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4-Isopropenyl-3-Tosylmethyl Pyrrolidines Through Radical Cyclizations of 4-Aza-1,6-Dienes - An Approach to Kainic Acids -

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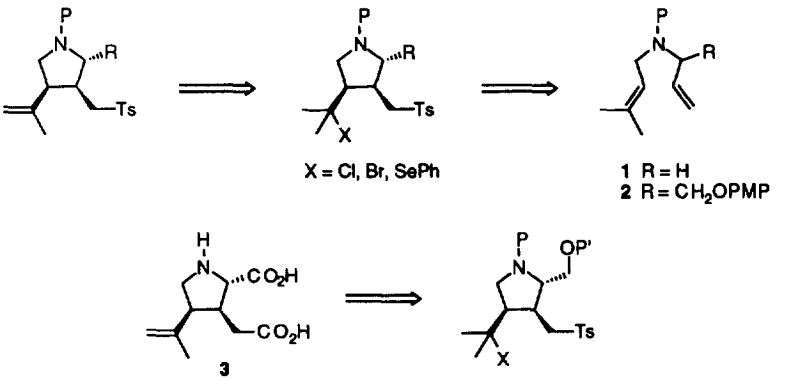
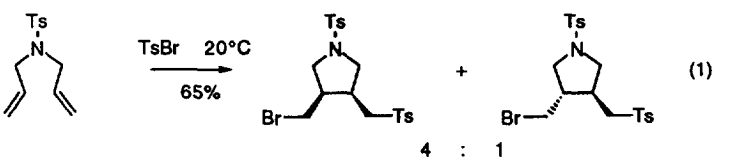
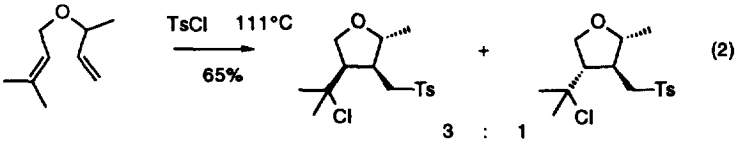
Abstract : The cyclofunctionalization of 4-aza-1,6-dienes **1** and **2** - bearing a prenyl chain - *via* the radical addition of PhSeTs (**4**) has been investigated as a potential route to 4-isopropenyl-3-tosylmethylpyrrolidines. Since the oxidative elimination of the resulting selenides afforded mainly the undesired olefinic regioisomer, an alternative pathway *via* the rearrangement of allylic sulfones **10-11**, was applied and provided, in good yields, the target heterocycles; **12a,b** are potential precursors of kainic acids.

During the course of our studies on tosyl radical-mediated cyclizations of 1,6-dienes,[1] we have investigated the reactivity of 4-aza-1,6-dienes (**1-2**) as potential precursors of isopropenyl substituted pyrrolidines. The underlying prospect of this work was the obvious potential application of this methodology to the preparation of a biologically active target, the α-kainic acid (**3**).[2-3]

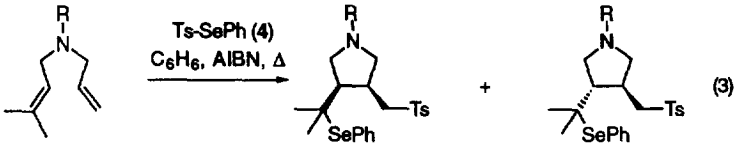


Stereocontrol in radical cyclizations is now well documented.[4] In particular the 5-exo-cyclizations of radicals bearing substituents in positions 1 and 2 are generally highly stereoselective.[4,5] As an example of directly related studies, the addition of tosyl bromide to N-tosyl diallylamine affords two diastereomers in a 4:1 ratio (eq 1), and the addition of tosyl chloride to 3,7-dimethyl-4-oxa-1,6-octadiene leads to only two products among the four possible, in a 3:1 ratio (eq 2).[1d]



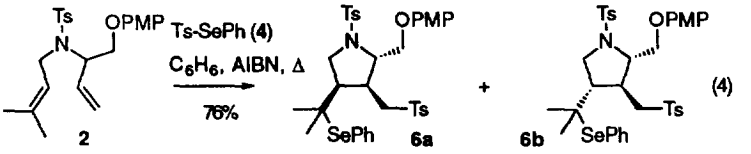


The first goal was to introduce the isopropenyl chain in position 4 on the pyrrolidine ring. In this respect, *para*-toluenephenylselenosulphonate (**4**) appeared as the choice precursor for tosyl radical[6] since the resulting selenides could readily be converted into selenoxides, the pyrolytic elimination of which could be performed under very mild conditions.[7] Thus we first investigated the addition of **4** to N-tosyl-4-aza-7-methyl-1,6-octadiene (**1a**) (eq 3). The reaction was chemoselective, as expected;[1a,d] it resulted in two diastereomeric adducts (**5a**, **5'a**) in a 57:43 ratio.



	1		5		5'
a	R = Ts	97%	57	:	43
b	R = Bn	55%	50	:	50
c	R = Bz	75%	55	:	45

The otherwise well documented **1,5-*cis*** stereocontrol [4,5] in the cyclization of 5-hexenyl radicals did not apply to that model compound.[8g] Since the selectivity might be sensitive to the nature of the N-protective group,[9] we changed the tosyl group into a benzyl or a benzoyl group, but no improvement of the diastereoselectivity was observed. The added influence of the *O*-protected hydroxymethyl group in position 2 with respect to the radical center in the intermediate 4-aza-5-hexenyl radical did not change either the 1,5-stereocontrol (eq 4).

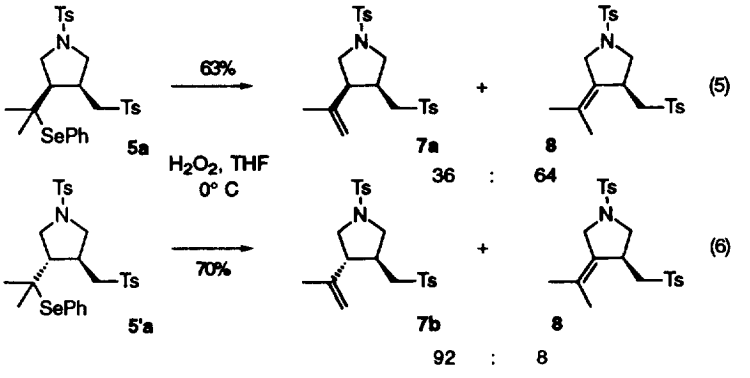


2 → **6a** : **6b** = 46 : 54

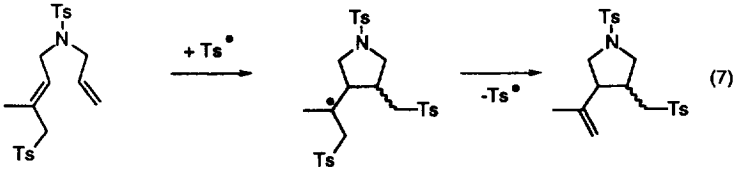
Among the four possible isomeric adducts, only the *trans*-2,3-disubstituted pyrrolidines **6a,b** were produced in 76% yield, however, the relative distribution of 3,4-*cis*- to 3,4-*trans* pyrrolidines was approximately 1:1.

In order to check the availability of the isopropenyl side-chain from the resulting selenides, the pure isolated stereoisomers **5a** and **5'a** were submitted to oxidative elimination on treatment with hydrogen peroxyde at 0°C in THF (eq 5-6). When starting from **5a**, the two regioisomers **7a** and **8** were obtained in 63% overall yield in a 36:64 ratio. The unwanted tetrasubstituted olefin **8** was the major product. On the contrary, when conducted on **5'a**, the oxidative elimination led to a mixture of **7b** and **8** in a 92:8 ratio. Obviously, the regioselectivity in the case of **5a**, was governed by the release of steric strain on going from the *cis* disubstituted cyclopentane to the isopropylidenecyclopentane. Taking into account the lack of regioselectivity in the oxidative elimination - at least from one isomer -, we concluded that the addition of phenylselenotosylate was not suited to

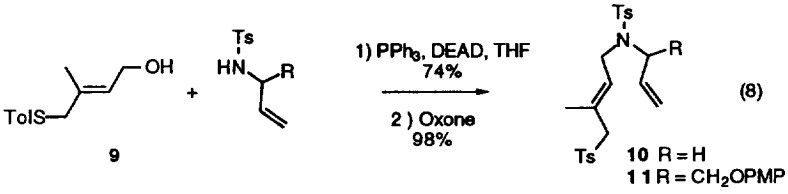
the synthesis of isopropenyl substituted five-membered rings.



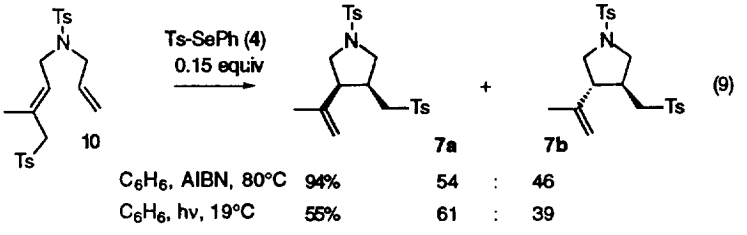
The best pathway for the direct construction of the 4-isopropenylpyrrolidine skeleton appeared thus to be the radical rearrangement of the adequate allylic sulfones, according to eq 7.[8]

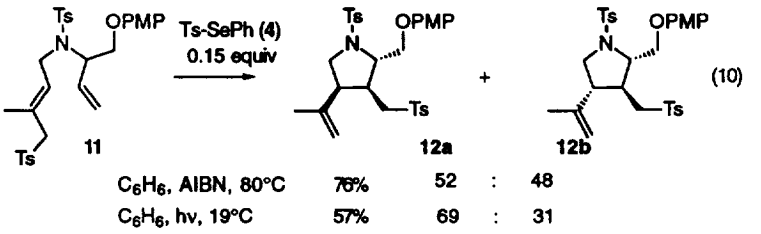


Dienes **10-11** were prepared through the Mitsunobu alkylation of the corresponding N-allyltosylamide with the hydroxysulfide **9**,[10] followed by treatment with oxone, according to eq 8.



The rearrangement of sulfone **10**, in the presence of a catalytic amount of **4** (0.15 equiv) proceeded in excellent yield, and so did the rearrangement of **11** (eq 9-10)[11], but the stereoselectivity remained very similar to that previously observed in the cyclizations of diene **1** and **2**. A significant improvement of the diastereomeric excess was achieved by performing the reaction at lower temperature (19 °C) *via* photochemical initiation but to the expense of the overall yield.





In conclusion, we have shown that the radical rearrangement of allylic sulfones is best suited to the construction of 4-isopropenyl-3-tosylmethyl pyrrolidines than the addition of phenylselenosulfonate (**4**) to 4-aza-1,6-dienes. High yields in the target heterocycles can be obtained, which opens a new route to kainic acids.

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11. In a typical experiment, a mixture containing **4** (15 mg, 0.048 mmol) and AIBN (2 mg, 0.012 mmol) was added by portions, under inert atmosphere, to a previously degassed refluxing solution of **10** (140 mg, 0.32 mmol) in benzene (25 ml). After 6 h, the solvant was evaporated and the residue was purified by flash chromatography on silicagel (EtOAc/pentane; 25/75). The isolated mixture contained **7a** and **7b** in a 54 : 46 ratio (130 mg, 0.30 mmol, 94%). Pure samples of each isomer were further isolated from semi-preparative HPLC (EtOAc/2,2,3-Trimethylpentane; 20/80).

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