Macrocyclic Studies of EZ and ZZ 12-membered Aza Macrocycles; Novel Molecular Rearrangement Observed

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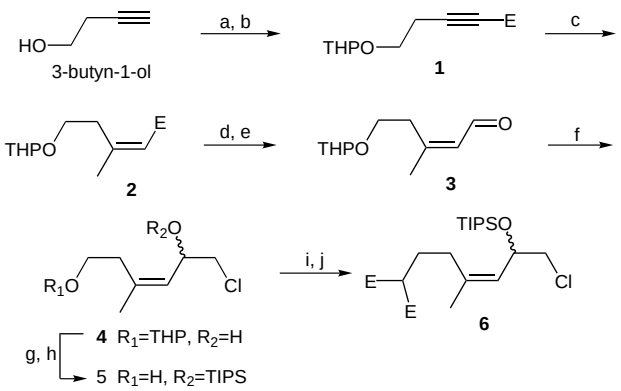
Abstract: EZ and ZZ hetero macrocyclic dienes **13a** and **14b** are generated respectively by an intramolecular displacement of α-chloroketones **11a** and **11b** using trifluoroacetamide as nucleophilic agent. Novel molecular rearrangements were observed.

Key words: macrocyclization, chloroketone, trifluoroacetamide, imide, lactam

We have recently reported the use of α-chloroketones for the synthesis of macrocycles via the intramolecular displacement with a carbon nucleophile.[1] We have also observed good yields of macrocyclization by the displacement of an allylic chloride with a nitrogen derived nucleophile.[2] We wish now to report a study on the intramolecular cyclization of EZ and ZZ α-chloroketone trifluoroacetamide dienes **11a** and **11b** which led us to observed unexpected molecular rearrangements during the macrocyclization step.

The trisubstitued Z-olefin **6** (Scheme 1) was obtained through a ten step sequence via the commercially available 3-butyn-1-ol which was protected as a tetrahydropyranyl acetal.[3] The corresponding lithium acetylide was treated with methyl chloroformate to give the adduct **1** in a combined yield of 72%. Carbocupration on the alkynic ester provided specifically the corresponding Z olefin **2** in a 95% yield.[4] The ester **2** was reduced by DIBAL-H and the resulting alcohol was oxidized to the aldehyde by the Swern's protocol.[5] The chlorohydrin **4** was obtained in 98% yield as a mixture of diastereoisomers upon treatment with chloromethyllithium.[6] Protection of this mixture as triisopropylsilylether followed by the removal of the tetrahydropyranyl group in acidic medium gave racemic adduct **5** in a combined yield of 92%. Using Corey's procedure,[7] the alcohol **5** was transformed to the iodide which was alkylated with dimethyl malonate to give synthon **6** in a global yield of 35%.[8]

Coupling of the latter with the commercially available dichlorides **7a** and **7b** (Scheme 2) afforded the corresponding dienes **8a** and **8b**. Displacement of the allylic chloride with sodium azide provided adducts **9a** and **9b** which were converted into the corresponding amines following the Staudinger's protocol.[9] Acetylation led to trifluoroacetamides **10a** and **10b**. The triisopropylsilylether was removed with tetrabutylammonium fluoride to generate the alcohols which were oxidized by Dess-Martin periodinane[10] to give chloroketones **11a** and **11b**. These



Scheme 1 (a) DHP, TsOH, THF, r.t., 95% (b) *n*-BuLi, $ClCO_2Me$, THF, -78°C, 76% (c) MeLi, CuI, THF, -78°C, 95% (d) DIBAL-H, CH_2Cl_2, -78°C, 88% (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 80% (f) Li, $BrCH_2Cl$, THF, -78°C, 98% (g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, -20°C, 98% (h) PPTS, *i*-PrOH, reflux, 94% (i) Ph_3P, I_2, imidazole, Et_2O/CH_3CN (3:1), r.t., 90% (j) E_2CH_2, NaH, THF/DMF (1:1), 80°C, 88%. E = CO_2Me.

precursors were submitted to the macrocyclization conditions and the results are shown in the Table 1.

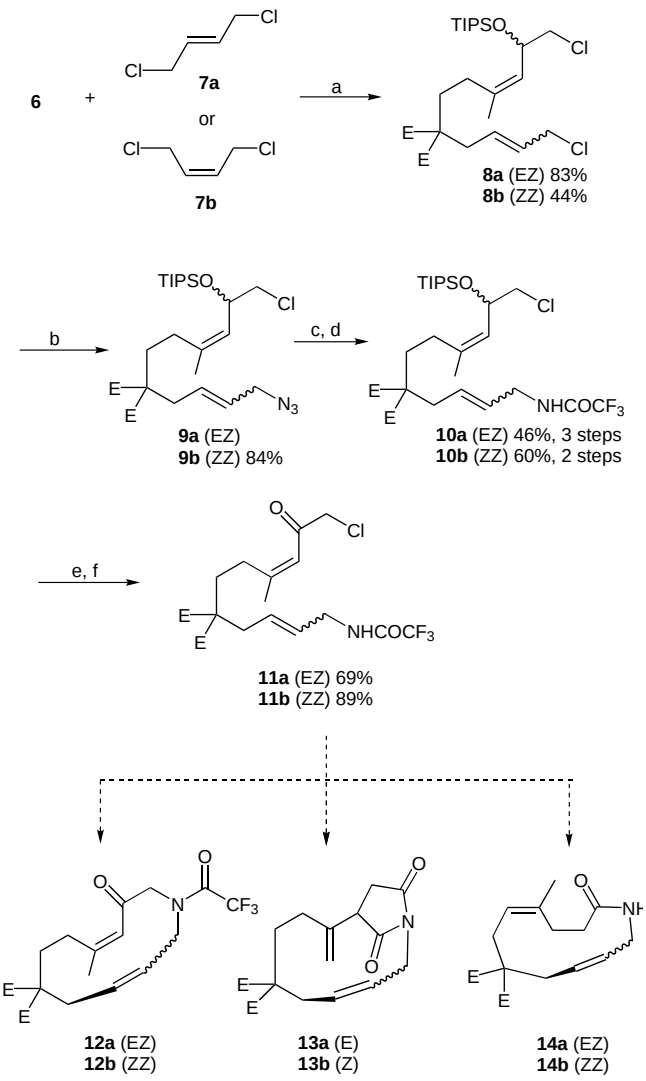
Table 1 Results for the macrocyclization step

Entry[a]	Substrate	Temp. (°C)	Time[b]	Yield (%)[c]
1	**11a**	35°C	8 h	**12a** (18%)
				13a (20%)
2	**11a**	45°C	8 h	**12a** (27%)
				13a (32%)
3[d]	**11a**	60°C	8 h	**12a** (0%)
				13a (24%)
4	**11b**	45°C	8 h	decomp.
5[e]	**11b**	45°C	8 h	**14b** (14%)
6[e]	**11b**	55°C	8 h	**14b** (19%)

[(a)] Macrocyclization was carried out at 2.0 X 10^{-3} M in CH_3CN using Cs_2CO_3 as a base. [(b)] Time of the substrate addition via a syringe pump. [(c)] Yield of isolated product. [(d)] Degradation products were observed. [(e)] DMF was used as solvent.

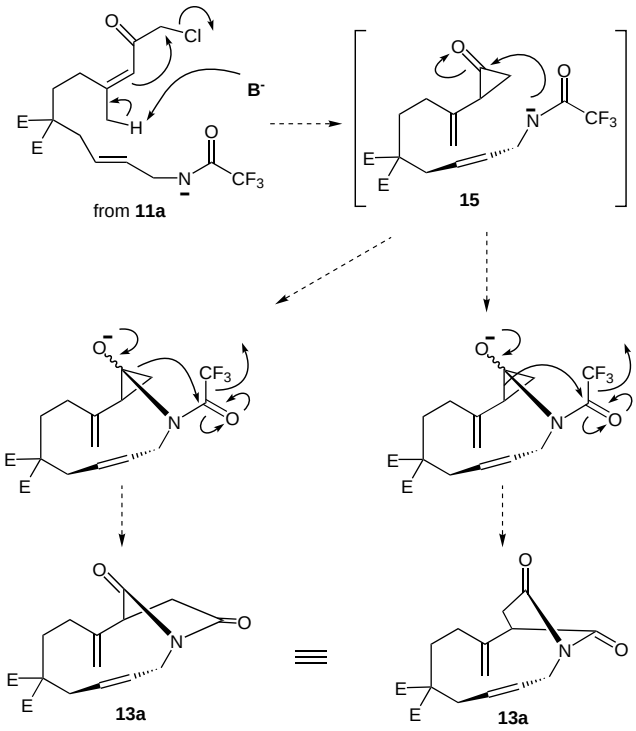
Results and discussion

Temperature was shown to influence the relative formation of the expected macrocycle **12a** and the unexpected



Scheme 2 (a) NaH, THF/DMF (1:1), r.t., then **7a** or **7b**, 75°C (b) NaN_3, DMSO, r.t., 18 h (c) Ph_3P, H_2O, THF, r.t., 18 h (d) TFAA, pyridine, CH_2Cl_2, 0°C (e) TBAF, THF, -20°C (f) Dess-Martin periodinane, CH_2Cl_2, r.t., 10 min. E = CO_2Me.

bicyclic macrocycle **13a** as indicated in entries 1-3.[11,12] When macrocyclization was carried out at 60°C, macrocycle **12a** was not formed but degradation products appeared. As shown in Scheme 3, we explained the formation of the bridged macrocycle **13a** by the competitive formation of a cyclopropanone intermediate which is usually occurring in the Favorskii's rearrangement.[13] Thus, chloroketone **11a** would first be converted to cyclopropanone **15**, trifluoroacetamide anion would then add to the carbonyl and the resulting intermediate would break down by attacking the fluoroacetamide carbonyl (two routes are possible) to finally eject trifluoromethane carbanion and produce the rearranged bicyclic macrocycle **13a**. The unexpected formation of the non-conjugated macrocyclic lactam **14b** (Scheme 4)[14] would start by the formation of cyclopropanone intermediate **16** by removing an allylic proton on the alkyl chain. This would be followed by a N-nucleophilic attack and cleavage of the resulting cyclopropanoxide on the allylic side providing the macrocyclic trifluoroketoimide **17**. This compound would then be hydrolysed in the reaction medium to give macrocyclic lactam **14b**. Single crystal X-ray diffraction analysis of compounds **13a** and **14b** confirmed unambiguously their structures (Figures 1-2).[15] Both series have demonstrated that the direct macrocyclization pathway is disfavored over the unexpected rearrangements.



Scheme 3 E = CO_2Me, B = Cs_2CO_3.

The above procedure using an α-chloroketone nucleophilic displacement by an heteroatom shows that it is possible to generate 12-membered macrocycles. Moreover, it also allowed us to observe a new molecular rearrangement leading to unusual bicyclic imides and macrocyclic lactams.

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References and Notes

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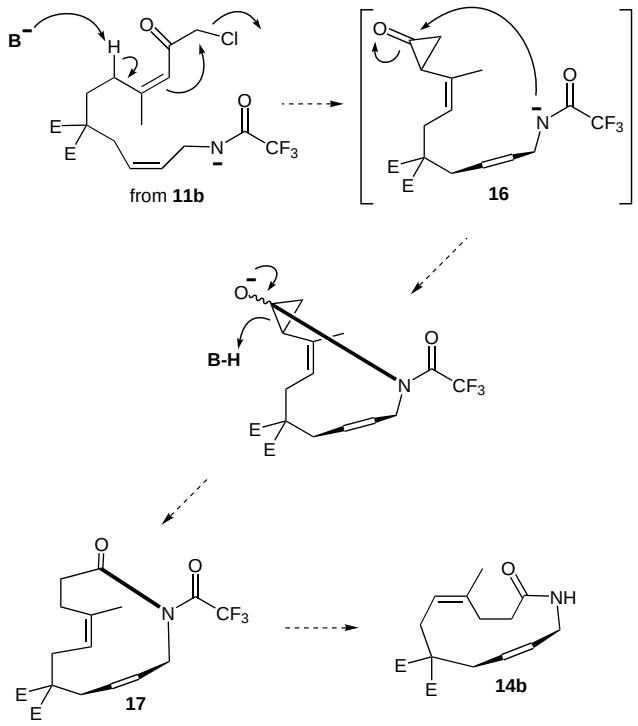
(2) Fortin, D. Unpublished results.



Scheme 4 E = CO_2Me, B = Cs_2CO_3.

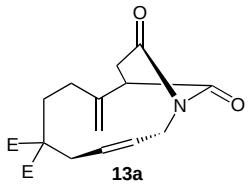


Figure 1 Stereoview of the ORTEP drawing of **13a**.

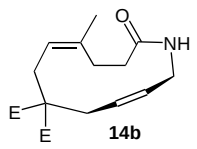


Figure 2 Stereoview of the ORTEP drawing of **14b**.

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(8) Adduct **6**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (d, J = 8.5 Hz, 1H, RC(CH_3)=C<u>H</u>R), 4.60-4.52 (m, 1H, <u>CH</u>OTIPS), 3.75 (s, 6H, 2 X COO<u>CH_3</u>), 3.48 (dd, J = 10.7, 6.4 Hz, 1H, <u>CH_2</u>Cl), 3.35 (dd, J = 10.7, 6.4 Hz, 1H, <u>CH_2</u>Cl), 3.34 (m, 1H, R<u>CH</u>($COOCH_3$)$_2$), 2.20-1.85 (m, 4H, <u>CH_2CH_2</u>), 1.73 (s, 3H, RC(<u>CH_3</u>)=CHR), 1.03 (s, 21H, OTIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 136.7, 128.0, 69.5, 52.5, 51.3, 49.2, 30.2, 27.0, 22.8, 17.9, 17.7, 12.3; IR (neat, cm^{-1}) 2945, 2866, 1739, 1462, 1436, 1155, 883, 681; HRMS: calc. for $C_{18}H_{32}O_5Si_1C_{11}$ (M - C_3H_9): 391.1707, found: 391.1714.

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(11) Macrocycle **12a**: amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (s, 1H, RC(CH_3)=C<u>H</u>COR), 5.60-5.36 (m, 2H, R<u>CH</u>=<u>CH</u>R), 4.30-3.80 (m, 2H, <u>CH_2</u>NR_2), 3.75 (s, 6H, 2 X COO<u>CH_3</u>), 2.74 (d, J = 6 Hz, 2H, CH=CH<u>CH_2</u>C($COOCH_3$)$_2$), 2.35-1.75 (m, 2H, <u>CH_2</u>CH_2), 1.84 (s, 3H, RC(<u>CH_3</u>)=CHCOR), 1.36-1.14 (m, 2H, CH_2<u>CH_2</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 197.0, 150.4, 148.8, 129.6, 129.2, 129.0, 124.8, 123.8, 56.2, 55.1, 52.9, 52.3, 52.2, 51.1, 34.6, 34.3, 32.7, 29.7, 26.0; IR (neat, cm^{-1}) 2928, 1727, 1692, 1448, 1255, 1207, 1154, 912; HRMS: calc. for $C_{18}H_{22}O_6N_1F_3$: 405.1399, found: 405.1393.

(12) Bicyclic imide **13a**: colorless flakes, mp 164°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07-5.85 (m, 2H, R<u>CH</u>=<u>CH</u>R), 5.15 (s, 1H, <u>CH_2</u>=CR_2), 5.03 (s, 1H, <u>CH_2</u>=CR_2), 4.38 (dd, J = 13.2, 6.0 Hz, 1H, <u>CH_2</u>N), 3.83 (dd, J = 13.2, 7.0 Hz, 1H, <u>CH_2</u>N), 3.72 (s, 3H, COO<u>CH_3</u>), 3.70 (s, 3H, COO<u>CH_3</u>), 3.47 (dd, J = 8.6, 1.2 Hz, 1H, <u>CH</u>CH_2COR), 2.96 (dd, J = 18.4, 8.7 Hz, 1H, CH<u>CH_2</u>COR), 2.86 (dd, J = 13.6, 8.2 Hz, 1H, CH<u>CH_2</u>C($COOCH_3$)$_2$), 2.41 (dd, J = 18.4, 1.6 Hz, 1H, CH<u>CH_2</u>COR), 2.34-2.20 (m, 2H, CH<u>CH_2</u>C($COOCH_3$)$_2$, <u>CH_2</u>CH_2), 1.95-1.40 (m, 2H, CH_2<u>CH_2</u>), 1.30-1.19 (m, 1H, <u>CH_2</u>CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 176.1, 172.1, 171.0, 144.7, 131.5, 130.3, 118.5, 55.9, 52.9, 52.5, 48.8, 38.9, 35.1, 33.4, 29.7, 24.7; IR (neat, cm^{-1}) 2955, 2257, 1732, 1703, 1602, 1436, 1388, 1322, 1244, 1168.

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(14) Lactam **14b**: colorless flakes, mp 135-137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (dd, J = 18.3, 7.5 Hz, 1H, RCH=<u>CH</u>CH_2N), 5.75 (s, 1H, NH), 5.14 (dd, J = 18.7, 8 Hz, 1H, R<u>CH</u>=CHCH_2N), 4.89 (t, J = 6.5 Hz, 1H, R<u>CH</u>=C(CH_3)R), 3.77 (s, 6H, 2 X COO<u>CH_3</u>), 3.65 (dd, J = 7.3, 5.8 Hz, 2H, <u>CH_2</u>NH), 2.66-2.61 (m, 4H, <u>CH_2</u>CH=CH, CH_2CH=C(CH_3)<u>CH_2</u>), 2.42-2.23 (m, 4H, <u>CH_2</u>CONH, <u>CH_2</u>CH=C(CH_3)CH_2), 1.77 (s, 3H, CH_2CH=C(<u>CH_3</u>)CH_2); IR (neat, cm^{-1}) 2978, 1733, 1663, 1442, 1216, 1110; HRMS: calc. for $C_{16}H_{23}O_5N_1$: 309.1576, found: 309.1579.

(15) Crystallographic data of compounds **13a** (CCDC 114598) and **14b** (CCDC 114599) have been deposited with the Cambridge Crystallographic Data Center, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, England.

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