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A [2+2+1] strategy for the conversion of olefins into cyclopentenones. Ring expansion of 2-*N*-methyl-*N*-tosyl-cyclobutanones

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Abstract

α-*N*-Methyl-*N*-tosylcyclobutanones prepared by asymmetric cycloadditions of the corresponding keteniminium triflate to olefins have been converted into a mixture of epoxides using dimethylsulfonium ylide. Treatment of these epoxides with lithium iodide unexpectedly yielded the corresponding cyclopentenones. This sequence amounts to a [2+2+1] cyclopentannulation of an olefin.

Keywords: cyclobutanones; epoxides; rearrangement; ring expansion; cyclopentenones; cyclopentannulation.

The stereospecific cycloaddition of keteniminium salts to alkenes and alkynes is a very general method of synthesis of four-membered ring ketones.[1] The use of keteniminium salts derived from amides bearing a chiral auxiliary has further extended the utility of the reaction by allowing the preparation of enantiopure cyclobutanones.[2] The asymmetric cycloaddition of keteniminium salt **2** to an olefin followed by the regioselective oxidation of the resulting cyclobutanone **3** represents one of the few general methods for the enantioselective vicinal acylation of an olefin (Scheme 1).[3] More recently we have considered the transformation of cyclobutanones **3** into the corresponding cyclopentanones. If successful, the two-step sequence — cycloaddition followed by ring expansion — would provide a useful method for the asymmetric cyclopentannulation of olefins by a [2+2+1] strategy.

An obvious method for the conversion of **3** to **4** would be the formation of an epoxide using Corey's ylid reagent[4] followed by a rearrangement catalysed by lithium iodide[5] or lithium bromide.[6] The racemic bicyclo[4.2.0]octanone **3a** was readily converted into a 1.5:1 mixture of diastereoisomeric epoxides by reaction with Me_2S^+–CH_2^- generated from trimethylsulfonium tetrafluoroborate and *n*-BuLi (Scheme 2). The two isomeric epoxides were easily separated by flash chromatography.[7] An X-ray diffraction analysis of *endo*-**5a** confirmed the stereochemical assignments.[8]

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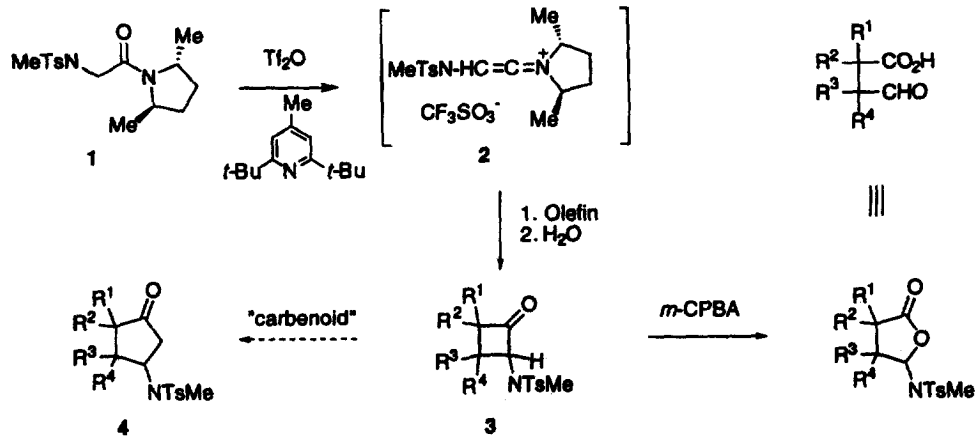
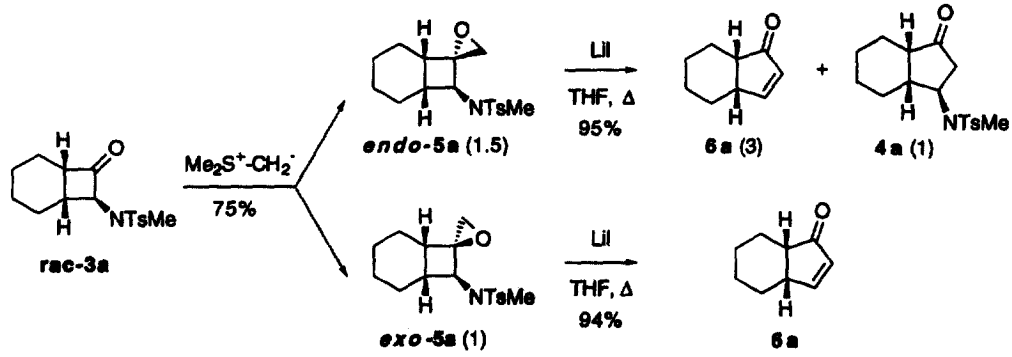


Scheme 1.



Scheme 2.

Upon treatment with LiI in refluxing THF, the major epoxide *endo*-**5a** unexpectedly yielded a 3:1 mixture of cyclopentenone **6a** and cyclopentanone **4a** (Scheme 2, Table 1).[9] The saturated ketone **4a** was the expected product from a regioselective ring-expansion reaction of **5a** controlled by the NTsMe group. Cyclopentanone **4a** was not the precursor of enone **6a**, this was demonstrated by the recovery of unchanged **4a** after treatment with LiI for one day in refluxing THF. The rearrangement of *exo*-**5a** exclusively gave enone **6a**. Table 1 shows that both a Lewis acid cation and a nucleophilic anion are necessary for the rearrangement (Table 1, entries 2, 3 versus 1, 4). Also it shows an unusual dependence of the course of the rearrangement on: (1) the nature of the anion (entries 1 and 4); (2) the stereochemistry of the epoxide ring (entries 1 and 4, *endo* versus *exo*). At this stage, we have no good rationale for these unexpected results.

The synthetic value of these observations is illustrated by the efficient two-step conversion of cyclobutanones **3b–d** into the corresponding cyclopentenones **6b–d**. In these cases both diastereoisomeric epoxides only yielded cyclopentenones **6b–d**. The ring expansion step did not require the separation of the isomeric epoxides (Scheme 3). The formation of **6c** and **6d** from **5c** and **5d** confirmed that the rearrangement of epoxides **5** took place with the same regioselectivity as that leading to **4**.

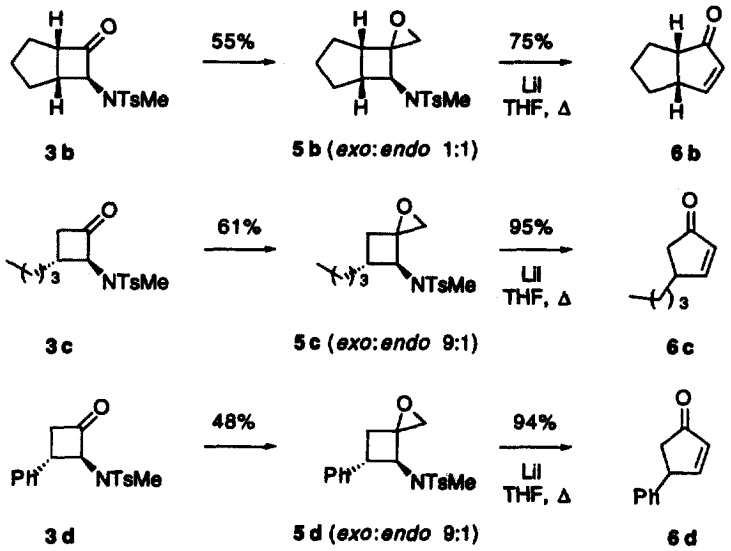
Using the chiral *N*-tosylsarcosinamide **1** for the cycloaddition step,[3] we were able to prepare the bicyclic cyclopentenone **6a** which showed the same enantiomeric purity as the cyclobutanone **3a** (Scheme 4).

This last result indicates that the sequence offers a useful synthetic route for the conversion of olefins into cyclopentenones of high enantiomeric purity. Applications of this synthetic strategy to the

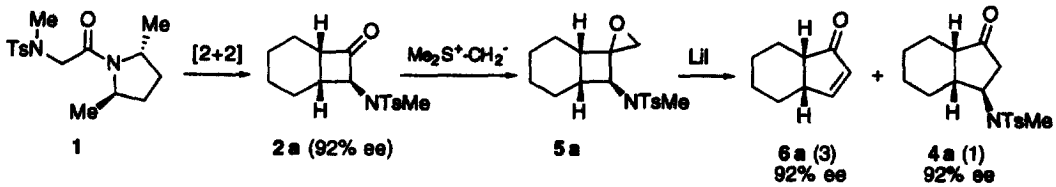
Table 1
Study of the rearrangement of 5a-*endo* and 5a-*exo* in refluxing THF

Entry	Catalyst	*endo*-5a		*exo*-5a	
	(1 equiv.)	Yield %	6a : 4a ratio[a]	Yield %	6a : 4a ratio[a]
1	LiI	95	3 : 1	94	100 : 0
2	LiI, 12-Crown-4	0	-	0	-
3	$LiNTf_2$	0	-	0	-
4	LiBr	98	0 : 100	95	100 : 0

[a] : Determined by NMR on the crude mixture.



Scheme 3.



Scheme 4.

asymmetric synthesis of biologically active products are being studied by our group. The mechanism of the unexpected direct conversion of **5** into **6** is also being investigated.

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7. General procedure for epoxidation of **3**: a 2.5 M solution of *n*-BuLi in hexane (1.2 equiv.) and a 0.05 M solution of trimethylsulfonium tetrafluoroborate (1 equiv.) in dry THF were mixed and stirred for fifteen minutes at −10°C. A 0.5 M solution of cyclobutanone **3** (1 equiv.) in dry THF was added dropwise to the resulting ylide solution at −78°C. The mixture was stirred at room temperature for 3–5 hours. Addition of water and extraction with diethylether gave a crude product which was purified by flash chromatography on silica gel (AcOEt:cyclohexane, 2:8) to yield the two diastereoisomeric epoxides. Compound *endo*-**5a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, 2H, ^3J=8.3 Hz), 7.22 (d, 2H, ^3J=8.3 Hz), 4.61 (dd, 1H, ^3J=8.3 Hz, ^4J=1.4Hz), 2.91 (s, 3H), 2.70–2.58 (m, 1H), 2.55 (d, 1H, ^2J=4.6 Hz), 2.36 (d, 1H, ^2J=4.6 Hz), 2.42 (s, 3H), 2.25 (m, 1H), 1.70–0.70 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 136.7, 129.5, 126.9, 66.5, 57.5, 46.8, 35.6, 33.4, 31.4, 24.9, 24.1, 22.3, 21.5, 21.4; IR 2927, 2854, 1340, 1158; MS (EI) 322 (2%), 238 (24%), 185 (24%), 155 (100%), 91 (72%); Anal. calculated for $C_{17}H_{23}NO_3S$ C%: 63.52; H%: 7.21; N%: 4.36; S%: 9.97; Found: C%: 63.43; H%: 7.30; N%: 4.13; S%: 10.04. Compound *exo*-**5a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, 2H, ^3J=8.2 Hz), 7.28 (d, 2H, ^3J=8.2 Hz), 4.83 (d, 1H, ^3J=9.1 Hz), 2.79 (s, 3H), 2.72 (d, 1H, ^2J=9.0 Hz), 2.49 (d, 1H, ^2J=9.0 Hz), 2.42 (s, 3H), 2.38–2.26 (m, 2H), 1.90–0.90 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.3, 136.4, 129.4, 127.2, 63.1, 57.9, 50.1, 32.9, 30.4, 29.6, 23.2, 22.4, 21.3, 21.4; IR 2929, 2852, 1340, 1161; MS (EI) 321 (4%), 238 (72%), 166 (36%), 155 (32%), 91 (60%), 42 (100%); Anal. calculated for $C_{17}H_{23}NO_3S$ C%: 63.52; H%: 7.21; N%: 4.36; S%: 9.97; Found: C%: 63.46; H%: 7.25; N%: 4.29; S%: 10.35.
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9. General procedure for the rearrangement of **5**: lithium iodide (1 equiv.) was added to a 0.1 M solution of the mixture of epoxides **6** (1 equiv.) in dry THF. The resulting solution was refluxed for two hours, then cooled to room temperature. The crude product was purified by flash chromatography on silica gel (AcOEt:cyclohexane, 2:8). Compound **4a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, 2H, ^3J=8.0 Hz), 7.31 (d, 2H, ^3J=8.0 Hz), 4.68 (d, 1H, ^3J=12.6 Hz), 2.60 (s, 3H), 2.43 (s, 3H), 2.40–2.15 (m, 4H), 2.10–1.00 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.5, 143.2, 136.8, 129.4, 127.6, 63.7, 43.9, 36.7, 31.4, 30.0, 29.2, 25.0, 24.2, 21.4, 19.6; IR 2927, 2854, 1749, 1338, 1156; MS (EI) 321 (28%), 165 (100%), 136 (100%), 91 (56%); Anal. calculated for $C_{17}H_{23}NO_3S$ C%: 63.52; H%: 7.21; N%: 4.36; S%: 9.97; Found: C%: 63.27; H%: 7.16; N%: 4.22; S%: 10.14. Compound **6a**: identical with an authentic sample: RN=81255-91-6.