Stereoselective Synthesis of Medium-Sized Carbocycles Using Alkoxy Radical Fragmentation as a Key Methodology

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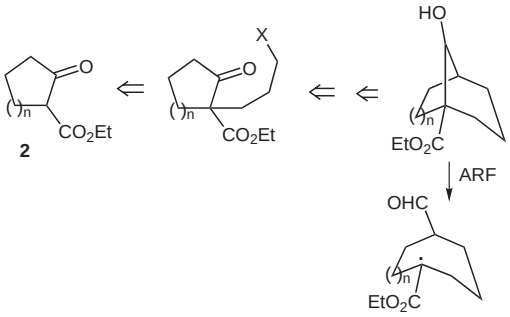
Abstract: Stereoselective and regioselective synthesis of functionalized seven- and eight-membered carbocyclic systems was achieved by the ring expansion–cleavage of readily prepared [3.2.1] and [3.3.1] bicyclic alcohols using alkoxy radical fragmentation at room temperature. Transannular migration in the cyclooctane system explain formation of unusual products.

Key words: carbocycles, bicyclic compounds, radical reaction, stereoselectivity, ring expansion

The skeleton of many natural products consists of medium-sized carbocycles[1–5] and their facile and simple synthesis remains a challenge for synthetic organic chemists. Among more important recently employed methods for construction of functionalized medium-sized ring are aldol, free radical and metathesis reactions.[6–10]

In continuation of our investigations[11,12] towards the synthesis of medium-sized rings we are constantly in search of simple methods of stereoselective synthesis of such functionalized carbocyclic systems. One attractive route involves ring enlargement by cleavage of [m.n.1] bicyclic systems. In fact base-catalyzed fission of [3.2.1] and [3.3.1] bicyclic ketones leading to medium-sized rings has been reported by several groups.[13] Alkoxy radical fragmentation[14] (ARF), which we have used successfully for other ring enlargements, provides an attractive alternative method. To achieve successful ARF, the presence of a radical stabilizing group α to the OH-bearing carbon is desirable, since it would control the regioselective cleavage of the bridgehead C–C bond, during the photochemical ARF reaction. We opted for the presence of a carbethoxy function as shown in Scheme 1, since α-carbethoxy cyclic ketones **2** are readily available simple compounds, which also provide an opportunity to compare base-induced cleavage[13] to photochemical ARF. A retrosynthetic analysis (see Scheme 1) indicates the advantage of a β-keto ester precursor **2** in facilitating the introduction of an appropriate side chain by a Michael addition, which can be followed by aldol ring closure to a bicyclic system.

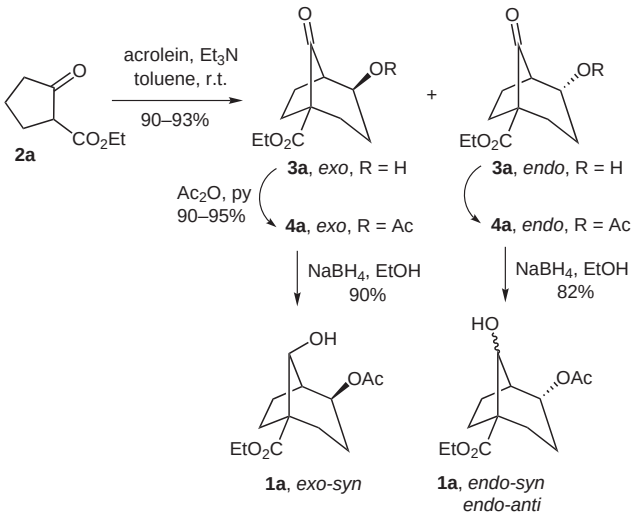
This can indeed be achieved in one step by treating 2-carbethoxycyclopentanone (**2a**) with acrolein in the presence of triethylamine in toluene at room temperature to afford



Scheme 1

4-hydroxy-8-oxobicyclo[3.2.1]octane-1-carboxylic acid ethyl ester[13a] (**3a**), which we were able to separate into *exo*-and *endo*-isomers in a 2:1 ratio (90% yield).

After protection of the hydroxyl function of **3a** by acetic anhydride in pyridine under reflux, the bridgehead ketone of **4a**[15] was reduced to the bridgehead hydroxyl function by sodium borohydride in 95% ethanol. The *exo*-isomer of compound **4a** underwent stereoselective reduction to the *exo-syn*-alcohol, 4-acetoxy-8-hydroxybicyclo[3.2.1]octane-1-carboxylic acid ethyl ester (**1a**)[16] due to steric hindrance by the *exo*-OAc function. On the other hand the ketone function of the *endo*-acetoxy isomer of **4a** was reduced to a mixture of both *syn*- and *anti*-alcohols at the 8-position (Scheme 2).



Scheme 2

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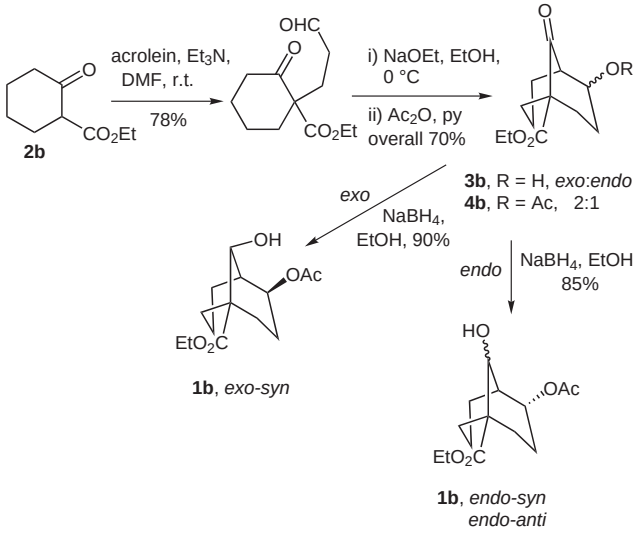
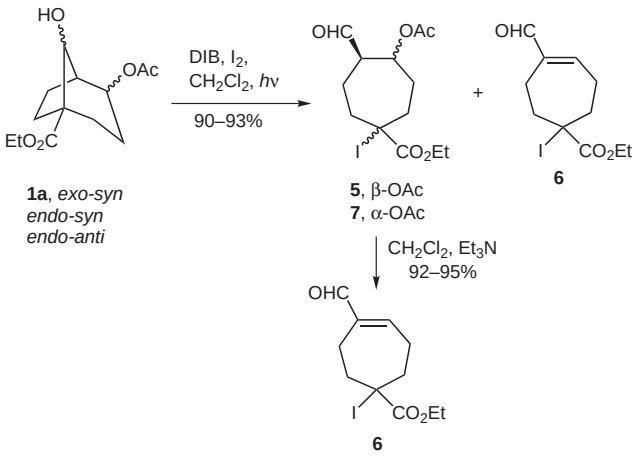
The same methodology was applied in the synthesis of 4-acetoxy-9-oxobicyclo[3.3.1] nonane-1-carboxylic acid ethyl ester (**1b**) from 2-carbethoxycyclohexanone **2b** (Scheme 3). In this case after Michael addition to acrolein in the polar solvent DMF, the reaction was stopped at the intermediate stage of an aldehyde ketone[17] which upon aldol condensation (NaOEt) afforded the *exo*- and *endo*-hydroxy ketones **3b**[13d] as an inseparable mixture. Separation of *exo*- and *endo*-isomers became feasible after acetylation of the hydroxyl function of **3b** to **4b**. Similar to the cyclopentanone case, sodium borohydride reduction of the bridgehead ketone afforded stereoselectively the *syn*-hydroxy product **1b** from the *exo*-isomer of **4b** and a mixture of *syn*- and *anti*-isomeric **1b** from the *endo*-isomer of **4b** (Scheme 3).



Scheme 3

The photochemical ARF reaction of the *exo-syn*-isomer of bicyclo[3.2.1]alcohol **1a**, in the presence of diacetoxy iodobenzene (DIB) and iodine in dichloromethane under irradiation with a 100 W tungsten filament lamp afforded the seven-membered ring carbocycles **5** and **6**.[18] In a similar reaction, the mixture of *endo-syn*- and *endo-anti*-isomers of compound **1a** afforded the *endo*-acetoxy compound **7** as well as olefin **6**.[18] Elimination of acetic acid from β- and α-acetoxy derivatives **5** and **7** occurred on treatment with triethylamine, affording olefin **6** (Scheme 4). Ultimately, the above sequence of events provided selectively a single seven-membered ring carbocyclic compound **6** possessing aldehyde, ester, iodine and olefin functions, in a very good yield, a ring enlargement of the original cyclopentane by two carbons.

The radical cleavage of the cyclohexanone-derived bicycle **1b** proceeded in a slightly different manner. In the event, the *exo-syn*-isomer of the bicyclic [3.3.1] alcohol derivative **1b** afforded three eight-membered ring aldehydes **8**, **9** and **10** in a total yield of 80%, among which the ethyl *syn*-4-acetoxy-5-formyl-1-iodocyclooctanecarboxylate (**8**) was the major product and **9** was devoid of iodine

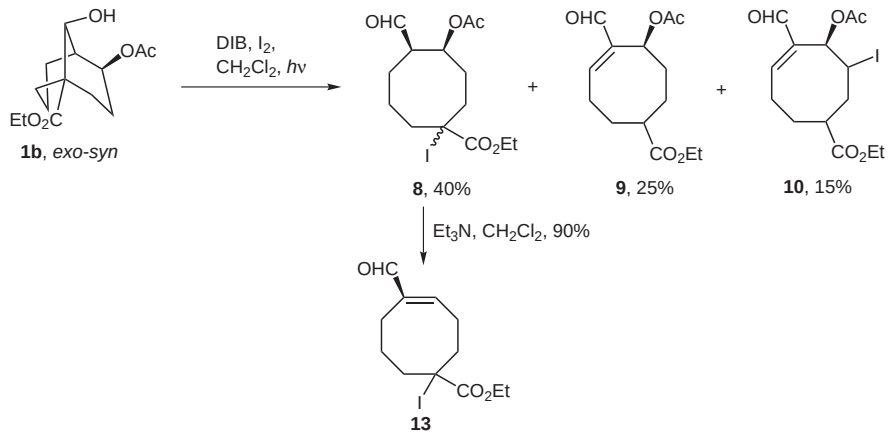


Scheme 4

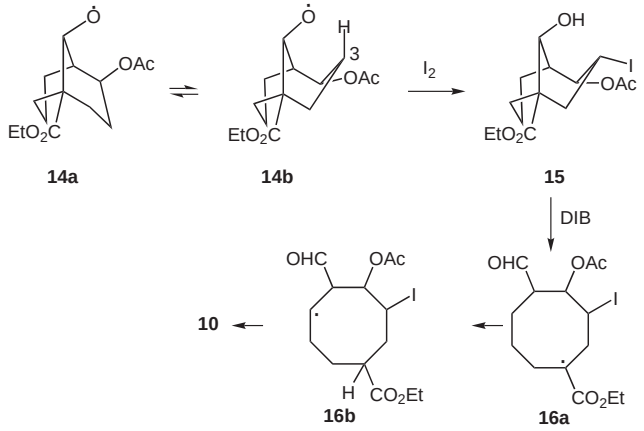
(Scheme 5). Most likely, after free-radical cleavage of the bridgehead carbon in *exo-syn*-**1b**, the resulting COOEt-stabilized radical, instead of trapping iodine, underwent a transannular hydrogen transfer. However, because the C-5 hydrogen geminal to the β-oriented aldehyde group is not easily accessible, H-transfer occurs from C-6 to the C-1 radical, ultimately affording compound **9**. Trans elimination of AcOH from **8** by means of Et_3N led to olefin **13**.[20]

The formation of product **10** is interesting as it contains an unexpected iodine substituent at the 3-position of the cyclooctane ring. The dt (J = 12.5, 3.0 Hz) in ^{1}H NMR of H-3 places the iodine *trans* to the acetoxy function. Formation of **10** is best explained on conformational grounds. In the *exo-syn*-isomer **1b**, the chair–chair conformation **14a**, which features a pseudoaxial acetoxy group, prefers to equilibrate to a chair–boat conformer **14b** in which the OAc substituent becomes equatorial, thus making available an axial H at C-3 for abstraction by the initially formed *syn*-alkoxy radical.[19] Quenching of the newly formed free radical at C-3 by iodine then leads to iodo product **15**. The latter, in the presence of DIB/I_2, forms a new alkoxy radical which undergoes fragmentation–ring enlargement to **16a**, followed by transannular H-abstraction from C-6 (see **16b**) and ultimately formation of **10** (Scheme 6).

On the other hand the mixture of *endo-syn*- and *endo-anti*-isomers of compound **1b** provided a diastereomeric mixture of eight-membered ring carbocycles **11** and **12**, each as two diastereomers, in very good yield. As in the case of **8**, the diastereomeric mixture of acetates **11** was converted into olefin **13** by treatment with triethylamine (Scheme 7). The formation of minor product **12** containing an additional iodine substituent at the 3-position is apparently again (similar as in the formation of **10**) due to an equilibration to conformation **17** of the *endo-syn*-isomer of **1b**, in which the pseudoaxial C-3 hydrogen becomes available for abstraction by the *syn*-alkoxy radical. In this case, however, the free radical analogous to **16a** is trapped by iodine to afford **12**.

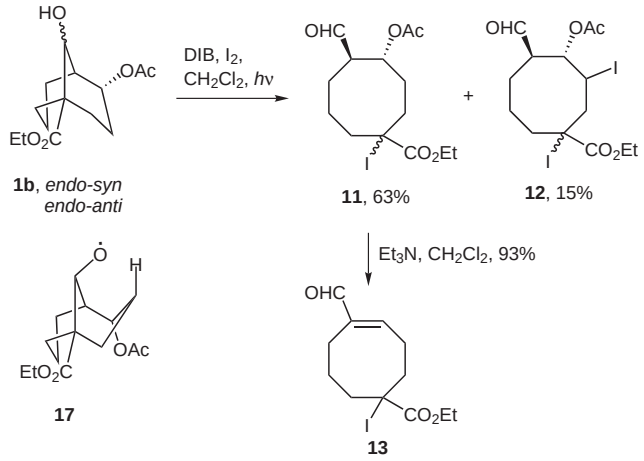


Scheme 5



Scheme 6

All new compounds were identified by chemical shift and coupling constant of ^{1}H NMR, ^{13}C NMR and COSY analysis as well as mass spectra. For example the chemical shift of axial H-4 proton in *endo*-isomer of **3a** appears at δ = 4.93 ppm with a coupling pattern of ddd, whereas in the *exo*-isomer the chemical shift of equatorial H-4 is at δ = 5.15 ppm as a broad singlet. The aldehyde peak of compound **9** is a singlet and its δ_C is 190 ppm indicating bonding to the quaternary carbon of an α,β unsaturated system.



Scheme 7

In conclusion, a facile stereo- and regioselective synthesis of functionalized seven- and eight-membered carbocycles by ring expansion of bicyclic compounds synthesized from simple ketones was developed. Trivalent iodine was used as the radical generating agent. The free-radical fragmentation led to transannular migrations in the cyclooctanes with formation of unusual products.

Acknowledgment

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(15) **Synthesis of 4-Acetoxy-8-oxobicyclo[3.3.1]octane-1-carboxylic Acid Ethyl Ester(4a) – Analytical Data**
endo-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.93 (ddd, *J* = 9, 6, 3 Hz, 1 H, CHO), 4.13 (q, *J* = 7 Hz, 2 H, CH_2O), 2.65–2.62 (m, 1 H), 2.59–2.45 (m, 1 H), 2.07–1.82 (m, 9 H), 1.78–1.59 (m, 1 H), 1.19 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR: δ = 208.9 (C=O), 170.8 (O–C=O), 169.6 (O–C=O), 74.2 (C^4HO), 61.2 (OCH_2), 56.8 (C^1), 50.6 (C^5H), 30.8, 26.8, 23.6, 21.0 ($COCH_3$), 17.0, 14.1 (CH_3CH_2). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{13}H_{18}O_5$: 254.115; found: 254.123 (27) $[M]^+$, 255.119 (45) $[MH]^+$.
exo-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H, CHO), 4.19–4.15 (m, 2 H, CH_2O), 2.61–2.42 (m, 3 H), 2.08–1.92 (m, 7 H), 1.78–1.61 (m, 2 H), 1.19 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR: δ = 209.9 (C=O), 170.9 (O–C=O), 170.2 (O–C=O), 78.7 (C^4HO), 61.3 (OCH_2), 57.0 (C^1), 48.6 (C^5H), 33.8, 25.8, 23.3, 21.1 ($COCH_3$), 19.2, 14.2 (CH_3CH_2). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{13}H_{18}O_5$: 254.115; found: 255.120 (33) $[MH]^+$.

(16) **Synthesis of 4-Acetoxy-8-hydroxybicyclo[3.2.1]octane-1-carboxylic Acid Ethyl Ester(1a) by $NaBH_4$/EtOH Reduction of 4a – Analytical Data**
exo-syn-Isomer of **1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.90 (br s, 1 H, CHO), 4.22 (d, *J* = 4.5 Hz, 1 H, HOC*H*), 4.12 (q, *J* = 7.0 Hz, 2 H, CH_2O), 2.98 (br s, 1 H, OH), 2.43–2.38 (m, 1 H), 2.22–2.11 (m, 1 H), 2.04–1.95 (m, 4 H), 1.90–1.58 (m, 5 H), 1.32–1.26 (m, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3). ^{13}C NMR: δ = 176.7 (O–C=O), 170.5 (O–C=O), 75.8 (CHO), 70.1 (CHO), 60.7 (OCH_2), 50.1 (C^1), 42.3 (C^5H), 29.1, 25.9, 23.6, 21.4 ($COCH_3$), 19.2, 14.2 (CH_3CH_2). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{13}H_{20}O_5$: 256.131; found: 257.142 (11) $[MH]^+$, 197.117 (34) $[MH – HOAc]^+$, 196.110 (43) $[M – HOAc]^+$, 150.070 (51) $[M – HOAc – EtOH]^+$.

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(18) **ARF Reaction of *exo-syn*-Isomer of 1a**
A solution of *exo-syn*-isomer of compound **1a** (0.512 g, 20 mmol), diacetoxy iodobenzene (1.28 g, 40 mmol) and iodine (1.52 g, 60 mmol) in CH_2Cl_2 (60 mL) taking in a round-bottomed flask was irradiated under one 100 W tungsten filament lamp for 2 h at r.t. The mixture was washed with $NaHSO_3$ solution (3 × 30 mL), brine (2 × 30 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue was chromatographed to obtain the colorless oily compound **5** as a mixture of diastereomers in an almost 1:1 ratio, and compound **6** [eluant: EtOAc–*n*-hexane (1:4)].
Compound **5** (diastereomeric mixture): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.2 Hz, 1 H, CHO), 9.59 (d, *J* = 1.2 Hz, 1 H, CHO), 5.28–5.22 (m, 2 H, CHO), 4.28–4.19 (m, 4 H, CH_2O), 2.80 (dd, *J* = 8.0, 15.0 Hz, 1 H), 2.66–2.56 (m, 3 H), 2.48–2.33 (m, 6 H), 2.04–1.97 (m, 5 H), 1.92–1.60 (m, 8 H), 1.47–1.32 (m, 1 H), 1.25–1.20 (m, 6 H). ^{13}C NMR: δ = 200.7, 200.5 (CHO), 172.3 (O–C=O), 170.2 (O–C=O), 71.8, 71.2 (CHO), 62.3 (OCH_2), 56.8, 56.3 (*C*HCHO), 44.7 (C–I), 42.1, 40.9, 37.1, 37.0, 30.4, 29.5, 23.0, 21.7, 21.2 ($COCH_3$), 13.8. (CH_3CH_2). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{13}H_{19}IO_5$: 382.028; found: 383.033 (5) $[MH]^+$, 355.013 (25) $[MH – CO]^+$, 339.010 (40) $[M – CH_3CO]^+$.
Compound **6 (**oil): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.33 (s, 1 H, CHO), 6.85 (m, 1 H, CH=C), 4.28 (q, *J* = 7 Hz, 2 H, CH_2O), 2.70–2.28 (m, 8 H), 1.30 (t, *J* = 7 Hz, 3 H, CH_3). ^{13}C NMR: δ = 193.4 (CHO), 172.4 (O–C=O), 154.2 (CH=), 146.0 (C=), 62.2 (OCH_2), 48.3 (C–I), 39.5, 39.3, 27.6, 21.9, 13.8. (CH_3). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{11}H_{15}IO_3$: 322.007; found: 320.999 (23) $[M – H]^+$, 194.076 (27) $[M – HI]^+$, 193.068 (45) $[M – H – HI]^+$.
Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.55 (br s, 1 H, CHO), 9.52 (br s, 1 H, CHO), 5.59–5.51 (m, 2 H, CHO), 4.28–4.16 (m, 4 H, CH_2O), 2.94 (dd, *J* = 7, 15 Hz, 1 H), 2.75–2.09 (m, 10 H), 2.01–1.78 (m, 11 H), 1.74–1.45 (m, 2 H), 1.27–1.22 (m, 6 H). ^{13}C NMR: δ = 200.1, 200.1 (CHO), 172.7, 172.3, 170.0, 169.9, 70.3, 70.2, 62.1, 62.1 (OCH_2), 55.8, 55.5 (*C*HCHO), 46.0, 45.0 (C–I), 41.9, 40.9, 36.3, 36.3, 30.0, 29.0, 21.0, 20.9, 20.9, 19.3, 13.6, 13.6. (CH_3CH_2). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{13}H_{19}IO_5$: 382.028; found: 382.029 (17) $[M]^+$, 383.033 (23) $[MH]^+$.

(19) In the seven-membered-ring analogue **1a** the C-3 hydrogen is less readily accessible for radical abstraction.

(20) Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.39 (s, 1 H, CHO), 6.69 (dd, *J* = 2.1, 3.3 Hz, 1 H, C*H*=CH_2), 4.20–4.10 (m, 2 H, CH_2O), 2.68 (dt, *J* = 16.0, 5.0 Hz, 1 H), 2.54–2.46 (m, 1 H), 2.34–2.28 (m, 1 H), 2.18–2.07 (m, 1 H), 2.95–1.85 (m, 1 H), 1.66 (dd, *J* = 10.0, 4.0 Hz, 1 H), 1.40–1.21 (m, 6 H), 0.82 (dd, *J* = 4.0, 6.6 Hz, 1 H). ^{13}C NMR: δ = 194.6 (CHO), 174.0 (O–C=O), 149.8 (CH=), 143.1 (C=), 60.9 (OCH_2), 29.7 (C–I), 28.3, 25.4, 23.3, 22.7, 20.1, 14.2 (CH_3). HRMS (CI, CH_4): *m/z* (%) calcd for $C_{12}H_{17}IO_3$: 336.022; found: 336.023 (24) $[M]^+$, 337.025 (47) $[MH]^+$.