Pergamon

Tetrahedron 54 (1998) 1817–1834

TETRAHEDRON

Multivariate Optimization and Mechanistic Considerations of the Amine Induced Ring-Opening Reaction of 2-Alkyl-3-bromo-5-methylthiophene-1,1-dioxides.

Anders Tsirk*, Salo Gronowitz[1] and Anna-Britta Hörnfeldt

Organic Chemistry 1, Chemical Center, University of Lund, P. O. Box 124,
S-221 00 Lund, Sweden.

Received 20 October 1997; revised 21 November 1997; accepted 27 November 1997

Abstract: In the optimization of the ring-opening reaction of thiophene-1,1-dioxides, 3-bromo-2,5-dimethylthiophene-1,1-dioxide (**1**) and 2-(2-hydroxyethyl)piperidine (**7**) were chosen as model reagents. Solvent, temperature, molar ratio between amine and dioxide and the amount of solvent were variables included in the optimization. A central composite design was chosen for the investigation and a canonical analysis of the response surface was performed. When reacting 3-bromo-2- isopropyl-5-trideuteriomethylthiophene-1,1-dioxide (**23**) with **7** a primary kinetic isotope effect, diminished by internal return, was found for the initial proton abstractions as well as an intramolecular deuterium transfer in the tautomerization of **23**.

INTRODUCTION

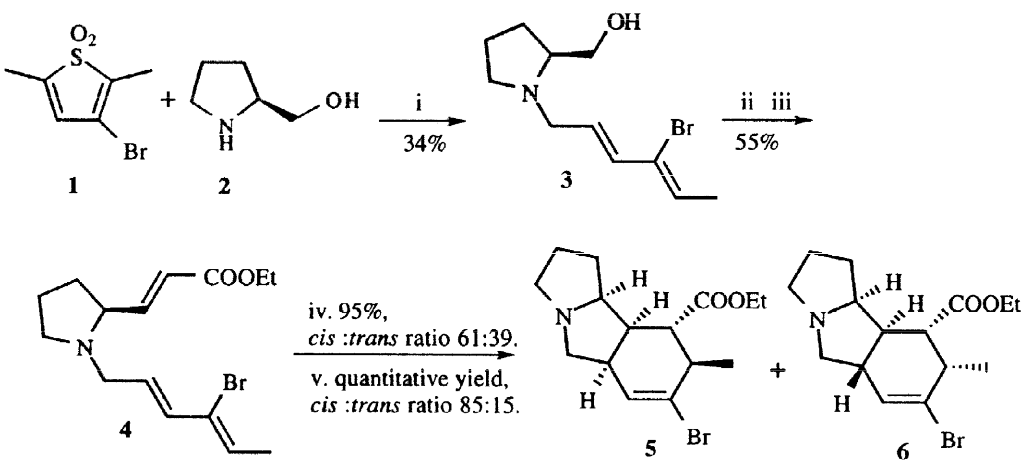
The amine induced ring-opening reaction of thiophene-1,1-dioxides was first reported in 1987.[1] A great number of dioxides and amines have been investigated in this reaction, which primarily leads to substituted *N*-hexadienyl amines. Using secondary amines with an ω-unsaturated side chain, azatrienes were obtained.[2,3] Recently, we found that when 2-substituted pyrrolidines and piperidines were used in the ring-opening reaction tetrahydrobenzo[*a*]pyrrolizidines, tetrahydrobenzo[*a* or *f*]indolizidines, and tetrahydrobenzo[*b*]quinolizidines were obtained, in just a few steps.[4,5]

A considerable effort has been made over the past years to synthesize and characterize alkaloids from the pyrrolizidine, indolizidine and quinolizidine families because of their highly interesting biological activities.[6-8] In order to develop a new and general method for the synthesis of such alkaloids we had to overcome some obstacles. Aminoalcohols proved to be ideal substrates in this context: they are readily available in both racemic and enantiopure form, the ring-opening reaction became faster, the hydroxy function could easily be transformed and good to excellent stereocontrol was obtained in the final intramolecular Diels-Alder reaction (IMDA) (*Scheme 1*). The last steps in the sequence gave a satisfactory overall yield, but a remaining problem was the poor yields in the ring-opening reaction, generally about 30%. In order to solve this problem, we decided to use a multivariate optimization procedure. The focus for this investigation was on the optimization, but some mechanistic observations were also made.

---

[1] Fax: 46 46 2224119 - Email: Salo.Gronowitz@orgk1.lu.se

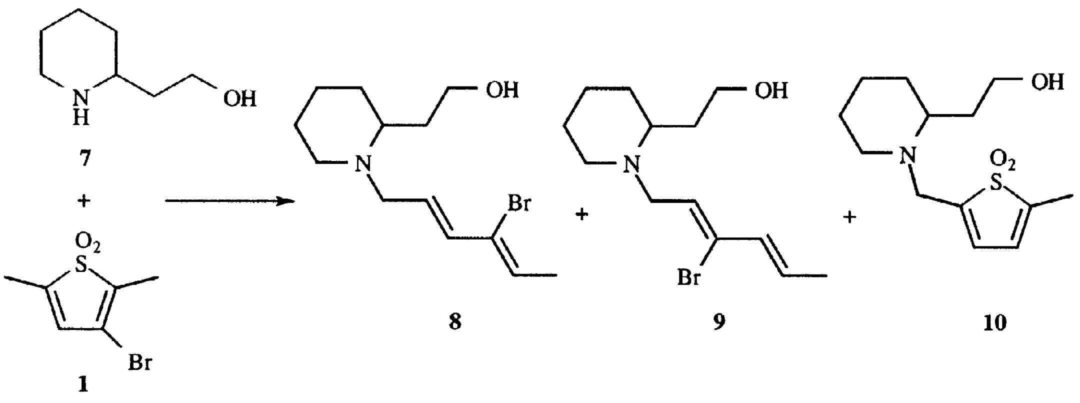
0040-4020/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(97)10390-8



Scheme 1. i. toluene, 100°C, argon. ii. Swern oxidation: 1. CH_2Cl_2, -78°C, argon, $(COCl)_2$, DMSO; 2. Et_3N, 2 h. iii. Wittig reaction: CH_2Cl_2, r.t., $Ph_3P{=}CHCOOEt$, 1 h. iv. thermal Diels-Alder reaction: toluene, argon, 150°C, 19 h. v. $TiCl_4$ catalyzed Diels-Alder reaction: 2 eq. $TiCl_4$, CH_2Cl_2, 0°C, 9 days.

RESULTS AND DISCUSSION

3-Bromo-2,5-dimethylthiophene-1,1-dioxide (**1**) and 2-(2-hydroxyethyl)piperidine (**7**) were chosen as model reagents to be used in the ring-opening reaction. Solvent, temperature, molar ratio between amine and dioxide and dilution, *i.e.* volume of solvent, were variables included in the optimization; not included were the addition order of the reagents and whether an inert atmosphere should be used or not. As the choice of solvent is a discrete variable, we decided to pick two candidates after an initial solvent screening performed under the standard conditions hitherto used. Carlsson *et al.* have analyzed over one hundred solvents by principal components analysis using nine descriptors.[9] Two principal components answered for 59.9% of the total variance, and they correspond roughly to the polarity and the polarizability of the solvents. Choosing solvents with a large variation in score values can give a good picture of which type of solvent to be used, and also which physical properties of the solvent that are important for the desired reaction. Solvents were chosen from



Scheme 2. Standard reaction: 0.251 M in **1**, 4 eq. amine, toluene, T = 100°C.

all four quadrants of the score plot, *i.e.* the plane spanned by the two principal components. Excluded were protic solvents since they favour other reactions.[1,10] The standard reaction gave three main products: 2-(1-[(2*E*,4*Z*)-3-bromo-2,4-hexadienyl]-2-piperidyl)-1-ethanol (**8**), 2-(1-[(2*E*,4*Z*)-4-bromo-2,4-hexadienyl]-2-piperidyl)-1-ethanol (**9**) and 2-(2-(2-hydroxyethyl)piperidyl)-methyl-5-methylthiophene-1,1-dioxide (**10**) in 30%, 2% and 3% yield, respectively (*Scheme 2*).[5] The formation of these were followed throughout the optimization procedure (Table 1). GLC yields were determined by using hexadecane as an internal standard.

Table 1. Solvent screening for the reaction between **7** and **1**.

	Product respones (%)		
Solvent	**8**	**9**	**10**
N,N-Dimethylformamide	0	0	7.27
Dimethylsulfoxide	0	0	3.85
pyridine	2.63	0	6.66
dl-α–Pinene[a]	16.67	0	2.14
Diethylenglycol dimethylether	17.95	0	5.25
Heptane	19.23	0.55	2.75
Chlorobenzene	24.48	0.79	4.76
Toluene	27.05	1.89	2.87
p-Xylene	27.91	0	2.44
Methylcyclohexane	29.56	1.16	3.24
Decaline	30.04	2.99	3.73

[a] neither dl-α-pinene nor a similar solvent were included in ref. 9.

The type of solvent was important, but some variation could be tolerated. The polarity of the solvent was however crucial: low dielectric constants, low dipole moments and low E_t values were preferred properties. Decaline and *p*-xylene were chosen as candidates for further investigation, since they were good representatives for the two solvent groups, alifatic and aromatic hydrocarbons, and because both could be used to explore a wider temperature range. The former had higher lipophilicity (log*P* value) and lower water solubility (log*M* value) than the latter. A central composite design was chosen for the investigation of the three variables: temperature (T), molar ratio between amine and dioxide (AD) and the solvent volume (V). By fitting a second-order polynomial in (k+1) dimensions a response surface can be modelled, which requires ($2^k + 2k + 1$) experiments.[11] For decaline we decided to run 19 experiments consisting of 8 factorial points, 6 axial points and 5 center points. The replicate center points would allow for a statistical evaluation of the lack of fit of the model (Table 2).

Table 2. Levels and variables for the reaction between **7** and **1** in decaline.

	Levels				
Variables	**-1.68**	**-1**	**0**	**1**	**1.68**
T (°C)	66	80	100	120	134
AD (mol eq.)	2.32	3.00	4.00	5.00	5.68
V (ml)	6.36	5.00	3.00	1.00	0*

*should have been an imaginary -0.36 ml

A response function was calculated.[12] Best fit of the model was obtained when the quadratic terms T^2 and AD^2, and the interaction terms T*AD and T*V were excluded from the response function, where y is the response of product **8** in %: $y = 20.339 + 1.719T + 2.631AD - 3.633V - 3.220AD*V - 1.375V^2$. For statistical evaluation an F-test was chosen: $s_1^2/ s_2^2 = 2.47 < F_{crit}$, which means that the model accurately describes the response. The best yield was obtained at $y(1, 1,-1) = 31.33$. A canonical analysis[11] did not lead to significantly better yields. The results suggested that more diluted reaction mixtures and higher amine-dioxide ratios should be used. Decaline was cumbersome to work with and as we suspected an inferior solubility of the reagents in this solvent we abandoned it. The domain had been too large. Therefore, we narrowed the conditions for *p*-xylene (Table 3):

Table 3. Levels and variables for the reaction between **7** and **1** in *p*-xylene.

	Levels				
Variables	**-1.41**	**-1**	**0**	**1**	**1.41**
T (°C)	106*	110	120	130	134*
AD (mol eq.)	2.59	3.00	4.00	5.00	5.41
V (ml)	9.18	8.00	6.00	4.00	3.18

*omitted; the curvature of y (T) was adequately described without the axial points and it resembled a parabola with y_{max} along an ascending ridge.

For *p*-xylene we decided to run 15 experiments consisting of 8 factorial points, 4 axial points and 3 center points; the axial points for T were omitted (Table 4). Best fit of the model was obtained when the quadratic term V^2, and the interaction terms T*AD and T*V were excluded from the response function: $y = 30.11 - 2.15T + 3.35AD + 1.08V + 3.21AD*V - 2.93T^2 - 3.03AD^2$. The model described the response within experi-

Table 4. Product responses for the reaction between **7** and **1** in *p*-xylene.

	Variable levels			Product responses (%)		
Experiment	T	AD	V	**8**	**9**	**10**
f1	-1	-1	-1	24.84	0	2.00
f2	+1	-1	-1	17.87	1.68	6.97
f3	-1	+1	-1	27.45	2.31	3.50
f4	1	+1	-1	15.48	0	2.76
f5	-1	-1	1	15.95	0	2.29
f6	1	-1	1	12.28	0.42	2.82
f7	-1	1	1	31.92	3.12	4.49
f8	1	1	1	24.13	2.36	5.07
a1	0	1.41	0	30.87	3.41	5.66
a2	0	-1.41	0	19.04	1.53	5.65
a3	0	0	1.41	34.13	3.04	4.21
a4	0	0	-1.41	26.13	2.83	5.57
m1	0	0	0	26.07	1.89	4.39
m2	0	0	0	34.01	4.06	7.32
m3	0	0	0	28.01	2.41	5.44

mental error, since $s_1^2/s_2^2 = 1.43 < F_{crit}$. A canonical analysis was undertaken to determine in what direction better yields would be obtained.[11] A stationary point was found at $y_0(-0.3669, -0.3364, -1.6788) = 29.0343$. This was used together with the coefficients to calculate a new response function that only included quadratic terms: $Y = y_0 - 2.93\,w_1^2 - 3.7221w_2^2 + 0.6921w_3^2$. In order to increase the yield w_3 should be maximized, while w_1 and w_2 should be set to zero; if $w_1 = 0$, then T= -0.3669 (116°C), if $w_2 = 0$, then AD = 0.3875515 + 0.43123V; w_3 = 1.541642 + 0.396AD + 0.9183V. Three different experiments were extrapolated and investigated (Table 5). The mean yield for the replicate experiments **c2** and **c4** was 42.9% for the reaction in *p*-xylene, which is a 33% improvement of the yield when operating under the standard conditions with toluene as solvent *vide supra*. The yield could thus be optimized from poor to fair. In previous work we reasoned that proton abstraction at the 2-methyl group in **1** is more facile than at the 5-methyl group and that the formation of **9** and **10** is a result from tautomerization from the 2-methyl side. Furthermore, we believed that the large amount of unidentifiable by-products formed in the reaction mainly originates from the decomposition of the high-energy ion pair formed after proton abstraction at the 2-methyl group.[5] This can partly explain the optimal yield of only 42.9%. To increase the yield, blocking the reaction from the 2-position would be an idea. The synthesis of 3-bromo-2-isopropyl-5-methylthiophene-1,1-dioxide (**11**) has been described.[3] Previous attempts to ring-open **11** failed, which can be rationalized in view of the present findings. The choice of amine was bad and the reaction conditions were not optimized. Since a slightly different dioxide was used in this work a small central composite design was chosen; we decided to run 10 experiments consisting of 4 factorial points, 4 axial points and 2 center points (Table 6 and 7); this was done in order to evaluate the extrapolation of results from one system to a related one. The temperature was kept constant at 116°C and *p*-xylene was used as solvent.

Table 5. Canonical analysis of the reaction between **7** and **1** in *p*-xylene.

	Variable levels			Yield (%)	
Experiment	T	AD	V	Y_{calc}.	$Y_{obs.}$
c1	0.3669 (116 °C)	1.3578 (5.36eq)	2.25 (1.5 ml)	40.93	38.82
c2	0.3669 (116 °C)	1.25 (5.25 eq)	2.00 (2 ml)	39.42	43.59
c3	0.3669 (116 °C)	1.4686 (5.47 eq)	2.50 (1 ml)	43.37	34.44
c4	0.3669 (116 °C)	1.25 (5.25 eq)	2.00 (2 ml)	39.42	42.28

Table 6. Levels and variables for the reaction between **7** and **11** in *p*-xylene, T = 116°C.

			Levels		
Variables	**-1.41**	**-1**	**0**	**1**	**1.41**
AD (mol eq.)	4.19	4.50	5.25	6.00	6.31
V (ml)	2.71	2.50	2.00	1.50	1.30

The following response function was obtained for 2-(1-[(2*E*,4*Z*)-4-bromo-6-methyl-2,4-heptadienyl]-2-

piperidyl)-1-ethanol (**12**): $y = 88.91 + 0.45AD - 3.66V + 10.44AD*V - 5.75T^2 - 4.19AD^2$. Statistics gave $s_1^2/s_2^2 = 1.25 < F_{crit}$. The same optimum conditions were valid for **11**, but now a considerably higher yield was obtained. The reaction was not entirely blocked from the 2-isopropyl side, but it was severely suppressed. The by-products **13** and **14** in this reaction were analogous to **9** and **10** described above according to mass analysis. The yield was limited upwards since the by-products were formed by a similar mechanism (*Figure 1*). 2-Hydroxymethylpiperidine (**15**) gave (1-[(2*E*,4*Z*)-4-bromo-6-methyl-2,4-heptadienyl]-2-piperidyl)methanol (**16**) in 88.56% yield. As there were no interaction terms between the temperature and the other variables, the temperature could be changed independently within the explored domain. This was necessary in the reaction between **11** and *L*-prolinol (**17**), which gave [1-[(2*E*,4*Z*)-5-bromo-2,4-heptadienyl]tetrahydro-1*H*-(2*S*)-2-

Table 7. Product responses for the reaction between **7** and **11** in *p*-xylene at 116°C.

	Variable levels		Product responses (%)		
Experiment	AD	V	**12**	**13**	**14**
f1	1	-1	75.46	3.28	3.59
f2	-1	-1	89.58	4.40	4.38
f3	1	1	88.07	3.33	2.48
f4	-1	1	60.41	2.06	2.32
a1	1.41	0	74.56	2.37	2.74
a2	-1.41	0	81.60	3.20	4.37
a3	0	1.41	76.68	2.01	2.78
a4	0	-1.41	85.67	2.90	4.86
m1	0	0	91.51	3.65	4.42
m2	0	0	86.30	3.16	4.24

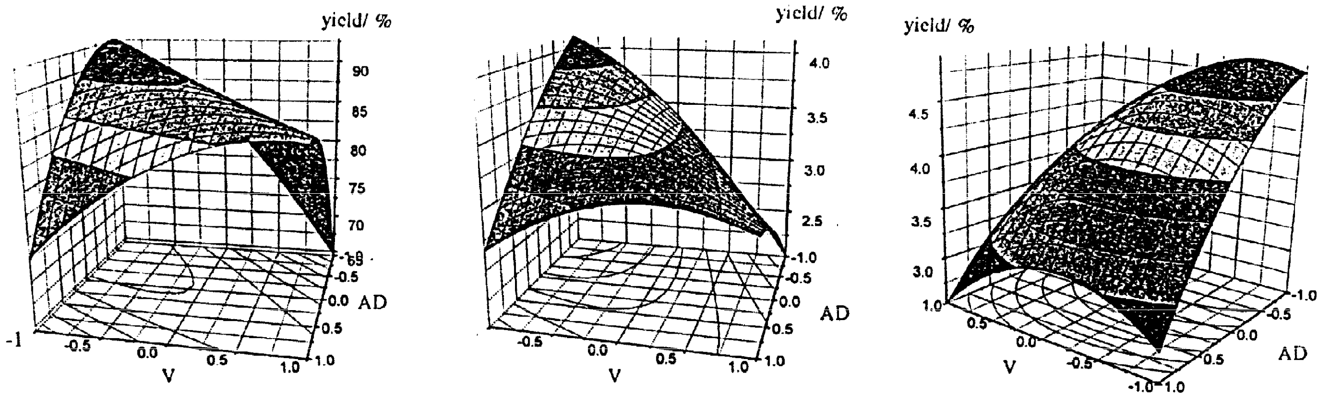
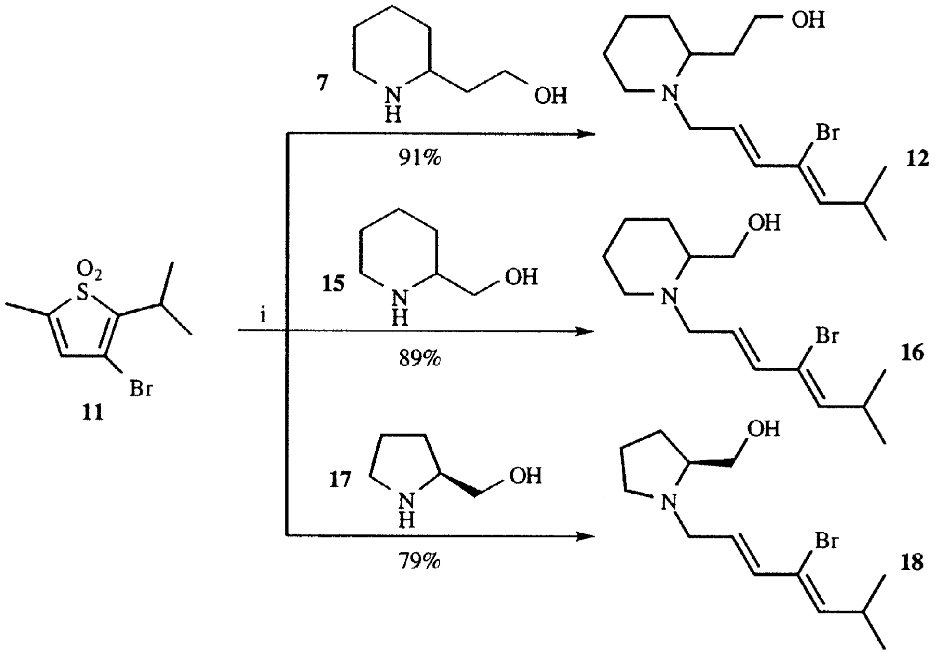


Figure 1. Response surfaces of compounds **12**, **13** and **14**.

pyrrolyl]methanol (18) in 79.0% yield at 103°C; the other variables were not changed (*Scheme 3*). Strictly the two latter reactions cannot be regarded as optimized since the reaction conditions were extrapolated from a slightly different system. However, from a preparative standpoint the yields were satisfactory.

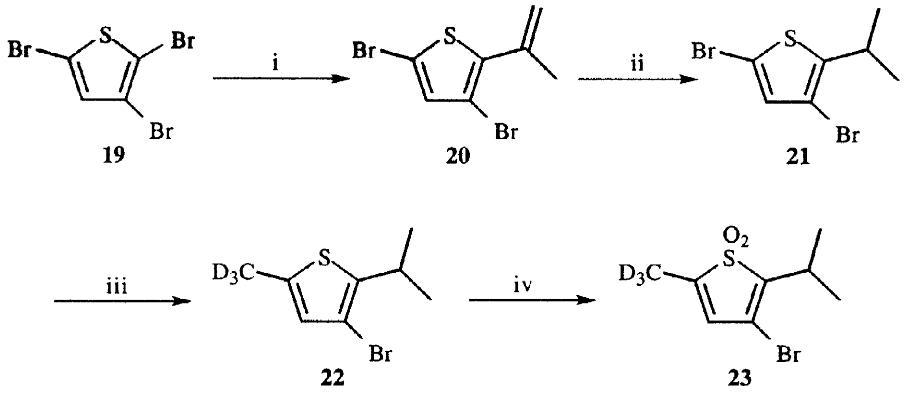


Scheme 3. i. *p*-xylene, 103-116°C, 5.25 eq amine, 0.1255 M in **11**.

Previously we suggested that the rate determining step for the ring-opening reaction was the amine-mediated tautomerization of double bonds and not the *Michael* addition or the disrotatory cheletropic elimination of sulfur dioxide.[2],[5] Now, it was feasible to study kinetic isotope effects (kie:s) by replacing the 5-methyl group with a 5-trideuteriomethyl group, as one major product was formed in very high yield. Furthermore, studying the deuterium incorporation into the ring-opened product was of high interest, since it would give further information about the mechanism. The synthesis of the desired dioxide was straightforward: 2,3,5-tribromothiophene (**19**), was treated with *sec*-butyllithium and acetone and then refluxed with oxalic acid under reduced pressure to give 3,5-dibromo-2-isopropenylthiophene (**20**) in 74.5% yield.[13] Hydrogenation with Wilkinson's catalyst yielded 3,5-dibromo-2-isopropyl-thiophene (**21**) in 92%.[13] Treating **3** with *sec*-butyllithium and deuterated dimethyl sulfate (CAUTION) gave 3-bromo-2-isopropyl-5-trideuteriomethyl-thiophene (**22**) in 78% yield. Oxidation of **22** with *m*-chloroperbenzoic acid gave 3-bromo-2-isopropyl-5-tri-deuteriomethylthiophene-1,1-dioxide (**23**) in 46% yield (*Scheme 4*).[14,3]

---

2. The formation of sulfur dioxide has been established by trapping the evolved gas in a potassium permanganate solution and observing the formation of manganese(IV) oxide.



Scheme 4. i. 1. *s*-BuLi; 2. acetone 3.$(COOH)_2$, yield 74.5%.
ii. H_2/ Wilkinson's catalyst, yield 92%.
iii. 1.*s*-BuLi 2.$(D_3CO)_2SO_2$, yield 78%. iv. mcpba, yield 46%.

Two parallel reactions were run in the same thermostated oil bath between amine **7** and dioxide **11** or **23** at the 0 level conditions of Table 6. The reaction was pseudo-first order in dioxide: $[\mathbf{11}] = [\mathbf{11}]_0e^{-k_{obs}t}$. The k^H_{obs}/k^D_{obs} ratio was 1.49. In order to make a comparative kinetic study and deuterium incorporation experiment *N,O*-dideuterio-2-piperidyl-1-ethanol (**24**) was synthesized from **7**. Compound **11** was reacted with **7** and **24**, respectively, in the same thermostated oil bath at the 0 level conditions of Table 6. The k^H_{obs}/k^D_{obs} ratio was in this case 1.39. The accuracy of the kinetic measurements was estimated to $k^H_{obs} = 0.0060 \pm 0.0001$ min^{-1}. The deuterated products **25** (from the former experiment) and **26** (from the latter experiment) were purified and analyzed by ^1H NMR and ^2H NMR (*Figure 2*). The amount of the protons present at the different positions was determined by integrating the ^1H signals using the non-labelled positions as internal standards.

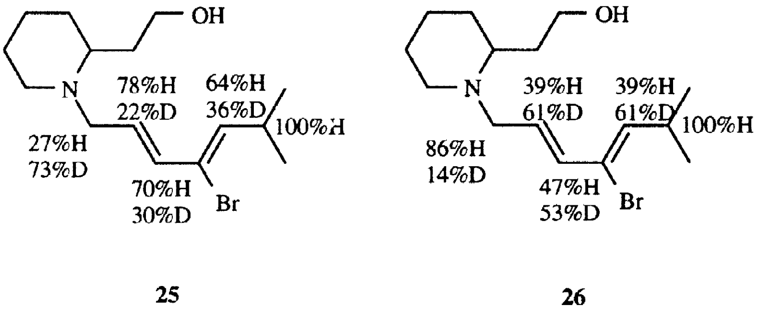
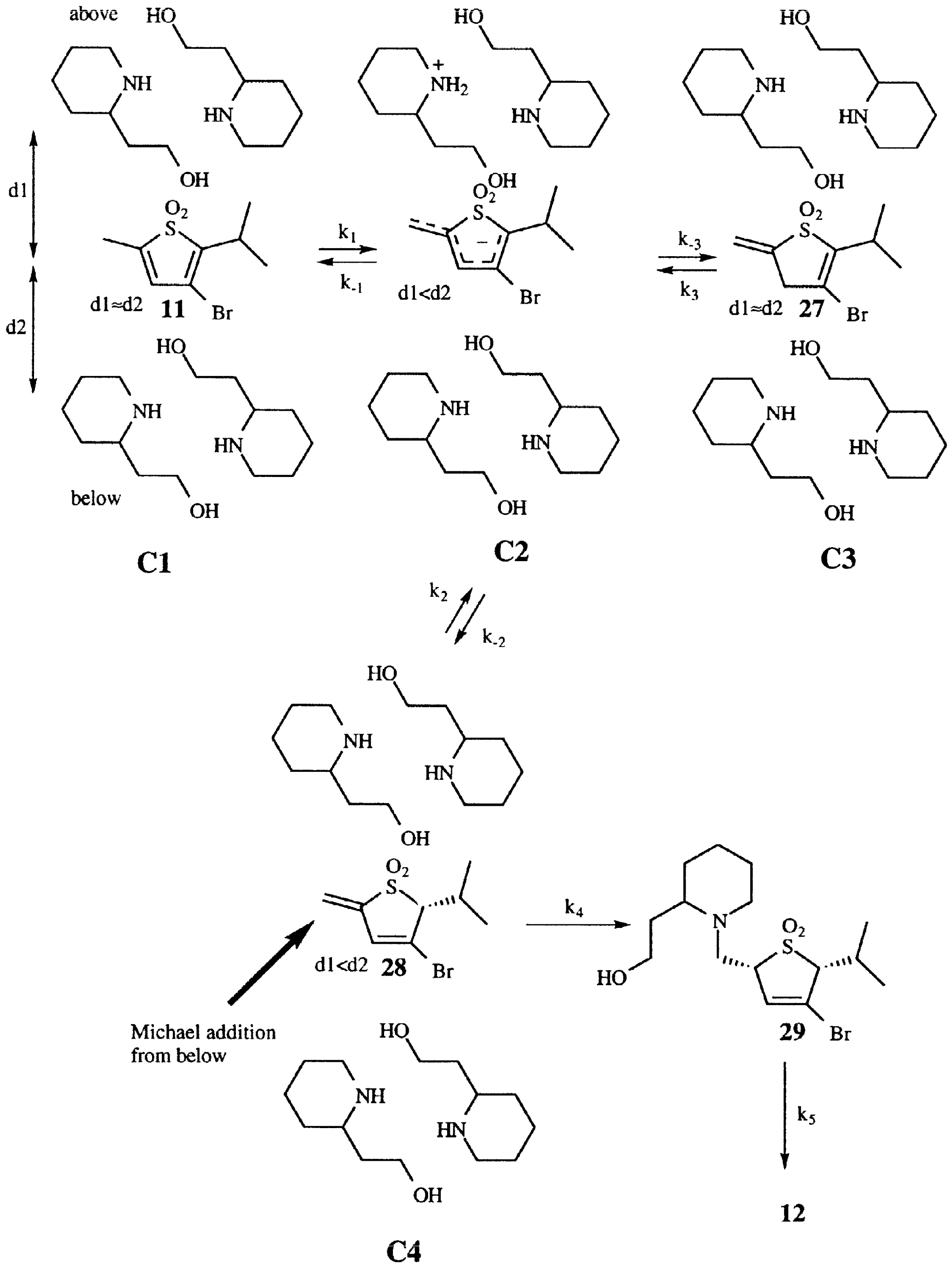


Figure 2. The deuterium labelled compounds **25** and **26**.

From the 5-methyl group of **23** 1.54 deuteron was abstracted and 0.88 (57%) of it was observed elsewhere in **25**: 22% at C(2), 30% at C(3) and 36% at C(5); positions that are markedly labelled by deuterium. If a statistical labeling had occurred only 12.8% (1.54/ (1.54 + 10.5) = 12.8%) would have been incorporated into each position, since there are 5.25 equivalents of aminoalcohol present. In **11** 1.81 proton was abstracted from the 5-methyl group and from C(4) and 0.78 (43%) of it was observed elsewhere in **26**: 39% at C(2) and 39% at C(5). If a statistical labeling had occurred only 14.7% (1.88/ (1.88 + 10.5) = 14.7%) would have been incorporated into each position. These results clearly indicate an intramolecular proton/deuteron transfer. In a previous work, we surmised that the ring-opening reaction was initiated by proton abstraction from a methyl



Scheme 5. The tautomerization and ring-opening of **11**. d1 and d2 are the distances between the plane of the dioxide moiety and the plane of the dimer moieties.

group. Some calculations were also made on the resonance stabilized carbanion obtained after the abstraction: the HOMO of this carbanion and the electrostatic charges of the carbon skeleton were concentrated to the methylene carbon at C(5) (coef. 0.33, charge -0.59), to C(4) (coef. 0.54, charge -0.69) and to C(2) (coef. 0.54, charge -0.44);[5,15] these were the positions where labeling could be expected and has now been verified. Using ammonium ion as counter ion to the carbanion in the calculations, we found several minima on the potential energy surface for the tight ion pair, which suggests that the tautomerization could be described in terms of a conducted tour mechanism analogous to the amine mediated tautomerization of indene systems.[16-21] Both labeling experiments confirm that a high degree of intramolecular proton/deuteron transfer occurs. The solvent screening verified that the non-polar character of the solvent was important. Tight hydrogen bonded ion pairs involving sensitive carbanions preferably form in such solvents, whereas dissociation to free or solvent bound ions is more pronounced in more polar solvents. Subsequently, base catalyzed alkene rearrangements show a high degree of intramolecular proton transfer in non-polar solvents, while exchange is more dominant in polar and protic solvents.[22] In dimethylsulfoxide and dimethylformamide reactions, which lead to massive decomposition of the dioxide, were favoured *vide supra*. Apparently, dissociation of the ion pair was detrimental to the reaction.

Furthermore, the optimization gave that a 5.25:1 molar ratio of reagents was required. This together with a strong concentration dependence suggest that a complex between several amine molecules and one dioxide molecule forms, and that this complex probably is maintained during the tautomerization process and possibly until the *Michael* addition, *i.e.* the addition of amine to the tautomerized exomethylene group. In a non-polar solvent such as *p*-xylene an aminoalcohol may form doubly hydrogen bonded dimers, and in doing so it will gain some extra stabilization energy. This dimer can form a weak complex with the dioxide, gaining a few kcal mol^{-1} compared to the free dimer and the free dioxide.[23] Adding another dimer at the other side of the dioxide also leads to some extra stabilization. A 2:1 complex (**C1**) is thus conceivable, where the hydrogen bonded dimers lie separated with the dioxide in between with a distance $d1 \approx d2$ (*scheme 5*). After the tautomerization a complex with $d1 < d2$ is formed (**C4**). The dioxide can then be attacked in a *Michael* addition from the side where bonding to the dimer is weaker. This can explain the high degree of deuterium and hydrogen labeling at C(2) in **25** and **26**. In a *Michael* addition to vinyl sulfones the reaction order in amine is second when benzene is the solvent while it is first in ethanol.[24] McDowell and Stirling argue that an extra amine molecule is needed in the transition state (TS); in ethanol a solvent molecule takes this role. These requirements were fulfilled in our case with an isotope enriched amine dimer complexing to the tautomer.

Formally, the tautomerization is a base assisted 1,5-proton transfer; but the extensive isotope labeling at C(3) in the products suggests that two consequtive 1,3-proton transfers also can take place. Protonation at C(4) will lead to the tautomer 3-bromo-2-isopropyl-5-methylidene-2-sulfolene (**27**), which has not been observed in the reaction mixture by either GLC or NMR; it is therefore thought to equilibrate back to the tight ion pair (**C2**). Labeling at C(3) in **25** and **26** was however a strong evidence that an intermediate like **27** existed.

Protonation at C(2) will lead to the tautomer 3-bromo-2-isopropyl-5-methylidene-3-sulfolene (**28**), which has not been observed in the reaction mixture either; it reacts as soon as it is formed through an attack at the exomethylene by the amine, *i.e. Michael* addition to a vinyl sulfone.[24,25-27] Protonation of the intermediate anion favours a *cis*-2,5-disubstituted 3-sulfolene (**29**) over a *trans* sulfolene. Since only *E,E* dienes with respect to the carbon chain are formed in the ring-opening reaction, the reaction has to occur *via* an intermediate *cis* sulfolene, which extrudes sulfur dioxide in a disrotatory cheletropic elimination.[28,29] Compound **29** has not been observed in the reaction mixture neither by GLC nor ^{1}H NMR analyses. As the reaction is pseudo first order in dioxide with a virtually constant amine concentration, we may treat the tautomers as complexes. If we then assume a steady-state approximation for **C2**, **C3** and **C4** and that $k_5 >> k_4$ the following rate function can be formulated for the ring-opening reaction:

$$k_{obs} = k_1(1 - K), \text{ where } K = k_{-1}/[k_{-1} + k_{-2}k_4/(k_2 + k_4)]$$

Compared to **27** the vinyl sulfone **28** is further activated towards nucleophilic attack by an α-vinyl group, which can explain the observed selectivity. In the case of **11** it is likely that $k_2 << k_4$. K will then express the percentage of **C2** that collapses back to **C1**. A considerable internal return of this kind was observed as C(1) in both **25** and **26** were labelled; a large k_{-1} would decrease the observed rate. A larger k_{-2} would lead to an increase in k_{obs}; the increased rate caused by using aminoalcohols instead of 2-allylpyrrolidines or 2-allylpiperidines[4] can in part be explained by a facilitated tautomerization, in which the proton is transferred intramolecularly by the oxygen to the other side of the anion. A smaller k_{-2} and, subsequently, a decrease in reaction rates would be the result when using more sterically demanding amines such as 2-[(1,3-dithiolan-2-yl)methyl]pyrrolidine and 2-[(1,3-dithiolan-2-yl)methyl]piperidine[4] or as in this case when using a 2-isopropyl substituted dioxide. Using bulky amines would probably also decrease k_4 leading to a decrease in k_{obs}; a decrease in k_4 would also be seen if there were β-substituents in the 3-sulfolene tautomer.[24] The proposed rate function seems to be valid as it can account for both the present and the previous observations. The rate determining step in base assisted allylic rearrangements is usually the initial proton abstraction.[30] A primary kie was therefore anticipated in the reaction of **23**. The k^H_{obs}/k^D_{obs} ratio was seemingly low only 1.49; but considering the internal return, leading to some hydrogen labeling, the actual ratio was undoubtedly higher since k^D_{obs} then would reflect a mixed rate constant somewhere in between the real k^H_1 and k^D_1. In the investigated reaction K was probably little affected by kie:s: if the assumption holds that $K \approx k_{-1}/[k_{-1} + k_{-2}]$, the effects on k_{-1} and k_{-2} respectively would cancel: thus, the ratio $(1 - K^H)/(1 - K^D) \approx 1$. In view of the reactants, a highly asymmetric TS could be expected for the proton abstraction, which precludes a maximum kie; an early reactant like TS could answer for the smaller kie.[31] We therefore conclude that there is a primary kie in the initial proton abstraction and that this effect is diminished by internal return.

CONCLUSIONS

Through multivariate optimization the yields of **8** and especially **12**, **16** and **18** were improved. Also some light was shed on the underlying mechanism of the ring-opening reaction. The molar ratio between the amine and the dioxide and the concentration of them were found to be the most important ones. The reaction temperature proved to be an independent variable, and could be kept constant within a range. The polarity of the solvent was crucial. Deuterium labeling experiments showed a kinetic isotope effect when using either 3-bromo-2-isopropyl-5-trideuterio-methylthiophene-1,1-dioxide or *N,O*-dideuterio-2-piperidyl-2-ethanol in the ring-opening reaction, implicating that the rate determining step was the initial proton abstraction of the tautomerization process. A 5.25:1 molar ratio of reagents was found at the optimum. This together with a strong concentration dependence suggest that a complex between several amine molecules and a dioxide forms and that this complex is maintained during the tautomerization process and possibly until the *Michael* addition.

Previously we have shown that the present reaction is a useful entry to the tetrahydrobenzo[*a*]pyrrolizidine, tetrahydrobenzo[*a* or *f*]indolizidine and tetrahydrobenzo[*b*]quinolizidine structures and therefore believe that these new results further enforce the utility of thiophene-1,1-dioxides as starting materials in a more general alkaloid synthesis.

EXPERIMENTAL

General. The ^{1}H NMR (at 299.943 MHz), ^{13}C NMR (at 75.43 MHz) and the ^{2}H NMR (at 46.04 MHz) spectra were recorded on a Varian XL300 instrument; δ in ppm relative to residual solvent signals; J in Hz; deuteriochloroform was consistently used as solvent, except for the ^{2}H NMR analyses where chloroform was used. The mass spectra were recorded on a JEOL-SX 102 mass spectrometer at 70 eV; m/z (rel. %). GLC analyses were carried out on a Varian 3600 gas chromatograph equipped with a SPB5 capillary column. The IR spectra were recorded on a Perkin Elmer 298 infrared spectrophotometer; ν in cm^{-1}. Optical rotations were measured at room temperature on a Perkin Elmer 241 polarimeter. Separations on a Chromatotron™ were made using rotors coated with Merck silica gel 60 (60 PF_{254}) containing gypsum. HPLC chromatography was performed on a semipreparative nucleosil silica column (500x10 mm). All solvents were distilled and purified according to standard procedures prior to use. Other commercial starting materials were of highest quality and they were used without further purification. Canonical analyses and calculations of response functions and response surfaces were made using MODDE 3.0.[12]

Optimization. The amount of dioxide used in each experiment was 0.251 mmol (56.00 mg of **1** or 63.00 mg of **11**). In the solvent screening 0.251 M solutions in dioxide were used. The amount of hexadecane was 57.65 mg. The reactions were monitored by TLC and GLC until the dioxide was consumed quantitatively. GLC yields were determined using hexadecane as an internal standard; hexadecane was weighed together with the dioxide. A portion of the crude reaction mixture was diluted five times with $CHCl_3$ (p.a.); then 0.5 μl of this mixture was analyzed on a Varian 3600 gas chromatograph equipped with a SPB5 capillary column. HPLC purified samples of **8**, **9**, and **10** were weighed together with hexadecane and were diluted to approximately the same concentration as the diluted reaction samples; these solutions were stored in a -17°C freezer and were freshly analyzed in direct connection with each series of GLC measurements to determine the response factors for each component.

Statistics. For statistical evaluation of the response functions an F-test was chosen: DF is the degree of freedom, y_{pred} is the response predicted by the model and y_{obs} is the observed response; y_{cent} is the observed response in a center point and y_{mean} is the mean value of the center points.

For the reaction between **1** and **7** in decaline the variance ratio was: $s_1^2/ s_2^2 = 2.47 < 5.91 = F_{crit}$ (for $n_1 = 12$, $n_2 = 4$ at 5% probability level);$s_1^2 = \Sigma(y_{pred} - y_{obs})^2/ DF = 206.52/ 13$; $s_2^2 = \Sigma(y_{cent} - y_{mean})^2/ DF = 25.75/4$.

For the reaction between **1** and **7** in *p*-xylene (Table 4) the variance ratio was: $s_1^2/ s_2^2 = 1.43 < 4.46 = F_{crit}$ (for $n_1 = 2$, $n_2 = 8$ at 5% probability level); $s_2^2 = \Sigma(y_{pred} - y_{obs})^2/ DF = 95.71/ 8$; $s_1^2 = \Sigma(y_{cent} - y_{mean})^2/ DF = 34.27/2$.

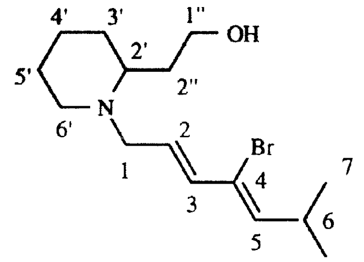
For the reaction between **11** and **7** in *p*-xylene (Table 7) the variance ratio was: $s_1^2/ s_2^2 = 1.25 < 224.6 = F_{crit}$ (for $n_1 = 4$, $n_2 = 1$ at 5% probability level); $s_1^2 = \Sigma(y_{pred} - y_{obs})^2/ DF = 87.14/ 4$; $s_2^2 = \Sigma(y_{cent} - y_{mean})^2/ DF = 27.14/1$.

Kinetics. The experimental size was scaled up threefold compared to the one used in the optimization. The reactions were run at optimal conditions: the p-xylene solution was 0.1255 M in dioxide and 0.6589 M in amine and the reaction temperature was 116°C. Eight samples were taken during the course of reaction starting with 30 min and ending with 60 min intervals and they were treated as above; GLC yields were determined using hexadecane as an internal standard. For purification of **25** and **26** we used the same procedure as for **12**, **16** and **18** *vide infra*.

Rate functions.

1. $-\delta[\mathbf{C1}]/\delta t = k_{obs}[\mathbf{C1}]$
2. $\delta[\mathbf{C1}]/\delta t = - k_1[\mathbf{C1}] + k_{-1}[\mathbf{C2}]$
3. $\delta[\mathbf{C2}]/\delta t = k_1[\mathbf{C1}] + k_2[\mathbf{C4}] + k_3[\mathbf{C3}] - (k_{-1} + k_{-2} + k_{-3})[\mathbf{C2}] = 0$; steady-state approximation.
4. $\delta[\mathbf{C4}]/\delta t = k_{-2}[\mathbf{C2}] - (k_2 + k_4)[\mathbf{C4}] = 0$; steady-state approximation.
5. $\delta[\mathbf{C3}]/\delta t = k_{-3}[\mathbf{C2}] - k_3[\mathbf{C3}] = 0$; steady-state approximation.
6. $k_{obs} = k_1 - k_{-1}[\mathbf{C2}]/[\mathbf{C1}]$ (from 1 and 2)
7. $[k_2k_{-1} + (k_{-1} + k_{-2})k_4][\mathbf{C2}]/(k_2 + k_4) = k_1[\mathbf{C1}]$ (from 3,4 and 5)
8. $k_{obs} = k_1(1- K)$, $K = k_{-1}/[k_{-1} + k_{-2}k_4/(k_2 + k_4)]$ (from 6 and 7)

or $k_{obs} = k_1/((k_2 + k_4)\, k_{-1}/k_{-2}k_4 + 1)$; if $k_2 << k_4$, then $k_{obs} = k_1/(k_{-1}/k_{-2} + 1)$.



Representative numbering for NMR assignments

2-(1-[(2E,4Z)-4-bromo-2,4-hexadienyl]-2-piperidyl)-1-ethanol (9). ^{1}H NMR: δ 6.10 (d, dq, J = 14.7, 6.5, 2H, 4-CH, 5-CH), 5.93 (t, J = 6.2, 1H, 2-CH), 3.92 (dd, J = -10.9, 4.2, 1H, 1''-CH_2), 3.73 (2H, 1-CH_2, 1''-CH_2), 3.46 (1H, 1''-CH_2), 2.96 (1H, 6'-CH_2-eq), 2.75 (m, 1H, 2'-CH), 2.35 (1H, 6'-CH_2-ax), 1.84 (d, J = 6.5, 3H, 6-CH_3) 1.91-1.25 (m, 8H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 2''-CH_2). ^{13}C NMR: δ 131.63 (4C), 130.43 (5C), 128.29 (2C), 127.30 (3C), 62.16 (1''C), 59.82 (2'C), 54.34 (1C), 51.00 (6'C), 32.21 (2''C), 28.03 (3'C), 23.47 (5'C), 23.07 (4'C), 18.01 (6C). HR-MS: calcd for $C_{13}H_{23}NOBr$ (M+H): 288.0963). Found: 288.0956. MS: 287/289 (0, M^{+}), 222/224 (40), 174/176 (100), 95 (42), 77 (85).

2-(2-(2-Hydroxyethyl)piperidyl)-methyl-5-methylthiophene-1,1-dioxide (10). ^{1}H NMR: δ 6.54 (1H, 3-CH), 6.31 (1H, 4-CH), 3.87 (1H, 1''-CH_2), 3.84 (1H, 1-CH_2), 3.71 (1H, 1''-CH_2), 3.60 (1H, 1-CH_2), 3.00 (1H, 6'-CH_2-eq), 2.74 (m, 1H, 2'-CH), 2.40 (1H, 6'-CH_2-ax), 2.10 (3H, 6-CH_3), 1.97-1.43 (m, 8H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 2''-CH_2). ^{13}C NMR: δ 141.58 (2C), 141.08 (5C), 125.59 (3C), 122.62 (4C), 61.59 (1''C), 59.26 (2'C), 50.38 (6'C), 47.99 (1C), 32.89 (2''C), 28.04 (3'C), 23.23 (5'C), 22.68 (4'C), 9.77 (6C). MS: 271 (<1, M^{+}), 253 (2), 216 (15), 186 (13), 173 (17), 140 (100), 105 (30), 83 (15).

3-Bromo-2-isopropyl-5-methylthiophene-1,1-dioxide (11) was synthesized according to the literature.[14,3] ^{1}H NMR: δ 6.26 (q, J = 2.0, 1H, 3-CH), 3.10 (sept, J = 7.1, 1H, CH(CH$_3$)$_2$), 2.09 (d, J = 2.0, 3H, CH_3), 1.38 (d, J = 7.1, 6H, CH(CH_3)$_2$). ^{13}C-NMR: δ 143.29 (2C), 140.64 (5C), 126.48 (4C), 119.32 (3C), 28.92 (CH(CH$_3$)$_2$), 19.66 (CH(CH$_3$)$_2$), 8.73 (CH$_3$).

Synthesis of 12, 16 and 18 via ring-opening of 11: 0.251 mmol of **11** was dissolved in 2.00 ml of *p*-xylene together with 1.317 mmol of **7**, **15** or **17** and placed with a condenser in an oil bath at 116°C or at 103°C for **17** and under argon, an optional precaution. The reaction was complete within 7 h 30 min, as determined by TLC and GLC; the reaction mixture was diluted with ether and washed with water to remove the excess of aminoalcohol. The ethereal phase was dried over magnesium sulfate and then evaporated *in vacuo* to give a crude oil. The products were separated on a Chromatotron™ with heptane:ethyl acetate: triethylamine: methanol (60:40:5:1) as eluent.

2-(1-[(2E,4Z)-4-Bromo-6-methyl-2,4-heptadienyl]-2-piperidyl)-1-ethanol (12). Reaction time: 7h 30 min; yield: 91%. IR (film): 3400*b* (OH) 1635*m* (C=C-stretch, conjug. diene), 947*s* (CH-bend, *trans*-RCH=CHR). ^{1}H NMR: δ 6.12 (d, *J* = 14.9, 1H, 3-C*H*), 6.03 (m, *J* = 14.9, 6.8, 5.6, 1H, 2-C*H*), 5.72 (d, *J* = 8.8, 1H, 5-C*H*), 3.93 (dt, *J* = -11.0, 1H, 1”-CH_2), 3.74 (dt, *J* = -11.0, 1H, 1”-CH_2), 3.61 (dd, *J* = -14.2, 5.6, 1H, 1-CH_2), 3.19 (dd, *J* = -14.2, 6.8, 1H, 1-CH_2), 3.00 (m, 1H, 6’-CH_2-eq), 2.82 (m, *J* = 8.8, 6.8, 1H, 6-C*H*), 2.62 (m, 1H, 2’-C*H*), 2.22 (m, 1H, 6’-CH_2-ax), 1.90-1.33 (m, 8H, 3’-CH_2, 4’-CH_2, 5’-CH_2, 2”-CH_2), 1.02 (d, *J* = 6.8, 6H, 7-CH_3). ^{13}C NMR: δ 140.57 (5C), 131.91 (3C), 130.53 (2C), 122.25 (4C), 61.61 (1”C), 59.34 (2’C), 54.75 (1C), 50.62 (6’C), 31.70 (2”C), 31.09 (6C), 28.00 (3’C), 23.46 (5’C), 22.98 (4’C), 21.75 (7C). HR-MS: calcd for $C_{15}H_{27}NOBr$ (M+H):316.1276. Found: 316.1282. MS: 315/317 (<2, *M*$^+$), 270/272 (100), 236 (22), 107 (42), 84 (22).

(1-[(2E,4Z)-4-Bromo-6-methyl-2,4-heptadienyl]-2-piperidyl)methanol (16). Yield: 89 %. IR (film): 3400*b* (OH), 1635*m* (C=C-stretch, conjug. diene), 947*s* (CH-bend, *trans*-RCH=CHR). ^{1}H NMR: δ 6.14 (d, *J* = 14.7, 1H, 3-C*H*), 6.06 (m, *J* = 14.7, 6.8, 4.9, 1H, 2-C*H*), 5.73 (d, *J* = 8.9, 1H, 5-C*H*), 3.80 (dd, *J* = -10.9, 1H, 1”-CH_2), 3.51 (dd, *J* = -14.8, 4.9, 1H, 1-CH_2), 3.46 (dd, *J* = -10.9, 1H, 1”-CH_2), 3.12 (dd, *J* = -14.8, 6.8, 1H, 1-CH_2), 2.94 (m, 1H, 6’-CH_2-eq), 2.85 (m, *J* = 8.9, 6.8, 1H, 6-C*H*), 2.37 (m, 1H, 2’-C*H*), 2.24 (m, 1H, 6’-CH_2-ax), 1.75-1.25 (m, 6H, 3’-CH_2, 4’-CH_2, 5’-CH_2), 1.03 (d, *J* = 6.8, 6H, 7-CH_3). ^{13}C NMR: δ 140.56 (5C), 131.76 (3C), 130.54 (2C), 122.27 (4C), 62.50 (1”C), 60.38 (2’C), 54.72 (1C), 51.60 (6’C), 31.10 (6C), 27.85 (3’C), 24.65 (5’C), 23.59 (4’C), 21.76 (7C). HR-MS: calcd for $C_{14}H_{25}NOBr$ (M+H) 302.1120. Found: 302.1109. MS: 300/302 (<1, *M*$^+$+H), 270/272 (100), 222 (46), 107 (65), 84 (48).

[1-[(2E,4Z)-5-Bromo-2,4-heptadienyl]tetrahydro-1H-(2S)-2-pyrrolyl]methanol (18). Reaction time: 1h 40 min; yield: 79%). [α]$_D$: -38.40 (c 0.83, chloroform). IR (film): 3406*b* (OH), 1639*m* (C=C-stretch, conjug. diene), 1456*s*, 948*s* (CH-bend, *trans*-RCH=CHR). ^{1}H NMR: δ 6.12 (d, *J* = 15.0, 1H, 3-C*H*), 6.04 (m, *J* = 14.7, 7.3, 4.9, 1H, 2-C*H*), 5.71 (d, *J* = 8.9, 1H, 5-C*H*), 3.60 (dd, *J* = -10.9, 1H, 1”-CH_2), 3.49 (dd, *J* = -14.8, 4.9, 1H, 1-CH_2), 3.40 (dd, *J* = -10.9, 1H, 1’’-CH_2), 3.10 (m, 1H, 5’-CH_2-eq), 3.00 (dd, *J* = -14.8, 7.3, 1H, 1-CH_2), 2.83 (m, *J* = 8.8, 6.8, 1H, 6-C*H*), 2.62 (m, 1H, 2’-C*H*), 2.28 (m, 1H, 5’-CH_2-ax), 1.95-1.63 (m, 4H, 3’-CH_2, 4’-CH_2), 1.01 (d, *J* = 6.8, 6H, 7-CH_3). ^{13}C NMR: δ 140.60 (5C), 131.23 (3C), 128.88 (2C), 122.27 (4C), 64.04 (2’C), 62.17 (1”C), 55.36 (1C), 54.41 (5’C), 31.09 (6C), 27.72 (3’C), 23.51 (4’C), 21.76 (7C). HR-MS: calcd for $C_{13}H_{23}NOBr$ (M+H): 288.0958. Found: 288.0963. MS: 286/288 (<1, *M*$^+$+H), 256/258 (100), 208 (58), 107 (76), 70 (42).

3-Bromo-2-isopropyl-5-trideuteriomethylthiophene (22): 1.79 g (6.31 mmol) of **21** was dissolved in 20 ml of anhydrous ether and was cooled to -78°C under an argon atmosphere; then 4.85 ml (6.31 mmol) of 1.3 M *sec*-butyllithium was added dropwise over 40 min. After 1h 1.00 g (7.57 mmol) of di(trideuteriomethyl)sulfate (CAUTION) in 10 ml of anhydrous ether was added *via* a needle, and the reaction was allowed to reach ambient temperature over 1h 45 min. The reaction was quenched with water and finally, a large volume of 10 % ammonia in EtOH was poured into the reaction vessel; this mixture was left overnight. The mixture was extracted several times with ether; the etheral layers were washed with a saturated ammonium chloride solution and water, dried with magnesium sulfate and evaporated *in vacuo* to give a 4:1 mixture of 5-alkylated:5-protonated thiophene in quantitative yield. The thiophenes were separated on a Chromatotron™ using heptane as eluent. 1.09 g (4.92 mmol) of **22** was obtained as an oil; yield 78 %. ^{1}H NMR: δ 6.26 (t, 1 H, 4-CH, J = 2.1), 3.10 (sept, 1 H, $CH(CH_3)_2$, J = 7.1), 2.50 (dq, 2 H, CH_2CH_3, J = 7.0, 2.1), 1.39 (d, 6 H, $CH(CH_3)_2$, J = 7.1), 1.24 (t, 3 H, CH_2CH_3, J = 7.0). HR-MS: calcd for $C_8H_8D_3SBr$: 220.9953. Found: 220.9953. MS: 221/223 (30, M^+), 206/208 (100), 127 (42).

3-Bromo-2-isopropyl-5-trideuteriomethylthiophene-1,1-dioxide (23) was synthesized according to the literature.[14,3] The oil was chromatographed on a Chromatotron™ using heptane:ethyl acetate as eluent. 1.11 g (5.00 mmol) of **22** was oxidized to give 585 mg (2.30 mmol) of **23** as a clear oil; yield 46 %. ^{1}H NMR: δ 6.26 (s, 1 H, 4-CH), 3.10 (sept, 1 H, $CH(CH_3)_2$, J = 7.1), 1.40 (d, 6 H, $CH(CH_3)_2$, J = 7.1). ^{2}H NMR: δ 2.11 (s, 1 H, 5-CD_3). ^{13}C NMR: δ 143.33 (2C), 140.54 (5C), 126.56 (4C), 119.30 (3C), 28.92 ($CH(CH_3)_2$), 19.66 ($CH(CH_3)_2$). HR-MS: calcd for $C_8H_8D_3O_2SBr$: 252.9851. Found: 252.9851. MS: 253/255 (12, M^+), 190/192 (13), 174 (33), 110 (100), 94 (27).

N,O-dideuterio-2-piperidyl-1-ethanol (24). Compound **7** was treated with 2.2 eq. of butyllithium in anhydrous ether under argon at -20°C; then 5 eq.deuterium oxide was added to the reaction mixture. An excess of anhydrous magnesium sulfate was added to the solution, which was left overnight under argon. The solution was filtered through celite, evaporated *in vacuo* and the pure product, as determined by ^{1}H NMR and mass analyses, was dried in an exsickator over phosphorus pentoxide.

Acknowledgements: We wish to thank Professor Rolf Carlson, Tromsø University for providing the MODDE program package, Mr Einar Nilsson for the mass analyses and the Swedish Natural Science Research Council for supporting this work financially.

REFERENCES

1. Gronowitz, S.; Hallberg, A.; Nikitidis, G. *Tetrahedron* **1987**, *43*, 4793.
2. Gronowitz, S.; Hörnfeldt, A.-B. ; Lukevics, E.;, Pudova, O. *Synthesis* **1994**, 40.
3. Tsirk, A.; Gronowitz, S.; Hörnfeldt, A.-B. *Tetrahedron* **1995**, *51*, 7035.
4. Tsirk, A.; Gronowitz, S.; Hörnfeldt, A.-B., *Tetrahedron* **1997**, *53*, 771.
5. Tsirk, A.; Gronowitz, S.; Hörnfeldt, A.-B., *Helv. Chim. Acta* **1997**, *80*, 1483.
6. Reviews on pyrrolizidines:
   a. Robins, D. J. *Nat. Prod. Rep.* **1993**, 487.
   b. Robins, D. J. *Nat. Prod. Rep.* **1992**, 313.
   c. Robins, D. J. *Nat. Prod. Rep.* **1989**, 221 and 577.
   d. Dai, W.-M.; Nagao, Y. *Heterocycles* **1990**, *30*, 1231.
   e. Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. G. *Synlett* **1990**, 433.
7. Reviews on indolizidines:
   a. Michael, J. P. *Nat. Prod. Rep.* **1994**, 639.
   b. Angle, S. R.; Breitenbucher, J. G.*Stud. Nat.Prod. Chem.* **1995**, *16*, 453.
   c. Jefford, C. W.; Lu, Z.-H.; Wang, J. B. *Pure Appl. Chem.* **1994**, *66*, 2075.
   d. Takahata, H.; Momose, H. in *Alkaloids* (Academic. Press) **1993**, *44*, 189.
   e. Cossy, J.; Vogel, P. *Stud. Nat. Prod. Chem.* **1993**, *12*, 275.
   f. Kibayashi, C. *ibid.* **1992**, *11*, 229.
   g. Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.
   h. Rajeswari, S.; Chandrasekharan, S.; Govindachari, T. R. *Heterocycles* **1987**, *25*, 659.
8. Reviews on quinolizidines:
   a. Robins, D. J. in *Alkaloids* (Academic. Press) **1995**, *46*, 1.
   b. Michael, J. P. *Nat. Prod. Rep.* **1994**, 17.
   c. Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 523.
   d. Fuji, T.; Ohba, M.; Yoshifuji, S. *Heterocycles* **1988**, *27*, 1009.
   e. Grundon, M. F. *Nat. Prod. Rep.* **1985**, *2*, 235.
9. Carlson, R. *Design and Optimization in Organic Synthesis* (Elsevier 1992), chapter 15, and references cited therein.
10. Gronowitz, S. in *Phosphorous, Sulfur, and Silicon* 1993, Vol 74, 113.

11. Carlson, R. ***Design and Optimization in Organic Synthesis*** (Elsevier 1992), chapter 12, and references cited therein.
12. MODDE 3.0, Umetri AB, Umeå, Sweden.
13. Karlsson, J. O.; Gronowitz, S.; Hallberg, A., *Chemica Scripta* **1982**, 37.
14. van Tilborg, W. J. M., *Synthetic Comm.* **1976**, 583.
15. SPARTAN version 4.0, Wavefunction Inc., Von Karman, Suite 370, Irvine, California 92715, U.S.A..
16. Wold, S.; Bergson, G. *Arkiv Kemi* **1967**, *28*, 245.
17. Almy, J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 4459.
18. Bergson, G.; Weidler, A.-M. *Acta Chem. Scand.* **1963**, *17*, 862.
19. Bergson, G.; Weidler, G. *Acta Chem. Scand.* **1963**, *17*, 1798.
20. Weidler, A.-M.; Bergson, G. *Acta Chem. Scand.* **1964**, *18*, 1487.
21. Almy, J.; Uyeda, R. T.; Cram, D. J. *J. Am. Chem. Soc.* **1967**, *89*, 6768.
22. Robinson, B. H. *Proton-Transfer Reactions* (1975 Chapman and Hall; Ed's E. Caldin, V. Gold), chapter 5.
23. Tsirk, A.; Gronowitz, S.; Hörnfeldt, A.-B. *Acta Chem. Scand.* **1998** (in press).
24. McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. (B)* **1967**, 343.
25. Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951.
26. McDowell, S. T.; C. J. M. Stirling, C. J. M. *ibid.*, 348.
27. McDowell, S. T.; Stirling, C. J. M. *ibid.*, 351.
28. McGregor, S. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 2858.
29. Mock, W. L. *J. Am. Chem. Soc.* **1975**, *97*, 3673.
30. DeWolfe, R. H. *Comprehensive Chemical Kinetics* (1973 Elsevier; Ed's C. H. Bamford, C. F. H. Tipper), *Vol 9*, chapter 5.
31. More O'Ferrall, R. A. *Proton-Transfer Reactions*, (1975 Chapman and Hall; Ed's E. Caldin, V. Gold), chapter 8.