Boron Trifluoride Mediated Addition of Nucleophiles to *endo*- and *exo*-Substituted Norbornene Derivatives

Alper İşleyen, Tuğmaç Sayraç, and Özdemir Doğan

Middle East Technical University, Department of Chemistry, 06531 Ankara, Turkey

Reprint requests to Assoc. Prof. Dr. Ö. Doğan. E-mail:dogano@metu.edu.tr. Fax: +90-312-210-1280

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Remote substituent effects on the regioselectivity and stereoselectivity in the boron trifluoride mediated addition of nucleophiles (iodide and bromide) to *endo*- and *exo*-2-substituted norbornene derivatives have been investigated. The main products of the reactions resulted from the regioselective addition of nucleophiles to the double bond of norbornene derivatives. Products resulting from the Wagner-Meerwein type rearrangement were also isolated in considerable amounts. All of the reactions gave the addition products in reasonably good yields with high regioselectivity. The *endo*/*exo* selectivity, on the other hand, changed depending on the nucleophile and the substrate.

Key words: Remote Substituent Effects, *endo*/*exo* Selectivity, Regioselectivity, Nucleophilic Additions, π-Facial Selectivity

Introduction

Control of π-facial selectivity in nucleophilic additions to carbonyl groups and in electrophilic additions to alkene groups have been studied extensively. The selectivity of additions to such π-systems were explained by hyperconjugative interactions at the transition states and electrostatic field effects [1]. Arjona *et al.* reported a systematic study on the remote substituent effect of the electrophilic additions of sulfur and selenium halides to 2-substituted norbornene derivatives [2]. Another systematic study on the effect of a remote substituent on regioselectivity in oxymercuration of unsymmetrically substituted norbornenes has been reported by Tam *et al.* [3]. To the best of our knowledge, no systematic study has been done on boron trifluoride mediated addition of nucleophiles to unsymmetrically substituted norbornene derivatives. We wish to report herein the initial results of the remote substituent effect on such additions to *endo*- and *exo*-2-substituted norbornenes.

Results and Discussion

The starting compounds, nitriles [4] **1a**, **1b**, and esters **3a** [3a] and **3b** were synthesized using known literature procedures. *Endo*- and *exo*-ketones **2a** and **2b**, on the other hand, were obtained from the corresponding *endo*- and *exo*-nitriles **1a** and **1b** in 75% and 73% yields, respectively, *via* the Grignard reactions using PhMgBr.

Boron trifluoride mediated nucleophilic addition reactions were studied first with the *endo*-substituted norbornene derivatives **1a**, **2a**, and **3a**. In the case of iodide addition to the double bond of nitrile-substituted norbornene derivative **1a**, the reaction yielded *exo*- and *endo*-addition products, **4** and **6** respectively, in nearly equal amounts along with the minor isomer **5** (Table 1, entry 1). Isomer **5** resulted from the Wagner-Meerwein rearrangement, which is quite common for norbornene systems. For ketone **2a**, the same nucleophile (I^-) gave *exo*-addition product **10** and rearrangement product **11** as the major products with a minor amount of *endo*-addition product **12** (Table 1, entry 3). In the case of iodide addition to *endo*-ester **3a**, three products **15**, **16**, and **17** were isolated, **15** being the major one (Table 1, entry 5).

Addition of bromide to **1a** was more selective compared to that of iodide by giving the *exo*-addition product **7** as the major one with minor isomers **8** and **9** (Table 1, entry 2). When bromide was added to *endo*-ketone **2a**, the reaction was even more selective by giving only the *exo* addition product **13** and rearrangement product **14** (Table 1, entry 4).

In order to compare the effect of *endo*- and *exo*-substituents on the addition of nucleophiles to the norbornene systems, *exo*-isomers (**1b**, **2b**, and **3b)** of ini-

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Table 1. Results of I^- and Br^- addition to *endo*- and *exo*-2-substituted norbornene derivatives.

			Relative ratio of the products[a]			Total
Entry	Substrate	Nu^-	**A**	**B**	**C**	yield(%)
1	**1a**	I^-	40 (**4**)	15 (**5**)	45 (**6**)	70
2	**1a**	Br^-	60 (**7**)	26 (**8**)	14 (**9**)	59[b]
3	**2a**	I^-	51 (**10**)	30 (**11**)	8 (**12**)	77[c]
4	**2a**	Br^-	75 (**13**)	25 (**14**)	–	58
5	**3a**	I^-	71 (**15**)	19 (**16**)	10 (**17**)	54[b]
6	**1b**	I^-	41 (**5**)	9 (**4**)	41 (**18**)	83[b,c]
7	**1b**	Br^-	73 (**8**)	27 (**7**)	–	67
8	**2b**	I^-	33 (**11**)	20 (**10**)	27 (**19**)	87[c,d]
9	**2b**	Br^-	39 (**14**)	28 (**13**)	–	80[b,d]
10	**3b**	I^-	36 (**16**)	14 (**15**)	38 (**20**)	60[b,c]

[a] Measured by the integration of 400 MHz ^{1}H NMR spectra of the crude reaction mixture; [b] calculated according to the recovered starting material; [c] minor amount of uncharacterized byproduct was also seen on the ^{1}H NMR spectrum of the crude reaction mixture; [d] these reactions also produced a regioisomer of **A** where nucleophile is attached to C-6 at *exo*-position.

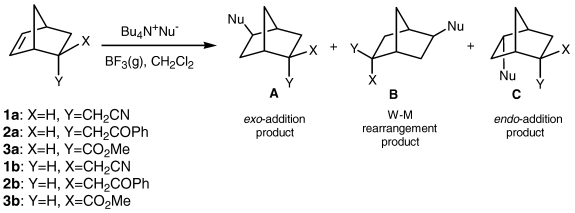


Fig. 1. Nucleophilic additions of I^- and Br^- to *endo*- and *exo*-2-substituted norbornene derivatives.

tially used compounds were also studied (Fig. 1, Table 1).

Nucleophilic addition of iodide to the double bond of BF_3-activated *exo*-nitrile **1b** resulted in the formation of three isomeric products **4**, **5**, and **18** (Table 1, entry 6). Compounds **4** and **5** were also seen in the case of iodide addition to *endo*-nitrile **1a** (Table 1 entry 1). The same nucleophile (I^-), when reacted with **2b**, gave *exo*- and *endo*-addition products (**11** and **19** respectively) with rearrangement product **10** (Table 1, entry 8). Another isomer **11'** which is more likely the regioisomer of **11** was also seen in this case (see the experimental part). Results of iodide addition reaction to *exo*-ester **3b** were very similar to the previous two cases, *exo*-addition, *endo*-addition, and rearrangement products **16**, **20**, and **15** respectively were isolated (Table 1, entry 10). Compared with iodide, bromide addition to *exo*-substituted norbornene derivatives **1b** and **2b** was more selective. Addition of bromide to *exo*-nitrile **1b** yielded *exo*-addition product **8** and rearrangement product **7** (Table 1, entry 7). Reaction of

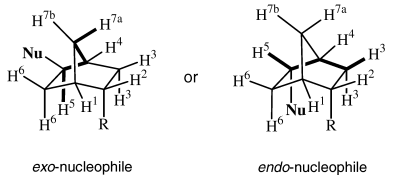


Fig. 2. Numbering system and W-couplings.

the same nucleophile with **2b** resulted in the formation of *exo*-addition product **14** and **13**, which resulted from Wagner-Meerwein rearrangement (Table 1, entry 7). In this reaction another isomer **14'** was also observed (see the experimental part). Based on ^{1}H, ^{13}C NMR, COSY (showed a W coupling between 6*endo*-H and 7a-H) spectra and HMBC (correlation between C-5 and 3*endo*-H) we believe that it is the regioisomer of **14**, not shown in Table 1.

The regio- and stereochemistry assignments of the products were based on the following spectroscopic data. W-type long-range coupling observed on the COSY spectrum for 5-H−7a-H of compounds **4**, **11**, and **15** indicated the *exo*-configuration of iodide. Same type of coupling observed for 5exo-H−3exo-H of compound **6** confirmed the *endo*-configuration of iodide attached to C-5 (Fig. 2).

Additional evidence for the *endo/exo* orientation of the nucleophile is the chemical shift value of proton 5-H. When this proton is *endo*, as in compounds **4**, **5**, **7**, **8**, **10**, **11**, **13**, **14**, **15**, and **16**, it resonates at 3.85 – 3.92 ppm and when it is *exo* as in compounds **6**, **9**, **12**, **17**, **18**, **19**, and **20**, it resonates at 4.20 – 4.33 ppm. These data are consistent with the literature data reported for the same protons of similar structures [5]. Another observation is the chemical shift difference observed for 7a-H and 7b-H. It is approximately 0.5 ppm for compounds **4**, **7**, **10**, **13**, **15** where halide is *exo* and the functional group is *endo*. The chemical shift difference for the same protons is in between 0.00 – 0.13 ppm for compounds **6**, **9**, and **12** where both the halide and the functional groups are *endo*. We have also observed that when C-2 substituent on the norbornene derivatives is *endo*, proton 3*endo*-H resonates at higher field (0.5 – 0.8 ppm) except for the esters and *endo*-halide substituted compounds (**6**, **9**, and **12**).

In order to further confirm the structure of the products, compounds **4**, **5**, and **6** obtained by iodide addition to **1a** were reacted with phenylmagnesium bromide (Fig. 3). The products obtained by this reaction matched on the ^{1}H and ^{13}C NMR with the ones obtained by iodide addition to **2a** (Table 1, entry 3).

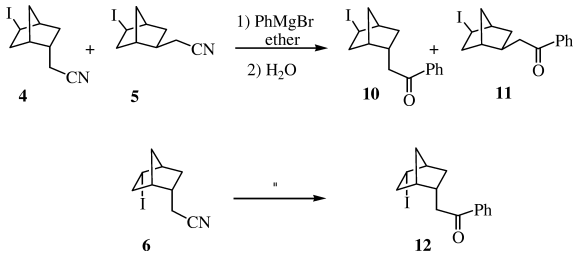


Fig. 3. Conversion of nitriles **4**, **5**, and **6** to the corresponding phenyl ketones **11**, **10**, and **12**.

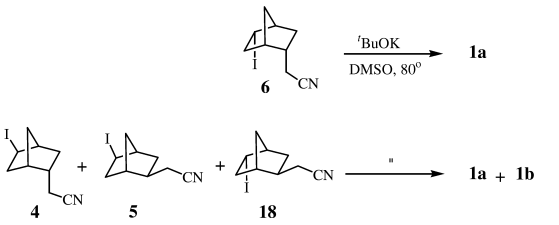
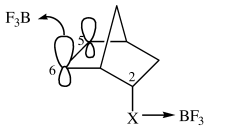


Fig. 4. Elimination reactions carried out with isomers **6** and **4**, **5**, and **18**.

In order to determine the configuration of the C-2 substituent of the products, elimination reactions were carried out [6]. When compound **6** was reacted with *t*BuOK in DMSO at 80 °C, only the *endo*-nitrile **1a** was isolated as the elimination product in 65% yield. When the same reaction was repeated with a mixture of **4**, **5**, and **18** of entry 6, the *exo*-nitrile **1b** and *endo*-nitrile **1a**, were isolated in 46% total yield (ratio = 55/10, respectively) with 26% unreacted starting material (Fig. 4). Isomer ratio of the recovered starting material **4**, **5**, and **18** changed from the original value of 9/41/41 to 18/55/27 (determined by ^{1}H NMR) respectively. This indicated that isomer **18** where iodide is *endo* undergoes elimination faster than the other two isomers. Our result is consistent with the result of Bartsch *et al.* where they examined the elimination rates of *endo* and *exo* halide substituted norbornane derivatives [6]. Carrying out the same reaction with the mixture of **4** and **5** of entry 1, *endo*-nitrile **1a** and *exo*-nitrile **1b** were isolated in 50% total yield (ratio = 49/10, respectively) with 21% unreacted starting material. Isomer ratio of the recovered starting material **4** and **5** changed from the original value of 27/10 to 10/19 respectively. This result shows that *endo*-nitrile **4** undergoes elimination faster than *exo*-nitrile **5**.

In the norbornene systems, the highest π-electron density of the double bond is on the *exo* side [7] thus the coordination of the Lewis acid/electrophile takes



X = COOMe, CH_2COPh, CH_2CN

Fig. 5. Polarization of double bond in norbornene derivatives.

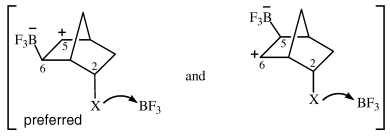


Fig. 6. Possible transition states.

place from this side in the first step of the reaction (Fig. 5). The high regioselectivity observed in all the additions of nucleophiles on the other hand can be attributed to the distortion of electron density. In natural population analysis, a theoretical study carried out by Tam *et al.* with a very similar compounds [3a], it was found that there is always an excess negative charge on C-6 relative to the other carbon centers. Thus, C-5 is lower and C-6 is higher in electron density as a result the nucleophile attacks the more electropositive center (C-5).

The regioselectivity of the addition reactions may also be explained by the relative stability of the possible transition states (Fig. 6). The positive charge on C-6 is more destabilized than the one on C-5, which is far from the electron withdrawing substituents on C-2 [3b]. Therefore, the transition state with a positive charge on C-5 would be more preferred in BF_3-catalyzed addition reactions leading to the observed regioselectivity of the products.

In the light of the results obtained from iodide and bromide additions to *endo*/*exo* substituted norbornene derivatives, it is reasonable to propose the following reaction mechanism (Fig. 7). For all *endo*- and *exo*-substituted norbornene derivatives, the first step is the regio- and *exo*-selective coordination of the double bond to BF_3. This leads to a non-classical type of a carbocation, also called the norpinyl carbocation. Addition of a nucleophile from the *endo*-side of intermediate I leads to the *endo*-addition products **C** after protonation. Although *endo* addition of nucleophiles to norbornene systems is not common, in the work of Kirmse *et al.* based on the norbornyl → norpinyl rearrangement, they have shown the *endo* product formation by the addition of a nucleophile to the norpinyl type of an intermediate carbocation. They have also reported that

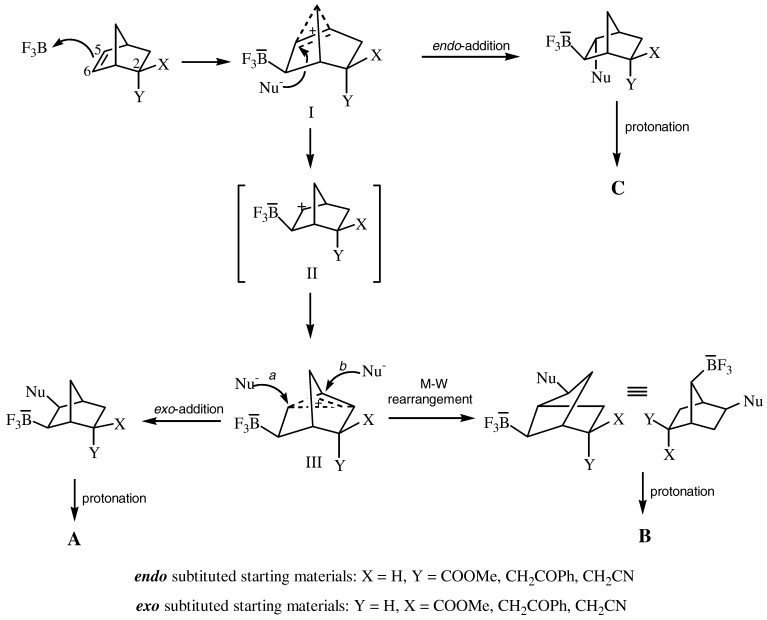


Fig. 7. Proposed mechanism for nucleophilic additions to *endo*/*exo*-2-substituted norbornene derivatives.

the fraction of *endo* product increased with the reactivity of the nucleophile [8]. In our case, *endo*-addition products were seen only in the case of iodide, which is a stronger nucleophile. Formation of products **A** and **B** can be explained by intermediate III. *Exo*-addition of nucleophile (arrow a) to this intermediate gives product **A** after protonation while addition of nucleophile to C-4 (arrow b) gives Wagner-Meerwein rearrangement product **B** after protonation.

Conclusion

As our results show, bromide addition reactions were highly *exo*-selective compared to iodide addition. *Endo*-addition of iodide could be explained by intermediate I; iodide is a stronger nucleophile than bromide and it can react with both intermediates I and III. On the other hand bromide cannot react with the less stable intermediate I due to its weaker nucleophilicity. High level *ab initio* calculations carried out by Schleyer *et al.* on the unsubstituted form of intermediate I showed a separation from the unsubstituted form of intermediate III by a barrier of only 1.2 kcal/mol [9]. Therefore it is more likely that our reactions are also proceeding through a norpinyl type of an intermediate I but it has a very short lifetime compared to intermediate III and less reactive nucleophiles like Br^- can not add to this intermediate. Compared to *endo*-ketone (**2a**) and -ester groups (**3a**), the *endo*-nitrile group (**1a**) leads to higher *endo* selectivity. This is more likely due to the higher steric effect of ketone and ester groups than the nitrile group. When the same groups (ketone and ester) are *exo*, the ratio of the *endo* addition products are quite high (Table 1, entries 8 and 10).

We have also performed an experiment with unsubstituted norbornene under the same conditions using iodide as the nucleophile. In this experiment, no *endo*-addition product was seen – only the *exo*-addition product was isolated. Based on this observation, it can be said that the substituents are effective for the formation of norpinyl-type (I) of intermediate. At this stage, we are not exactly sure about the nature of the stereoelectronic effect of the remote substituents but our investigations are still ongoing. We are also performing some molecular modeling studies. Results of these studies will be reported in due course.

Experimental Section

All reactions were carried out in oven- or flame-dried glassware under argon atmosphere unless otherwise stated. Solvents were purified and dried beyond commercial grade as follows: Diethyl ether was distilled from Na/benzophenone under argon. CH_2Cl_2 and DMSO were distilled from CaH_2 under argon. Analytical thin layer chromatography (TLC) was performed on E. Merck 0.25 (0.5) mm precoated silica gel 60 F-254. Flash chromatography was performed using E. Merck silica gel 60 (230 – 400 mesh). The relative proportion of solvents in mixed

chromatography solvents refers to the volume: volume ratio. R_f values were determined in hexanes/EtOAc (10:1) solvent system, unless otherwise indicated. Melting points are uncorrected. Nuclear Magnetic Resonance (^{1}H, ^{13}C, DEPT, and 2-D) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer. NMR samples were prepared in CCl_4-$CDCl_3$ (2/3) solvent system. ^{1}H NMR spectra were recorded at 400 MHz and reported in ppm on the δ scale relative to residual $CHCl_3$ (δ 7.25), TMS (δ 0.00). ^{13}C NMR spectra were acquired at 100 MHz and are reported in parts per million (ppm) on the δ scale relative to $CHCl_3$ (δ 77.00). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer in $CHCl_3$. IR samples were prepared in $CHCl_3$. GC-MS spectra were obtained with a ThermoQuest (TSP) TraceGC-2000 Series instrument equipped with a Phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 μm), MS: Thermo Quest Finnigan multi Mass (EI, 70 eV). High resolution mass spectra (HRMS) were obtained on a VG ZabSpec spectrometer with double focusing magnetic sector using electron impact (EI).

*(endo-2-Bicyclo[2.2.1]hept-5-en-2-yl)-1-phenylethanone (***2a***)*

Mg turnings (117 mg, 4.88 mmol), bromobenzene (0.59 ml, 5.62 mmol) and dry diethyl ether (3 ml) were placed in a 10 ml two-necked flask fitted with a reflux condenser. The reaction flask was heated up to 40 °C and refluxed for 30 min until all the Mg turnings had disappeared. Then the flask was placed in an ice-bath and a solution of *endo* nitrile **1a** (0.50 g, 3.76 mmol) in dry diethyl ether (2 ml) was added dropwise to the mixture at 0 °C. Then the resulting mixture was stirred for 30 min at 0 °C and for 1 h at room temperature until all *endo*-nitrile **1a** was consumed (monitored by TLC). Saturated ammonium chloride solution (5 ml) was added and the resulting mixture was extracted with diethyl ether (3×10 ml). The combined organic phase was dried over sodium sulfate, filtrated, and concentrated under reduced pressure. Final purification was achieved by flash column chromatography (silica gel, 15:1 hexane/ethyl acetate) to give *endo*-ketone **2a** in 75% yield as a light yellow oil (598 mg, 2.82 mmol); R_f 0.66. – ^{1}H NMR: $\delta = 7.90$ (d, $J = 7.7$ Hz, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.42 (t, $J = 7.4$ Hz, 2H), 6.18 (dd, $J = 3.0$, 5.5 Hz, 1H), 5.96 (dd, $J = 2.8$, 5.5 Hz, 1H), 2.87 (br s, 1H), 2.86 – 2.66 (m, 3H), 2.63 (m, 1H), 2.03 (m, 1H), 1.45 (d, $J = 8.1$ Hz, 1H), 1.31 (d, $J = 8.1$ Hz, 1H), 0.59 (td, $J = 3.2$, 11.7 Hz, 1H). – ^{13}C NMR: $\delta = 199.9$, 138.2, 137.7, 133.0, 132.8, 128.8, 128.4, 50.2, 46.1, 44.1, 43.0, 34.6, 33.0. – IR: $\nu = 2967$ (s), 1680 (s), 1596 (m), 1448 (m), 1367 (m), 1319 (m), 1289 (m), 1232 (m), 1212 (m), 990 (m), 924 (w), 825 (w) cm^{-1}. – MS: *m/z* (%) = 212 (20) [M$^+$], 147 (54), 105 (100), 78 (52), 66 (78). – HRMS: calcd. for $C_{15}H_{16}O$ [M$^+$] 212.1201, found 212.1192.

*(exo-2-Bicyclo[2.2.1]hept-5-en-2-yl)-1-phenylethanone (***2b***)*

Applying the Grignard procedure given above, *exo*-nitrile **1b** (0.50 g, 3.76 mmol) was converted to the *exo*-ketone **2b** which was isolated in 73% yield as a light yellow solid (582 mg, 2.75 mmol); R_f 0.67. – M.p. 38 – 39 °C. – ^{1}H NMR: $\delta = 7.94$ (d, $J = 7.5$ Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.44 (t, $J = 7.4$ Hz, 2H), 6.12 (dd, $J = 3.0$, 5.7 Hz, 1H), 6.03 (dd, $J = 2.9$, 5.7 Hz, 1H), 3.08 (dd, $J = 3.2$, 12.1 Hz, 1H), 3.02 (dd, $J = 3.2$, 12.1 Hz, 1H), 2.84 (br s, 1H), 2.59 (br s, 1H), 1.99 (m, 1H), 1.44 (t, $J = 10.0$ Hz, 1H), 1.38 (br s, 2H), 1.18 (td, $J = 3.8$, 11.7 Hz, 1H). – ^{13}C NMR: $\delta = 199.7$, 137.7, 136.9, 136.8, 133.1, 128.9, 128.5, 46.9, 45.7, 45.6, 42.5, 34.7, 33.4. IR: $\nu = 2959$ (s), 1674 (s), 1598 (m), 1446 (m), 1364 (m), 1326 (m), 1275 (m), 1231 (m), 1174 (m), 991 (m), 902 (w), 832 (w) cm^{-1}. – MS: *m/z* (%) = 212 (3) [M$^+$], 147 (44), 105 (100), 78 (40), 66 (60). – HRMS: calcd. for $C_{15}H_{16}O$ [M$^+$] 212.1201, found 212.1186.

General procedure for BF_3-mediated additions of nucleophiles to endo/exo-2-substituted-5-norbornene derivatives

Tetrabutylammonium iodide or bromide (amounts are indicated in mmols for each experiment in the following paragraphs) was placed in a flask (10 or 25 ml). Then the flask was connected to a vacuum line and heated at low temperature (30 – 40 °C) for 30 min. A solution of nitrile **1a/b** (500 mg, 3.76 mmol), *endo*-/*exo*-ketone **2a/b** (100 mg, 0.472 mmol), or ester **3a/b** (100 mg, 0.658 mmol) in dry CH_2Cl_2 (3 – 15 ml) was added to the flask at 20 °C under argon atmosphere. Then the flask was cooled to −78 °C and BF_3 gas was slowly bubbled through the solution by means of a syringe needle for 3 – 5 h. Meanwhile the temperature was allowed to warm up to −5 °C. Then the resulting reaction mixture was stirred at room temperature overnight. At the end of this period, the mixture was hydrolyzed with sat NH_4Cl solution (3 – 10 ml) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 ($3 \times 5 - 10$ ml) and the combined organic layer was dried over Na_2SO_4. Concentrated crude reaction mixture was filtered through a small column (silica gel; 20:1 hexane/ethyl acetate) to remove quaternary ammonium salts. This was necessary for the NMR analysis of the crude reaction mixture. Further purification was done by flash column chromatography using the appropriate solvent system.

Reaction of endo-nitrile **1a** with iodide (Table 1, Entry 1)

The general experimental procedure was followed using NBu_4I (2.08 g, 5.63 mmol) and *endo*-nitrile **1a** in CH_2Cl_2 (15 ml). BF_3 gas was bubbled for 5 h. From the flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) two fractions were collected. The first one contained compound **6** isolated in 36% yield as a colorless oil (350 mg, 1.34 mmol),

and the second one was an inseparable mixture of isomers **4** and **5** isolated in 34% yield as a light yellow oil (336 mg, 1.29 mmol).

a. (2-endo-5-exo-Iodo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**4**)

R_f 0.24. – ^{1}H NMR: $\delta = 3.88$ (m, 5-H), 2.62 (d, $J =$ 4.5 Hz, 4-H), 2.35 (br s, H_1), 2.37 – 2.15 (m, $2 \times$ 8-H and $2 \times$ 6-H and 2-H), 2.09 (d, $J = 10.3$ Hz, 7b-H), 1.96 (m, 3*exo*-H), 1.57 (d, $J = 10.3$ Hz, 7a-H), 0.82 (ddd, $J = 2.6$, 4.7, 13.4 Hz, 3*endo*-H). – ^{13}C NMR: $\delta = 118.1$ (CN), 48.5 (C-4), 41.7 (C-1), 37.7 (C-6), 37.5 (C-7), 35.6 (C-2), 35.5 (C-3), 26.6 (C-5), 19.4 (C-8). – IR: $\nu = 2962$ (s), 2249 (m), 1450 (m), 1226 (s), 1178 (m), 1136 (m), 944 (m), 910 (w), 591(m) cm^{-1}. – MS: *m/z* (%) = 261 (1) [M$^+$], 134 (100), 127 (86), 93 (90), 79 (63), 67 (58), 53 (43), 41 (54).

b. (2-exo-5-exo-Iodo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**5**)

This compound is also the major product of entry 6, and NMR data were obtained from the mixture of this entry. R_f 0.24. – ^{1}H NMR: $\delta = 3.89$ (m, H_5), 2.67 (d, $J = 3.5$ Hz, 4-H), 2.45 – 2.15 (m, 1-H, $2 \times$ 8-H, and $2 \times$ 6-H), 1.91 (d, $J = 11.0$ Hz, 7b-H), 1.85 (m, 2-H), 1.67 (m, 3*endo*-H), 1.50 (d, $J = 11.0$ Hz, 7a-H), 1.20 (td, $J = 4.0$, 12.0 Hz, 3*exo*-H). – ^{13}C NMR: $\delta = 118.2$ (CN), 48.3 (CH), 44.8 (CH_2), 42.5 (CH), 37.7 (CH), 36.3 (CH_2), 32.9 (CH_2), 25.9 (CH), 23.1 (CH_2). – MS: *m/z* (%) = 261 (5) [M$^+$], 134 (100), 127 (33), 93 (92), 79 (39), 67 (32), 53 (16), 41 (41).

c. (2-endo-5-endo-Iodo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**6**)

R_f 0.30. – ^{1}H NMR: $\delta = 4.30$ (m, 5-H), 2.53 (dd, $J = 6.8$, 16.8 Hz, 8-H), 2.44 (br s, 4-H), 2.40 (dd, $J = 6.8$, 16.8 Hz, 8-H), 2.28 (m, 6*exo*-H and 2-H), 2.25 (br s, 1-H), 1.98 (m, 3exo-H), 1.77 (dt, $J = 3.9$, 14.2 Hz, 6*endo*-H), 1.61 (d, $J = 10.3$ Hz, 7b-H), 1.50 – 1.43 (m, 3*endo*-H and 7a-H). – ^{13}C NMR: $\delta = 118.5$ (CN), 46.1 (C-4), 41.2 (C-1), 38.5 (C-7), 37.3 (C-2), 36.0 (C-6), 34.7 (C-3), 31.3 (C-5), 19.4 (C-8). – IR: $\nu = 2963$ (s), 2249 (m), 1454 (m), 1246 (m), 1219 (m), 1192 (m), 1160 (m), 963 (m), 883 (w), 618 (w), 570 (w) cm^{-1}. – MS: *m/z* (%) = 261 (< 1), [M$^+$], 134 (100), 127 (40), 93 (82), 79 (20), 67 (12), 53 (5), 41 (7). – HRMS: calcd. for $C_9H_{12}IN$ [M$^+$] 261.0014, found 261.0007.

Reaction of endo-nitrile **1a** with bromide (Table 1, Entry 2)

The general experimental procedure was followed using NBu_4Br (3.63 g, 11.25 mmol) and *endo*-nitrile **1a** in CH_2Cl_2 (15 ml). BF_3 gas was introduced for 5 h. From the flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) three fractions were collected. The first one was the unreacted starting material **1a** (250 mg, 1.88 mmol), the second one was compound **9** isolated in 6% yield as a colorless oil (40.0 mg, 0.19 mmol), and the third one was an inseparable mixture of isomers **7** and **8** isolated in 24% yield as a colorless oil (195 mg, 0.92 mmol).

a. (2-endo-5-exo-Bromo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**7**)

R_f 0.24. – ^{1}H NMR: $\delta = 3.88$ (m, 5-H), 2.54 (d, $J =$ 4.9 Hz, 4-H), 2.41 (br s, 1-H), 2.34 – 2.06 (m, $2 \times$ 8-H, 2 x 6-H , 2-H and 3*exo*-H), 2.04 (d, $J = 10.4$ Hz, 7b-H), 1.51 (d, $J = 10.4$ Hz, 7a-H), 0.76 (ddd, $J = 2.4$, 4.5, 13.4 Hz, 3*endo*-H). – ^{13}C NMR: $\delta = 118.5$ (CN), 51.7 (C-5), 47.6 (C-4), 41.3 (C-1), 37.3 (C-7), 37.0 (C-6), 35.8 (C-2), 34.9 (C-3), 19.9 (C-8). – IR: $\nu = 2965$ (s), 2249 (m), 1450 (s), 1312 (m), 1230 (s), 1142 (m), 941 (m), 891 (m), 621 (m), 526 (w) cm^{-1}. – MS: *m/z* (%) = 134 (100) [M$^+$-Br], 93 (66), 79 (13), 67 (16).

b. (2-exo-5-exo-Bromo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**8**)

This isomer is also the major product of entry 7, and NMR data were obtained from the mixture of this entry R_f 0.24. – ^{1}H NMR: $\delta = 3.91$ (m, 5-H), 2.58 (d, $J = 3.9$ Hz, 4-H), 2.41 (br s, 1-H), 2.30 – 2.01 (m, $2 \times$ 8-H, $2 \times$ 6-H), 1.88 (d, $J = 10.8$ Hz, 7b-H), 1.77 (m, 2-H), 1.62 (m, 3*endo*-H) 1.45 (d, $J = 10.8$ Hz, 7a-H), 1.29 (td, $J = 4.7$, 13.2 Hz, 3*exo*-H). – ^{13}C NMR: $\delta = 118.7$ (CN), 51.3 (CH), 47.3(CH), 44.1(CH_2), 42.1(CH), 38.1(CH), 35.6 (CH_2), 32.7 (CH_2), 23.6 (CH_2). – MS: *m/z* (%) = 134 (100) [M$^+$-Br], 93 (66), 79 (12), 67 (18).

c. (2-endo-5-endo-Bromo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**9**)

R_f 0.29. – ^{1}H NMR: $\delta = 4.33$ (m, H_5), 2.54 (dd, $J = 6.8$, 16.6 Hz, 8-H), 2.47 (br s, 4-H), 2.42 (dd, $J = 6.8$, 16.6 Hz, 8-H), 2.34 (br s, 1-H), 2.30 (m, 2-H), 2.24 (m, 6*exo*-H), 1.88 (m, 3*endo*-H), 1.70 – 1.64 (m, 6*endo*-H and 3*endo*-H), 1.61 (br s, $2 \times$ 7-H). – ^{13}C NMR: $\delta = 118.5$ (CN), 52.6 (C-5), 44.7 (C-4), 40.6 (C-1), 39.1 (C-7), 36.5 (C-2), 33.9 (C-6), 30.3 (C-3), 18.9 (C-8). – IR: $\nu = 2964$ (s), 2249 (m), 1454 (m), 1254 (m), 1221 (m), 1167 (w), 965 (m), 887 (w), 642 (m), 577 (w) cm^{-1}. – MS: *m/z* (%) = 134 (100) [M$^+$-Br], 93 (73), 79 (13), 67 (18). – HRMS: calcd. for $C_9H_{12}BrN$ [M$^+$] 213.0153, found 213.0140.

Reaction of endo-ketone **2a** with iodide (Table 1, Entry 3)

The general experimental procedure was followed using NBu_4I (305 mg, 0.83 mmol) and *endo*-ketone **2a** in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 3 h. From the flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) a single fraction was collected as an inseparable mixture of isomers **10**, **12**, and **11** in 77% yield as a light yellow solid

(124 mg, 0.36 mmol). Although the major isomer was compound **10**, it was slowly converted to compound **11** upon standing.

a. (2-endo-5-exo-Iodo-bicyclo[2.2.1]hept-2-sperrenyl)-1-phenylethanone (**10**)

R_f 0.41. – M.p. 45 – 47 °C. – ^{1}H NMR: $\delta = 7.90$ (d, $J =$ 7.6 Hz, 2H, phenyl), 7.53 (t, $J = 7.3$ Hz, 1H, phenyl), 7.43 (t, $J = 7.3$ Hz, 2H, phenyl), 3.92 (m, 5-H), 2.99 (dd, $J = 8.0$, 17.2 Hz, 8-H), 2.85 (dd, $J = 8.0$, 17.2 Hz, 8-H), 2.58 (d, $J = 4.4$ Hz, 4-H), 2.48 – 2.42 (m, 6*exo*-H and 2-H), 2.26 (br s, 1-H), 2.16 (m, 3*exo*-H), 2.06 – 1.97 (m, 6*endo*-H and 7b-H), 1.57 (d, $J = 10.1$ Hz, 7a-H), 0.76 (ddd, $J = 2.2$, 5.1, 13.2 Hz, 3*endo*-H). – ^{13}C NMR: $\delta = 198.9$ (C=O), 137.4 (Cq, phenyl), 133.3 (CH, phenyl), 128.9 (2×CH, phenyl), 128.3 (2×CH, phenyl), 49.0 (CH_2), 42.4 (CH_2), 41.4 (CH), 39.1 (CH), 38.0 (CH), 36.9 (CH), 34.9 (CH_2), 29.0 (CH_2). – IR: $\nu = 2961$ (s), 1681 (s), 1591 (m), 1446 (m), 1280 (m), 1224 (m), 1176 (m), 989 (m), 692 (m), 595 (m) cm^{-1}. – MS: *m/z* (%) = 340 (< 1) [M$^+$], 213 (16), 127 (1), 105 (100), 77 (37), 67 (6), 51 (9).

b. (2-exo-5-exo-Iodo-bicyclo[2.2.1]hept-2-yl)-1-phenylethanone (**11**)

R_f 0.41. – ^{1}H NMR: $\delta = 7.90$ (d, $J = 7.5$ Hz, 2H, phenyl), 7.54 (t, $J = 7.4$ Hz, 1H, phenyl), 7.44 (t, $J = 7.4$ Hz, 2H, phenyl), 3.94 (m, 5-H), 2.95 (dd, $J = 7.6$, 16.8 Hz, 8-H), 2.81 (dd, $J = 7.6$, 16.8 Hz, 8-H), 2.62 (d, $J = 3.7$ Hz, 4-H), 2.27 – 2.17 (m, 2 × 6-H), 2.06 (d, $J = 3.8$ Hz, 1-H), 2.02 (m, 2-H), 1.88 (d, $J = 10.5$ Hz, 7b-H), 1.69 (m, 3*endo*-H), 1.53 (d, $J = 10.5$ Hz, 7a-H), 1.16 (td,$J = 4.6$, 13.3 Hz, 3*exo*-H). – ^{13}C NMR: $\delta = 198.24$ (C=O), 136.9 (Cq, phenyl), 132.7 (CH, phenyl), 128.4 (2×CH, phenyl), 127.8 (2×CH, phenyl), 48.4 (C-4), 45.4 (C-6), 44.8 (C-8), 42.8 (C-1), 38.2 (C-3), 37.1 (C-2), 33.3 (C-7), 27.8 (C-5). – IR: $\nu = 2959$ (s), 1682 (s), 1597 (m), 1448 (m), 1279 (m), 1209 (m), 1134 (w), 994 (w), 910 (w), 691 (m), 659 (w), 588 (w) cm^{-1}. – MS: *m/z* (%) = 212 (100) [M$^+$-I], 127 (22), 105 (60), 77 (79), 67 (33), 51 (31).

c. (2-endo-5-endo-Iodo-bicyclo[2.2.1]hept-2-yl)-1-phenylethanone (**12**)

This compound was also synthesized by the Grignard reaction shown in Fig. 3. So the characterization was based on the product obtained in this reaction. R_f 0.44. – M.p. 36 – 38 °C. – ^{1}H NMR: $\delta = 7.98$ (d, $J = 7.4$ Hz, 2H, phenyl), 7.54 (t,$J = 7.4$ Hz, 1H, phenyl), 7.45 (t, $J = 7.4$ Hz, 2H, phenyl), 4.31 (m, 5-H), 3.17 (dd, $J = 7.7$, 17.0 Hz, 8-H), 3.05 (dd, $J = 6.8$, 17.0 Hz, 8-H), 2.46 (m, 2-H), 2.40 (br s, 4-H), 2.20 (m, 6*exo*-H), 2.16 (br s, 1-H), 2.03 (m, 3*exo*-H), 1.86 (dt, $J = 3.7$, 13.9 Hz, 6*endo*-H), 1.54 (d, $J = 9.8$ Hz, 7b-H), 1.48 (d, $J = 9.8$ Hz, 7a-H), 1.44 (m, 3*endo*-H). – ^{13}C NMR: $\delta = 199.95$ (C=O), 137.6 (Cq, phenyl), 133.3 (CH, phenyl), 129.0 (2×CH, phenyl), 128.5 (2*x*CH, phenyl), 46.0 (C-4), 41.5 (C-1), 40.7 (C-8), 38.6 (C-7), 36.7 (C-6), 36.1 (C-2), 35.2 (C-3), 33.4 (C-5). – IR: $\nu = 2956$ (s), 1678 (s), 1594 (m), 1448 (m), 1370 (m), 1285 (m), 1243 (m), 1182 (m), 1152 (m), 994 (m), 686 (m), 607 (w), 577 (w) cm^{-1}. – MS: *m/z* (%) = 340 (< 1), [M$^+$], 213 (34), 127 (3), 105 (100), 77 (83), 67 (13), 51 (20).

Reaction of endo-ketone **2a** with bromide (Table 1, Entry 4)

The general experimental procedure was followed using NBu_4Br (349 mg, 1.08 mmol) and *endo*-ketone **2a** in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 3 h. From the flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) a single fraction was collected as an inseparable mixture of isomers **13** and **14** in 58% yield as a white solid (80 mg, 0.27 mmol).

a. (2-endo-5-exo-Bromo-bicyclo[2.2.1]hept-2-yl)-1-phenylethanone (**13**)

R_f 0.46. – M. p. 78 – 80 °C. – ^{1}H NMR: $\delta = 7.90$ (d, $J = 7.6$ Hz, 2H, phenyl), 7.53 (t, $J = 7.5$ Hz, 1H, phenyl), 7.43 (t, $J = 7.5$ Hz, 2H, phenyl), 3.91 (m, 5-H), 2.94 (dd,$J =$ 6.5, 16.6 Hz, 8-H), 2.83 (dd,$J = 6.5$, 16.6 Hz, 8-H), 2.48 (d,$J = 4.5$ Hz, 4-H), 2.42 – 2.36 (m, 6*exo*-H and 2-H), 2.32 (br s, 1-H), 2.10 – 2.03 (m, 6*endo*-H), 2.02 – 1.94 (m, 3*exo*-H and 7b-H), 1.50 (d,$J = 1.4$ Hz, 7a-H), 0.69 (td, $J =$ 2.6, 13.4 Hz, 3*endo*-H). – ^{13}C NMR: $\delta = 198.9$ (C=O), 137.5 (Cq, phenyl), 133.3 (CH, phenyl), 129.0 (2×CH, phenyl), 128.4 (2×CH, phenyl), 53.3 (CH), 47.6 (CH), 41.5 (CH), 41.4 (CH_2), 37.3 (CH_2), 35.8 (CH_2), 34.6 (CH), 33.1 (CH_2). – IR: $\nu = 2962$ (s), 1681 (s), 1597 (m), 1448 (m) , 1373 (m), 1280 (m), 1227 (m), 1184 (m), 995 (m), 943 (m), 695 (m), 660 (w), 627 (w) cm^{-1}. – MS: *m/z* (%) = 294/292 (13/13) [M$^+$], 213 (14), 120 (50), 105 (100), 77 (28), 67 (3), 51 (4).

b. (2-exo-5-exo-Bromo-bicyclo[2.2.1]hept-2-yl)-1-phenylethanone (**14**)

This isomer is also the major product of entry 9, and NMR data were obtained from the mixture of this entry. R_f 0.46. – ^{1}H NMR: $\delta = 7.90$ (d, $J = 7.6$ Hz, 2H, phenyl), 7.53 (t, $J =$ 7.5 Hz, H, phenyl), 7.43 (t, $J = 7.5$ Hz, 2H, phenyl), 3.92 (m, 5-H), 2.99 – 2.78 (m, 2-H), 2.50 (d, $J = 3.5$ Hz, 4-H), 2.35 (m, 2-H), 2.10 – 1.92 (1-H, and 2 × 6-H, overlapping with the signals of isomer **13**), 1.96 (d, $J = 12.3$ Hz, 7b-H), 1.65 (m, 3*endo*-H), 1.45 (d, $J = 12.3$ Hz, 7a-H), 1.20 (td, $J = 5.5$, 13.9 Hz, 3*exo*-H). – ^{13}C NMR: $\delta = 198.9$ (C=O), 137.4 (Cq, phenyl), 133.3 (CH, phenyl), 128.9 (2×CH, phenyl), 128.3 (2×CH, phenyl), 52.8 (CH), 47.4 (CH), 45.2 (CH_2), 44.6 (CH_2), 42.4 (CH), 37.8 (CH_2), 36.7 (CH), 36.4 (CH_2). – MS: *m/z* (%) = 294/292 (18/18) [M$^+$], 213 (10), 120 (62), 105 (100), 77 (28), 67 (5), 51 (4).

Reaction of endo-ester **3a** with iodide (Table 4, Entry 5)

The general experimental procedure was followed using NBu_4I (734 mg, 1.99 mmol) and *endo*-ester **3a** in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 4 h. From the flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) two fractions were collected. The first one was the unreacted starting material (40 mg, 0.26 mmol), and the second one was an inseparable mixture of isomers **15**, **16**, and **17** isolated in 35% yield as a colorless liquid (60 mg, 0.23 mmol).

a. 5-exo-Iodo-bicyclo[2.2.1]heptane-2-endo-carboxylic acid methyl ester (**15**)

R_f 0.49. – ^{1}H NMR: $\delta = 4.01$ (m, 5-H), 3.66 (s, OCH_3), 2.75 (m, 2-H), 2.65 (br s, 1-H), 2.53 (d, $J = 4.2$ Hz, 4-H), 2.25 – 2.11 (m, $2 \times$ 6-H), 2.07 (d, $J = 10.2$ Hz, 7b-H), 1.74 (d, $J = 2.4$ Hz, 3-H), 1.71 (d, $J = 2.4$ Hz, 3-H), 1.54 (d, $J = 10.2$ Hz, 7a-H). – ^{13}C NMR: $\delta = 174.46$ (C=O), 51.9 (OCH_3), 48.8 (C-1), 45.1 (C-2), 42.4 (C-4), 40.8 (C-6), 38.5 (C-7), 31.9 (C-3), 27.5 (C-5). – IR: $\nu = 2957$ (s), 1728 (s), 1444 (w), 1357 (w), 1302 (w), 1203 (s), 1178 (m), 1123 (w), 1036 (w), 943 (w), 585 (w) cm^{-1}. – MS: *m/z* (%) = 249 (21) [M^+-OMe], 221 (11), 153 (100), 127 (23), 121 (14), 93 (44), 87 (89), 77 (25), 67 (30), 54 (13), 41 (20). – HRMS: calcd. for $C_9H_{13}O_2I$ [M^+] 279.9960, found 279.9949.

b. 5-exo-Iodo-bicyclo[2.2.1]heptane-2-exo-carboxylic acid methyl ester (**16**)

This isomer is also the major product of entry 10, and NMR data were obtained from the mixture of this entry. R_f 0.49. – ^{1}H NMR: $\delta = 3.85$ (m, 5-H), 3.60 (s, OCH_3), 2.61 (d, $J = 4.4$ Hz, 4-H), 1.88 (d, $J = 10.4$ Hz, 7b-H), 1.62 (d, $J = 10.4$ Hz, 7a-H), other signals overlapped with the signals of **15** and **20**. – ^{13}C NMR: $\delta = 175.5$, 52.0, 48.0, 45.7, 45.1, 44.7, 42.8, 34.8, 29.4. – MS: *m/z* (%) = 249 (37) [M^+-OMe], 221 (31), 153 (100), 127 (42), 121 (38), 93 (74), 87 (86), 77 (54), 67 (58), 54 (37), 41 (43).

c. 5-endo-Iodo-bicyclo[2.2.1]heptane-2-endo-carboxylic acid methyl ester (**17**)

^{1}H NMR: $\delta = 4.20$ (m, 5-H), all other signals were overlapped with the signals of **15** and **16**. – MS: *m/z* (%) = 249 (10) [M^+-OMe], 221 (11), 153 (85), 127 (16), 121 (12), 93 (36), 87 (100), 77 (25), 67 (28), 54 (13), 41 (40).

Reaction of exo-nitrile **1b** with iodide (Table 1, Entry 6)

The general experimental procedure was followed using NBu_4I (416 mg, 1.13 mmol) and *exo*-nitrile **1b** (100 mg, 0.75 mmol) in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 5 h. From the flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) two fractions were collected. The first one contained the unreacted *exo*-nitrile **1b** (18 mg, 0.14 mmol), and the second one was an inseparable mixture of isomers **4**, **5**, **18**, and an uncharacterized isomer isolated in 67% yield as a light yellow oil (130 mg, 0.50 mmol).

a. (2-exo-5-endo-Iodo-bicyclo[2.2.1]hept-2-yl)-acetonitrile (**18**)

R_f 0.24. – ^{1}H NMR: $\delta = 4.20$ (m, 5-H), all other signals were overlapped with the signals of **4** and **5**. – ^{13}C NMR: $\delta =$ 118.4 (CN), 44.9 (CH), 43.3 (CH_2), 41.2 (CH), 38.0 (CH), 36.6 (CH_2), 32.9 (CH_2), 28.1 (CH), 23.2 (CH_2). – MS: *m/z* (%) = 261 (5) [M^+], 134 (65), 127 (24), 93 (100), 79 (25), 67 (22), 53 (10), 41 (27).

Reaction of exo-nitrile **1b** with bromide (Table 1, Entry 7)

The general experimental procedure was followed using NBu_4Br (725 mg, 2.25 mmol) and *exo*-nitrile **1b** (100 mg, 0.75 mmol) in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 5 h. From the flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) two fractions were collected. The first one contained the unreacted *exo*-nitrile **1b** (19 mg, 0.14 mmol), and the second one was an inseparable mixture of isomers **8** and **7** isolated in 67% yield as a white solid (87 mg, 0.41 mmol, m. p. 49 – 51 °C).

Reaction of exo-ketone **2b** with iodide (Table 1, Entry 8)

General experimental procedure was followed using NBu_4I (305 mg, 0.83 mmol) and *exo*-ketone **2b** (100 mg, 0.47 mmol) in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 3 h. From the flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) a single fraction was collected as an inseparable mixture of isomers **10**, **19**, **11**, and **11'** in 87% yield as a light yellow solid (140 mg, 0.41 mmol, m.p. 78 – 80 °C, relative ratio of the isomers obtained from ^{1}H NMR spectrum of the crude reaction mixture: 20:27:33:19 respectively).

a. (2-exo-5-endo-Iodo-bicyclo[2.2.1]hept-2-yl)-1-phenylethanone (**19**)

R_f 0.41. – ^{1}H NMR: $\delta = 4.20$ (m, 5-H), all other signals were overlapped with the signals of isomers **10**, **11**, and **11'**. – ^{13}C NMR: $\delta = 198.3$ (C = O), 137.0 (Cq, phenyl), 132.7 (CH, phenyl), 128.4 (2×CH, phenyl), 128.0 (2×CH, phenyl), 49.0 (CH), 45.0 (CH), 43.5 (CH_2), 41.5 (CH), 38.2 (CH_2), 37.0 (CH_2), 33.3 (CH_2), 29.6 (CH). – MS: *m/z* (%) = 340 (< 1) [M^+], 213 (15), 127 (2), 105 (100), 77 (37), 67 (6), 51 (8).

b. (2-exo-6-exo-Iodo-bicyclo[2.2.1]hept-2-yl)-1-phenylethanone (**11'**)

^{1}H NMR: $\delta = 4.04$ (m, 6-H), all other signals were overlapped with the signals of isomers **10**, **11**, and **19**. – ^{13}C

NMR: δ = 197.4 (C=O), 136.9 (Cq, phenyl), 132.6 (CH, phenyl), 128.3 (2×CH, phenyl), 128.0 (2×CH, phenyl), 52.8 (CH), 45.0 (CH_2), 44.0 (CH_2), 38.2 (CH), 37.2 (CH_2), 36.8 (CH), 33.7 (CH_2), 28.4 (CH). – MS: *m/z* (%) = 340 (< 1) [M^+], 213 (15), 127 (2), 105 (100), 77 (37), 67 (6), 51 (8).

Reaction of exo-ketone **2b** with bromide (Table 1, Entry 9)

The general experimental procedure was followed using NBu_4Br (701 mg, 2.17 mmol) and *exo*-ketone **2b** (200 mg, 0.94 mmol) in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 3 h. From the flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) two fractions were collected. The first one contained the unreacted *exo*-ketone **2b** (40 mg, 0.19 mmol) and the second one was a mixture of isomers **13**, **14**, and **14'** isolated in 64% yield as a white solid (175 mg, 0.60 mmol, m. p. 83 – 85 °C, relative ratio of the isomers obtained from ^{1}H NMR spectrum of the crude reaction mixture: 28:39:33 respectively). With successive flash column chromatography runs (silica gel, 30:1 hexane/ethyl acetate), a mixture enriched in **14'** was obtained and used for spectroscopic analysis.

a. 2-exo-(6-exo-Bromo-bicyclo[2.2.1]hept-2--yl)-1-phenylethanone (**14'**)

^{1}H NMR: δ = 7.91 (d, J = 7.5 Hz, 2H, phenyl), 7.54 (t, J = 7.0 Hz, 1H, phenyl), 7.44 (t, J = 7.0 Hz, 2H, phenyl), 4.05 (m, 6-H), 3.02 (dd, J = 6.5, 16.9 Hz, 8-H), 2.84 (dd, J = 6.5, 16.9 Hz, 8-H), 2.38 – 2.32 (m, 2-H and 1-H), 2.12 – 1.95 (m, 2 × 5-H and 4-H), 1.86 (d, J = 10.4 Hz, 7b-H), 1.52 (m, 3*endo*-H), 1.44 (d, J = 10.4 Hz, 7a-H), 1.09 (m, 3*exo*-H). – ^{13}C NMR: δ = 198.5 (C=O), 137.4 (Cq, phenyl), 133.3 (CH, phenyl), 128.9 (2×CH, phenyl), 128.4 (2*x*CH, phenyl), 53,0 (C-6), 51,9 (C-1), 45,3 (C-8), 43.2 (C-5), 37.8 (C-2), 37.4 (C-3), 36.2 (C-4), 33.5 (C-7). – IR: ν = 2962 (s), 1681 (s), 1597 (m), 1448 (m) , 1373 (m), 1280 (m), 1227 (m), 1184 (m), 995 (m), 943 (m), 695 (m), 660 (w), 627 (w) cm^{-1}. – HRMS: calcd. for $C_{15}H_{17}BrO$ [M^+] 292.0463, found 292.0455.

Reaction of exo-ester **3b** with iodide (Table 1, Entry 10)

The general experimental procedure was followed using NBu_4I (734 mg, 1.99 mmol) and *exo*-ester **3b** (100 mg, 0.66 mmol) in CH_2Cl_2 (3 ml). BF_3 gas was introduced for 4 h. From the flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) two fractions were collected. The first one contained the unreacted-*exo* ester 2**b** (25 mg, 0.16 mmol) and the second one was an inseparable mixture of isomers **15**, **16**, **20**, and an uncharacterized isomer isolated in 46% yield as a light yellow liquid (84 mg, 0.30 mmol).

a. 5-endo-Iodo-bicyclo[2.2.1]heptane-2-exo-carboxylicacid methyl ester (**20**)

R_f 0.49. – ^{1}H NMR: δ = 4.20 (m, 5-H), all other signals overlapped with the signals of **15** and **16**. – ^{13}C NMR: δ = 175.4, 52.1, 46.0, 45.1, 43.4, 41.4, 34.9, 33.5, 33.4. – MS: *m/z* (%) = 249 (26) [M^+-OMe], 221 (24), 153 (100), 127 (41), 121 (30), 93 (68), 87 (83), 77 (52), 67 (52), 54 (35), 41 (39).

*Conversion of nitriles **4**, **5**, and **6** to the corresponding phenyl ketones*

The Grignard procedure, used for the synthesis of *endo*- and *exo*-ketones **2a** and **2b**, was followed using bromobenzene (0.06 ml, 0.57 mmol), Mg turnings (11.8 mg, 0.49 mmol), and compound **6** (100 mg, 0.38 mmol) in dry diethyl ether (1 ml). From the flash column chromatography (silica gel, 10:1 hexane/ethyl acetate), ketone **12** was isolated in 69% yield as a yellow colored solid (89.0 mg, 0.26 mmol). The same procedure for the mixture of isomers **4** and **5** (100 mg, 0.38 mmol) provided a mixture of ketones **10** and **11** in 71% yield as a yellow colored solid (90.3 mg, 0.27 mmol).

a. Elimination reaction of nitrile **6**

A solution of nitrile **6** (42.6 mg, 0.16 mmol) in dry DMSO (0.5 ml) was added to a two-necked flask containing *t* BuOK-DMSO solution (0.5 ml, 0.25 M). The flask was equipped with reflux condenser. Then the reaction mixture was stirred at 80 °C for 5 h under argon atmosphere. After this period of time, system was allowed to cool to room temperature. Then H_2O (3 ml) was added to the flask and the resulting mixture was extracted with diethyl ether (3 × 5 ml). Combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by a small flash column (silica gel, 20:1 hexane/ethyl acetate) to remove DMSO. This process yielded *endo*-nitrile **1a** in 65% yield as a colorless oil (14 mg, 0.11 mmol).

b. Elimination reaction of mixture of nitriles **4**, **5**, and **18**

The elimination procedure described above was applied to the mixture of nitriles **4**, **5**, and **18**, and uncharacterized isomer (101.5 mg, 0.39 mmol) in DMSO (1.2 ml) and *t*BuOK-DMSO solution (1.2 ml, 0.25 M). The crude reaction mixture was purified by flash column chromatography (silica gel, 10:1 hexane/ethyl acetate). Two fractions were collected. The first one, a colorless oily mixture of *exo*- and *endo*-elimination products **1b** and **1a** was isolated in 46% yield (24 mg, 0.18 mmol, 55:10 ratio). The second one was unreacted starting material **4**, **5**, and **18** in 26% yield (20.7 mg, 0.079 mmol, 18:55:27 ratio).

c. Elimination reaction of mixture of nitriles **4** and **5**

The elimination procedure described above was applied to the mixture of nitriles **4** and **5** (42.2 mg, 0.16 mmol). The crude reaction mixture was purified by flash column chromatography (silica gel, 10:1 hexane/ethyl acetate). Two fractions were collected. The first one, a colorless oily mixture of *endo*- and *exo*-elimination products **1a** and **1b** was isolated in 50% yield (10.6 mg, 0.080 mmol, 49:10 ratio). The second one was unreacted starting material **4** and **5** isolated in 21% yield **(**8.6 mg, 0.033 mmol, 10:19 ratio).

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