase from the preparation of ***exo*-7a**, 38% yield (relative to starting *exo-/endo*-ester mixture **7a**).

*tert-Butyl bicyclo[6.1.0]non-4-ene-*endo*-9-carboxylate* (**endo-9**)

1.0 g (4.5 mmol) of the *exo-/endo*-mixture **9** were refluxed with 350 mg (6.3 mmol) of KOH in 30 ml of *tert*-butanol for 2h, then poured onto ice. The mixture was extracted twice with 100 ml of ether. After drying (Na_2SO_4) the solvent was removed leaving a colorless oil. Yield 360 mg (72% relative to material present in the mixture **9**). – ^{1}H NMR (250 MHz): δ 5.62–5.59 (m, 2 H), 2.52–2.45 (m, 2 H), 2.24–2.16 (m, 2 H), 2.09–2.04 (m, 2 H), 1.87–1.79 (m, 2 H), 1.61 (t, J = 8.85 Hz, 1 H; C-9-*exo*-H), 1.46 (s, 9 H), 1.35–1.28 (m, 2 H).

*Bicyclo[6.1.0]non-4-ene-*exo*-9-carboxylic acid* (**exo-10**)

was prepared from ***endo*-9** analogously to ***exo*-7a** from **7a** (mixture) except that stirring at room temperature was continued for 48 h. 85 % yield were obtained on usual workup. M.p. 83–85 °C (lit. [11]: 82–84 °C). – ^{1}H NMR (250 MHz): δ 5.69–5.58 (m, 2 H), 2.35–2.03 (m, 6 H), 1.68–1.44 (m, 4

H), 1.19 (t, 1 H, J = 4.5 Hz). – ^{13}C NMR (62.89 MHz): δ 181.0, 129.9, 28.8, 28.2, 27.7, 26.6. – Anal.calcd. for $C_{10}H_{14}O_2$ (166.2) C 72.26 H 8.49; found C 72.47 H 8.59.

Bicyclo[6.1.0]non-4-ene-endo-*9-carboxylic acid* (**endo-10**)

820 mg (3.7 mmol) of ***endo*-9** were heated with 10 mg 99% H_3PO_4 for 3 h at 100–120 °C. The solid formed was crystallized repeatedly from petroleum ether (b.p. 40–60 °C). M.p. 104–105 °C, 590 mg (96%) yield. – ^{1}H NMR (250 MHz): δ 5.66–5.55 (m, 2 H), 2.54–2.44 (m, 2 H), 2.28–2.16 (m, 2 H), 2.11–1.99 (m, 2 H), 1.91–1.80 (m, 2 H), 1.73 (t, 1 H, J = 8.7 Hz), 1.55–1.45 (m, 2 H). – ^{13}C NMR (62.89 MHz): δ 178.8, 129.5, 27.0, 25.4, 22.6, 21.1. – Anal. calcd. for $C_{10}H_{14}O_2$ (166.2) C 72.26 H 8.49; found C 72.21 H 8.35.

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